SEVENTH EDITION

PRINCIPLES OF SURGERY

COMPANION HANDBOOK

SCHWARTZ
SHIRES
SPENCER
DALY
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GALLOWAY

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PREFACE

This handbook has resulted from the need of students and house officers to be able to carry a book with them for easy reference when there is limited access to the companion textbook. This portable handbook is not meant to supersede the textbook and should be used in conjunction with the seventh edition of *Principles of Surgery.* The material prepared by the contributors to the handbook is based solely on the chapters from the seventh edition and is meant to be a concise synopsis of the work of those original authors.

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ACKNOWLEDGMENTS

The abstracts of the chapters of the seventh edition of Principles of Surgery, which comprise this companion handbook, were produced by members of the Department of Surgery at the University of Rochester School of Medicine and Dentistry. I am indebted to them for their efforts.

I also express my deep appreciation to Andrea Weinstein of the University of Rochester, who worked with the contributors, the publisher, and with me in every step of the production of the book.

Seymour I. Schwartz,
Editor-in-Chief

CHAPTER

1

THE SYSTEMIC RESPONSE TO INJURY

The host response to injury—surgical, traumatic, or infectious—is characterized by various endocrine, metabolic, and immunologic alterations. If the inciting injury is minor and of limited duration, wound healing and restoration of metabolic and immune homeostasis occur readily. More significant insults lead to further deterioration of the host regulatory processes, which, without appropriate intervention, often precludes full restoration of cellular and organ function or results in death. The spectrum of cellular metabolic and immunologic dysfunction resulting from injury suggests a complex mechanism for identifying and initially quantifying the injurious event. This initial response is inherently inflammatory, inciting the activation of cellular processes designed to restore or maintain function in tissues while also promoting the eradication or repair of dysfunctional cells. These dynamic processes imply the existence of anti-inflammatory or counterregulatory processes that promote the restoration of homeostasis. A discussion of the response to injury must account for the collective dynamics of neuroendocrine, immunologic, and metabolic alterations characteristic of the injured patient.

ENDOCRINE RESPONSE TO INJURY

Overview of Hormone-Mediated Response

The classic response to injury comprises multiple axes. These hormone response pathways are activated by (1) mediators released by the injured tissue, (2) neural and nociceptive input originating from the site of injury, or (3) baroreceptor stimulation from intravascular volume depletion. The hormones released in response to these activating stimuli may be divided into those primarily under hypothalamopituitary control and those primarily under autonomic nervous system control (Table 1-1). The interaction between these origins forms the basis of the hypothalamic-pituitary axis, which

TABLE 1-1
HORMONES REGULATED BY THE HYPOTHALAMUS, PITUITARY, AND AUTONOMIC SYSTEM

Hypothalamus	Pituitary	Autonomic System
Corticotropin-releasing hormone	Anterior pituitary:	Norepinephrine
Thyrotropin-releasing hormone	ACTH	Epinephrine
Growth hormone–releasing hormone	Cortisol/glucocorticoid	Aldosterone
Luteinizing hormone–releasing hormone	Thyroid-stimulating hormone	Renin-angiotensin
	Thyroxine	Insulin
	Triiodothyronine	Glucagon
	Growth hormone	Enkephalins
	Gonadotrophins	
	Sex hormones	
	Insulinlike growth factors	
	Somatostatin	
	Prolactin	
	Endorphins	
	Posterior pituitary:	
	Arginine in vasopressin	
	Oxytocin	

represents a series of signaling and feedback loops that regulate the endocrine response to injury.

Hormone-Mediated Receptor Activity Hormones may be classified according to chemical structure and to the mechanisms by which they elicit biologic effects (Tables 1-2 and 1-3). Central to

TABLE 1-2
CHEMICAL CLASSES OF HORMONES

		Fatty Acid Derivatives	
Polypeptides	Amino Acid Derivatives	Cholesterol	Arachidonic Acid
Luteinizing hormone	Thyroxine	Glucocorticoids	Prostaglandins
Insulin	Epinephrine	Androgens	Leukotrienes
Glucagon	Norepinephrine	Estrogens	
Arginine vasopressin	Dopamine	Mineralocorticoids	
Oxytocin	Serotonin		
Interleukins	Histamine		
TNF	Triiodothyronine		
Interferon			
Endothelins			
Opioids			

TABLE 1-3
HORMONE CLASSIFICATIONS BASED ON MECHANISM OF ACTION

Group I: Hormones That Bind to Intracellular Receptors

Androgens	Mineralocorticoids
Calcitriol	Progestins
Estrogens	Retinoic acid
Glucocorticoids	Thyroid hormones

Group II: Hormones That Bind to Cell Surface Receptors

A. The second messenger is cyclic AMP

α_2-Adrenergic catecholamines[a]	Follicle-stimulating hormone[b]
β_2-Adrenergic catecholamines[b]	Glucagon[b]
ACTH[b]	Lipotropin[b]
Angiotensin II[a]	Luteinizing hormone[b]
Antidiuretic hormone[b]	Melanocyte-stimulating hormone[b]
Calcitonin[b]	Parathyroid hormone[b]
Chorionic gonadotropin[b]	Somatostatin[a]
Corticotropin-releasing hormone[b]	Thyroid-stimulating hormone[b]
Opiods[a]	

B. The second messenger is cyclic GMP

Atrial natriuretic peptide
Nitric oxide

C. The second messenger is calcium or phosphatidylinositides (or both)

α_1-adrenergic catecholamines	Epidermal growth factor
Acetylcholine (muscarinic) [a]	Gonadotropin-releasing hormone
Angiotensin II[a]	Platelet-derived growth factor
Antidiuretic hormone	Thyrotropin-releasing hormone

D. The second messenger is a kinase/phosphatase cascade

Chorionic somatomammotropin	Insulinlike growth factors
Epidermal growth factor	Nerve growth factor
Erythropoietin	Oxytocin
Fibroblast growth factor	Prolactin
Growth hormone	
Insulin	

[a]Hormones known to *inhibit* adenylate cyclase.

[b]Hormones known to *stimulate* adenylate cyclase.

SOURCE: Modified from Granner DK: Hormonal action, in Becker KL, et al (eds): *Principles and Practice of Endocrinology and Metabolism*, 2d ed. Philadelphia, JB Lippincott 1996, chap 3, with permission.

the hormone-mediated response at the cellular level is the hormone (ligand)—receptor interaction and subsequent postreceptor activity. Most macroendocrine hormone receptors can be categorized on the basis of their mechanisms of signal transduction into three major types: (1) receptor kinases with ligands such as insulin and insulin-like growth factors, (2) guanine nucleotide–binding or G protein–coupled receptors that are activated by peptide hormones, neurotransmitters, and prostaglandins, and (3) ligand-gated ion channels that permit ion transport on ligand-receptor binding (Fig. 1-1).

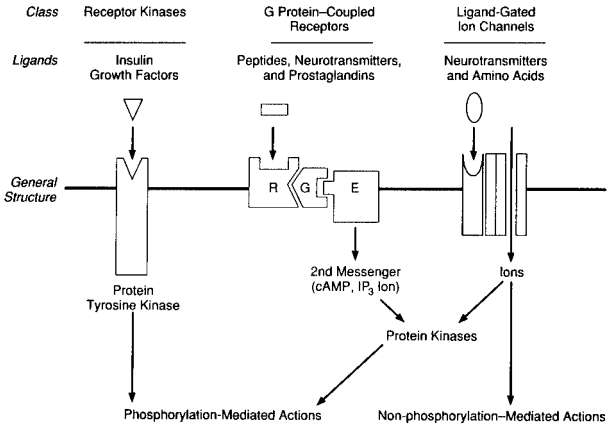


FIGURE 1-1 Three major classes of membrane receptors for hormones and neurotransmitters. *Receptor Kinases:* Mediators such as insulin bind receptors that activate the tyrosine kinase pathway that leads to phosphorylation of proteins. *G Protein-Coupled Receptors:* Some hormones, such as the peptides, neurotransmitters, and prostaglandins, bind to receptors (R) coupled to guanine nucleotide-binding or G proteins (G). The G proteins in turn activate effectors (E), which may be enzymes such as adenylate cyclase. G proteins coupled to adenylate cyclase increase cAMP. If G protein is coupled to phospholipase C, the active second messenger products are inositol triphospate (IP_3) and diacylglycerol (DAG). IP_3 stimulates the release of free calcium from the endoplasmic reticulum. The free calcium then binds to calmodulin to activate a specific phosphorylase kinase. DAG (not shown) remains in the membrane, where it activates protein kinase C, which opens a membrane channel for calcium entry. This activity, resulting from the initial activation of G proteins, may be coupled with the activity of *Ligand-Gated Ion Channels.* (From: *Habener JF: Genetic control of hormone formation, in Wilson JD, Foster DW: Williams Textbook of Endocrinology, 8th ed. Philadelphia, WB Saunders, 1992, chap 4, with permission.*)

Hormone-Mediated Intracellular Pathways One of the most common intracellular second messengers by which hormones exert their effects is the modulation of cyclic adenosine monophosphate (cAMP). Receptor occupation by stimulatory hormones induces a cell membrane alteration that activates the enzyme adenylate cyclase. Adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cAMP, which activates various intracellular protein kinases. Substances that decrease cAMP generally exert an influence opposite to those observed for substances that increase cAMP. Increases in intracellular cAMP are associated with functional lymphocyte responses that generally are immunosuppressive. In T lymphocytes, agents that increase cAMP levels diminish proliferation, lymphokine production, and cytotoxic functions. Plasma cell production of immunoglobulins is markedly attenuated. Neutrophils manifest decreased chemotaxis and reduced production of superoxides, H_2O_2, and lysosomal enzymes. Basophils or mast cells demonstrate a decreased release of histamine. Many prolonged hormone-mediated responses to injury increase intracellular cAMP levels through a direct action on membrane receptors or by increasing the sensitivity of leukocytes to substances that directly increase cAMP.

Hormonal actions are further mediated by intracellular receptors. These intracellular receptors have binding affinities for the hormone and for the targeted gene sequence on the DNA. These intracellular receptors may be located within the cytosol or may already be localized in the nucleus, bound to the DNA. The classic example of a cytosolic hormonal receptor is glucocorticoid receptor. Intracellular glucocorticoid receptors are maintained in an active state by linking to the stress-induced protein heat-shock protein (HSP). When the hormone ligand binds to the receptor, the dissociation of HSP from the receptor activates the receptor-ligand complex, which is transported to the nucleus.

Hormones Under Anterior Pituitary Regulation

Corticotropin-Releasing Hormone Pain, fear, anxiety, or emotional arousal generate neural signals to the paraventricular nucleus of the hypothalamus, stimulating the synthesis of corticotropin-releasing hormone (CRH), which is then delivered by way of the hypothalamic-hypophyseal portal circulation to the anterior pituitary. Proinflammatory cytokines and arginine vasopressin (AVP) also can induce CRH synthesis and release. In the anterior pituitary, CRH serves as the major stimulant of adrenocorticotropic hormone (ACTH, adrenocorticotropin) production and release (Fig. 1-2).

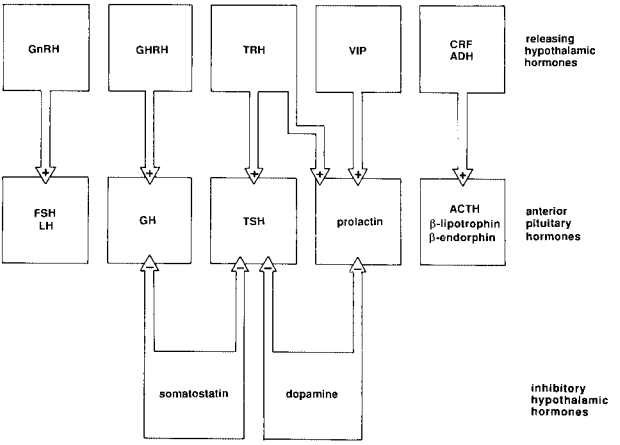


FIGURE 1-2 Hormones produced by the anterior pituitary and the hypothalamic hormones that regulate their secretion. Somatostatin and dopamine are endogenous inhibitors. (From: *Reichlin S: Neuroendocrine control of pituitary function, in Besser GM, Cudworth AG (eds): Clinical Endocrinology: An Illustrated Text. Philadelphia, JB Lippincott, 1987, with permission.*)

This is accomplished by CRH-mediated activation of adenylate cyclase in the ACTH-producing corticotrophs, which increases intracellular cAMP levels and activates the pathway leading to increased ACTH production. CRH secretion can be activated by angiotensin II, neuropeptide Y (NPY), serotonin, acetylcholine, interleukin-1 (IL-1), and IL-6. The release of CRH can be inhibited by γ-aminobutyric acid (GABA), substance P, atrial natriuretic peptide (ANP), endogenous opioids, and L-arginine. Circulating glucocorticoids serve as potent negative feedback signals to the hypothalamus and have demonstrated in animal models an ability to reduce CRH mRNA transcription. CRH-binding proteins (CRH-BPs) synthesized by the liver also serve as regulators of CRH activity. These collectively demonstrate endogenous pathways that may potentially regulate or preclude excessive CRH-mediated responses to injury. Injured tissues also produce CRH that may contribute locally to the inflammatory response.

Adrenocorticotropic Hormone ACTH is synthesized, stored, and released by the anterior pituitary on CRH stimulation. ACTH

is a 39–amino acid peptide that is synthesized as a larger precursor complex known as *proopiomelanocortin* (POMC). POMC is cleaved within the cytosol to the components α-melanocyte-stimulating hormone (α-MSH), β-lipotropin, the endogenous opioid β-endorphin, and ACTH. In the nonstressed healthy human, ACTH release is regulated by circadian signals; the greatest elevation of ACTH occurs late at night and lasts until just before sunrise. This pattern is dramatically altered or obliterated in injured subjects. Most injury is characterized by elevations in CRH and ACTH that are proportional to the severity of injury. While pain and anxiety are prominent mediators of ACTH release, other ACTH-promoting mediators may become relatively more active in the injured patient. These include vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal polypeptide (VIP), catecholamines, oxytocin, and proinflammatory cytokines. Within the zona fasciculata of the adrenal gland, ACTH signaling activates intracellular adenylate cyclase, the cAMP-dependent protein kinase pathway, and the mitochondrial cytochrome P-450 system. This chain of activities leads to increased glucocorticoid production via desmolase-catalyzed side-chain cleavage of cholesterol. Conditions of excess ACTH stimulation result in adrenal cortical hypertrophy.

Cortisol/Glucocorticoids Cortisol is the major glucocorticoid in humans and is essential for survival after significant physiologic stress. Cortisol levels in response to injury are not under the influence of normal diurnal variations and can remain persistently elevated, depending on the type of systemic stress. Burn patients have demonstrated elevated circulating cortisol levels for up to 4 weeks, and patients with soft tissue injury and hemorrhage may sustain elevated cortisol levels for up to a week. Circulating cortisol rapidly returns to normal levels on restoration of blood volume after hemorrhage. Conversely, adequate cortisol levels after mild hemorrhage are a prerequisite for timely restitution of blood volume in experimental animals. Coexisting systemic stress, such as infections, also can prolong the elevated cortisol levels after injury.

Cortisol is a major effector of host metabolism. It potentiates the actions of glucagon and epinephrine, leading to hyperglycemia in the host. In the liver, cortisol stimulates the enzymatic activities favoring gluconeogenesis, including induction of phosphoenol pyruvate carboxykinase and transaminases. Peripherally, it decreases insulin binding to insulin receptors in muscles and adipose tissue. In skeletal muscle, cortisol induces proteolysis and augments the release of lactate. The release of available lactate and amino acids has the net effect of shifting substrates for hepatic gluconeogenesis. Cortisol also stimulates lipolysis and inhibits glucose uptake by

adipose tissues. It increases the lipolytic activities of ACTH, growth hormones, glucagon, and epinephrine. The resulting rises in plasma free fatty acids, triglycerides, and glycerol from adipose tissue mobilization serve as available energy sources and additional substrates for hepatic gluconeogenesis.

About 10 percent of plasma cortisol is present in the free, biologically active form. The remaining 90 percent is bound to corticosteroid-binding globulin (CBG) and albumin. With injury, total plasma cortisol concentrations increase, but CBG and albumin levels decrease by as much as 50 percent. This can lead to an increase in the free cortisol level of as much as 10 times the normal.

Acute adrenal insufficiency is a life-threatening complication most commonly associated with adrenal suppression from the use of exogenous glucocorticoids with consequent atrophy of the adrenal glands. These patients present with weakness, nausea, vomiting, fever, and hypotension. Objective findings include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Although hyponatremia and hyperkalemia generally are a result of insufficient mineralocorticoid (aldosterone) activity, the loss of cortisol activity also contributes to electrolyte abnormalities.

Glucocorticoids have long been used as effective immunosuppressive agents. Administration of glucocorticoids can induce rapid lymphopenia, monocytopenia, eosinopenia, and neutrophilia. Immunologic changes include thymic involution and depressed cell-mediated immune responses reflected by decreases in T-killer and natural-killer functions. Neutrophil function is affected by glucocorticoid treatment in terms of intracellular superoxide reactivity and depressed chemotaxis. Phagocytosis of polymorphonuclear leukocytes (PMNs) remains unchanged. Glucocorticoids are omnibus inhibitors of immunocyte proinflammatory cytokine synthesis and secretion. This glucocorticoid-induced downregulation of cytokine stimulation serves an important negative regulatory function in the inflammatory response to injury.

Thyrotropin-Releasing Hormone and Thyroid-Stimulating Hormone Thyrotropin-releasing hormone (TRH) serves as the primary stimulant for the synthesis, storage, and release of thyroid-stimulating hormone (TSH) in the anterior pituitary. TSH in turn stimulates thyroxine (T_4) production from the thyroid gland. T_4 is converted to triiodothyronine (T_3) by peripheral tissues. T_3 is more potent than T_4, but both are transported intracellularly by cytosolic receptors, which then bind DNA to mediate the transcription of multiple protein products. Free forms of T_4 and T_3 in the circulation can

inhibit the hypothalamic release of TRH and pituitary release of TSH via negative feedback loops. TRH and estrogen stimulate TSH release by the pituitary, and T_3, T_4, corticosteroids, growth hormones, somatostatin, and fasting inhibit TSH release.

Thyroid hormones (thyronines), when elevated above normal levels, exert various influences on cellular metabolism and function. Thyronines enhance membrane transport of glucose and increase glucose oxidation. These hormones increase the formation and storage of fat when carbohydrate intake is excessive, but this process decreases during starvation. The increase in cellular metabolism from excess thyroid hormone production leads to proportional elevations in overall oxygen consumption as well as heat production. Although T_3 levels are frequently decreased after injury, there is no compensatory rise in TSH release. After major injury, reduced available T_3 and circulating TSH levels are observed, and peripheral conversion of T_4 to T_3 is impaired. This impaired conversion may be explained in part by the inhibitory effects of cortisol and an increased conversion of T_4 to the biologically inactive molecule known as *reverse* T_3 (rT_3). Proinflammatory cytokines also may contribute to this effect. Elevated rT_3 but reduced T_4 and T_3 is an observation characteristic of acute injury or trauma, referred to as *euthyroid sick syndrome* or *nonthyroidal illness.*

While total T_4 (protein bound and free) levels may be reduced after injury, free T_4 concentrations remain relatively constant. In severely injured or critically ill patients, a reduced free T_4 concentration has been predictive of high mortality. One consequence of exposure to thyronines is an increase in the uptake of amino acids and glucose into the cell. Whether this is a direct effect of thyroid hormones or a secondary effect of increased cellular metabolism is unknown. Leukocyte metabolism measured by oxygen consumption is increased in hyperthyroid individuals and subjects to whom thyroid hormones have been administered. Animal studies have demonstrated that surgically or chemically induced thyroid hormone depletion significantly decreases cellular and humoral immunity. Conversely, thyroid hormone repletion is associated with enhancement of both types of immunity. Human monocytes, natural killer cells, and activated B lymphocytes express receptors for TSH. Exposure of B cells to TSH in vitro induces a moderate increase in immunoglobulin secretion.

Growth Hormones Hypothalamic growth hormone–releasing hormone (GHRH) travels through the hypothalamic-hypophyseal portal circulation to the anterior pituitary and stimulates the release of growth hormone (GH) in a pulsatile fashion mostly during the sleeping hours. In addition to GHRH, GH release is influenced by autonomic stimulation, thyroxine, AVP, ACTH, α-melanocyte-

stimulating hormone, glucagon, and sex hormones. Other stimuli for GH release include physical exercise, sleep, stress, hypovolemia, fasting hypoglycemia, decreased circulating fatty acids, and increased amino acid levels. Conditions that inhibit GH release include hyperglycemia, hypertriglyceridemia, somatostatin, beta-adrenergic stimulation, and cortisol.

The role of GH during stress is to promote protein synthesis while enhancing the mobilization of fat stores. Fat mobilization occurs by direct stimulation in conjunction with potentiation of adrenergic lipolytic effects on adipose stores. In the liver, hepatic ketogenesis also is promoted by GH. GH inhibits insulin release and decreases glucose oxidation, leading to elevated glucose levels. The protein synthesis properties of GH after injury are partially mediated by the secondary release of insulinlike growth factor-1 (IGF-1). This hormone, which circulates predominantly in bound form with several binding proteins, promotes amino acid incorporation and cellular proliferation and attenuates proteolysis in skeletal muscle and in the liver. IGFs, formerly referred to as *somatomedins*, are mediators of hepatic protein synthesis and glycogenesis. In adipose tissue, IGF increases glucose uptake and lipid synthesis. In skeletal muscle it increases glucose uptake and protein synthesis. IGF also has a role in skeletal growth by promoting the incorporation of sulfate and proteoglycans into cartilage. Interleukin-1α, tumor necrosis factor-alpha (TNF-α), and IL-6 can inhibit the effects of IGF-1.

There is a rise in circulating GH levels after injury, major surgery, and anesthesia. The associated decrease in protein synthesis and observed negative nitrogen balance is attributed to a reduction in IGF-1 levels. GH administration has improved the clinical course of pediatric burn patients. Its use in injured adult patients is unproved. The liver is the predominant source of IGF-1, and preexisting hepatic dysfunction may contribute to the negative nitrogen balance after injury. IGF-binding proteins also are produced within the liver and are necessary for effective binding of IGF to the cell. IGF has the potential for attenuating the catabolic effects after surgical insults.

Leukocytes express high-affinity surface receptors for GH. GH and IGF-1 are immunostimulatory and promote tissue proliferation. Macrophages also respond to GH with a modest respiratory burst. GH-deficient human beings do not demonstrate any significant immunologic abnormalities. Normal subjects given intravenous GH demonstrate no significant immunologic changes except for neutrophilia.

Gonadotrophins and Sex Hormones Luteinizing hormone–releasing hormone (LHRH) or gonadotropin-releasing hormone

(GnRH) is released from the hypothalamus and stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the anterior pituitary. The most relevant clinical correlation is seen after injury, stress, or severe illness, when LH and FSH release is suppressed. The reduction in LH and FSH consequently reduces estrogen and androgen secretion. This is attributed to the inhibitory activities of CRH on LH and FSH release and accounts for the menstrual irregularity and decreased libido reported after surgical stress and other injuries.

Estrogens inhibit cell-mediated immunity, natural killer cell activity, and neutrophil function but are stimulatory for antibody-mediated immunity. Conditions associated with high estrogen levels appear to predispose the patient to increased infectious complications. Androgens appear to be predominantly immunosuppressive. Castration is associated with enhanced immune function that can be reversed by exogenous androgens.

Prolactin The hypothalamus suppresses prolactin secretion from the anterior pituitary by the activities of LHRH/GnRH and dopamine. Stimulants for prolactin release are CRH, TRH, GHRH, serotonin, and vasoactive intestinal polypeptide (VIP). Elevated prolactin levels after injury have been reported in adults, whereas reduced levels are noted in children. The hyperprolactinemia also may account for the amenorrhea frequently seen in women after injury or major operations. Like growth hormone, prolactin has immunostimulatory properties. There is increasing evidence that prolactin also is synthesized and secreted by T lymphocytes and may function in an autocrine or paracrine fashion.

Endogenous Opioids Elevated endogenous opioids are measurable after major operations or insults to the patient. The β-endorphins have a role in attenuating pain perception, and they are capable of inducing hypotension through a serotonin-mediated pathway. Conversely, the enkephalins produce hypertension. In the gastrointestinal (GI) tract, the activation of opioid receptors reduces peristaltic activity and suppresses fluid secretion. The role of endogenous opioids in glucose metabolism is complex. While β-endorphins and morphine induce hyperglycemia, they also increase insulin and glucagon release by the pancreas. Studies demonstrating the presence of opioid receptors in the adrenal medulla also suggest a role in regulating catecholamine release.

Certain immune cells also release endorphins that share an antinociceptive role in modulating the response of local sensory neurons to noxious stimuli. Endorphins also influence the immune system by increasing natural killer cell cytotoxicity and T-cell blas-

togenesis. IL-1 activates the release of POMC from the pituitary gland.

Hormones Under Posterior Pituitary Regulation

Arginine Vasopressin Vasopressin or arginine vasopressin (AVP) (or antidiuretic hormone, ADH) is synthesized in the anterior hypothalamus and transported by axoplasmic flow to the posterior pituitary for storage. The major stimulus for AVP release is elevated plasma osmolality, which is detected by sodium-sensitive hypothalamic osmoreceptors. There is evidence of extracerebral osmoreceptors for AVP release in the liver or the portal circulation. AVP release is enhanced by beta-adrenergic agonists, angiotensin II stimulation, opioids, anesthetic agents, pain, and elevated glucose concentrations. Changes in effective circulating volume of as little as 10 percent can be sensed by baroreceptors, left atrial stretch receptors, and chemoreceptors, leading to AVP release. Release is inhibited by alpha-adrenergic agonists and atrial natriuretic peptide (ANP).

In the kidney, AVP promotes reabsorption of water from the distal tubules and collecting ducts. Peripherally, AVP mediates vasoconstriction. This effect in the splanchnic circulation may cause the trauma-induced ischemia-reperfusion phenomenon that precedes gut barrier impairment. AVP, on a molar basis, is more potent than glucagon in stimulating hepatic glycogenolysis and gluconeogenesis. The resulting hyperglycemia increases the osmotic effect that contributes to the restoration of effective circulating volume. Elevated AVP secretion is another characteristic of trauma, hemorrhage, open-heart surgery, and other major operations. This elevated level typically persists for 1 week after the insult.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) refers the excessive vasopressin release that is manifested by low urine output, highly concentrated urine, and dilutional hyponatremia. This diagnosis can be made only if the patient is euvolemic. Once normal volume is established, a plasma osmolality below 275 mOsm/kg H_2O and a urine osmolality above 100 mOsm/kg H_2O are indicative of SIADH. SIADH is commonly seen in patients with head trauma and burns.

In the absence of AVP, central diabetes insipidus occurs, and there is voluminous output of dilute urine. Frequently seen in comatose patients, the polyuria in untreated diabetes insipidus can precipitate a state of hypernatremia and hypovolemic shock. Attempts at reversal should include free water and exogenous vasopressin (desmopressin).

Oxytocin Oxytocin and AVP are the only known hormones secreted by the posterior pituitary. They share structural similarities, but the role of oxytocin in the injury response is unknown.

Hormones of the Autonomic System

Catecholamines Catecholamines exert significant influence on the physiologic response to stress and injury. The hypermetabolic state observed after severe injury has been attributed to activation of the adrenergic system. Both the major catecholamines, norepinephrine and epinephrine, are increased in plasma after injury, with average elevations of three to four times above baseline immediately after injury, reaching their peak in 24–48 h before returning to baseline levels. The patterns of norepinephrine and epinephrine appearance parallel each other after injury. Most of the norepinephrine in plasma results from synaptic leakage during sympathetic nervous system activity, whereas virtually all plasma epinephrine derives from the secretions of chromaffin cells of the adrenal medulla.

Catecholamines exert metabolic, hormonal, and hemodynamic influences on diverse cell populations. In the liver, epinephrine promotes glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. It causes decreased insulin secretion but increased glucagon secretion. Peripherally, epinephrine increases lipolysis in adipose tissues and inhibits insulin-facilitated glucose uptake by skeletal muscle. These collectively promote the often evident stress-induced hyperglycemia, not unlike the effects of cortisol on blood glucose. Catecholamines also increase the secretion of thyroid and parathyroid hormones, T_4 and T_3, and renin but inhibit the release of aldosterone.

Catecholamines exert discernible influences on immune function; e.g., epinephrine occupation of beta receptors on leukocytes increases intracellular cAMP. This ultimately decreases immune responsiveness in lymphocytes. Like cortisol, epinephrine enhances leukocyte demargination with resulting neutrophilia and lymphocytosis. Immunologic tissue such as the spleen, thymus, and lymph nodes possess extensive adrenergic innervation. Chemical sympathectomy of peripheral nerves has been demonstrated to augment antibody response after immunization with a specific antigen. Normal volunteers infused with epinephrine exhibited depressed mitogen-induced T lymphocyte proliferation.

Aldosterone The mineralocorticoid aldosterone is synthesized, stored, and released in the adrenal zona glomerulosa. Its release may be induced by angiotensin II, hyperkalemia, and the pituitary hormone known as *aldosterone-stimulating factor* (ASF), but ACTH

is the most potent stimulus for aldosterone release in the injured patient.

The major function of aldosterone is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. While the major effect is exerted in the kidneys, this hormone also is active in the intestines, salivary glands, sweat glands, vascular endothelium, and brain. In the early distal convoluted tubule, aldosterone increases sodium and chloride reabsorption and excretion of hydrogen ions. In the late distal convoluted tubule, further sodium reabsorption takes place while potassium ions are excreted. Vasopressin also acts in concert with aldosterone to increase osmotic water flux into the tubules.

Patients with aldosterone deficiency develop hypotension and hyperkalemia, whereas patients with aldosterone excess develop edema, hypertension, hypokalemia, and metabolic alkalosis. After injury, ACTH stimulates a brief burst of aldosterone release. Angiotensin II induces a protracted aldosterone release that persists well after ACTH returns to baseline. As with cortisol, normal aldosterone release also is influenced by the circadian cycle, although this effect is lost in the injured patient.

Renin-Angiotensin Renin is synthesized and stored primarily within the renal juxtaglomerular apparatus near the afferent arteriole. The juxtaglomerular apparatus comprises the juxtaglomerular neurogenic receptor, the juxtaglomerular cell, and the macula densa. Renin initially exists in an inactive form as prorenin. The activation of renin and its release are mediated by ACTH, AVP, glucagon, prostaglandins, potassium, magnesium, and calcium. The juxtaglomerular cells are baroreceptors that respond to a decrease in blood pressure by increasing renin secretion. The macula densa detects changes in chloride concentration in the renal tubules.

Angiotensinogen is a protein primarily synthesized by the liver but also identified in the kidney. Renin catalyzes the conversion of angiotensinogen to angiotensin I within the kidney. Angiotensin I remains physiologically inactive until it is converted in the pulmonary circulation to angiotensin II by angiotensin-converting enzyme present on endothelial surfaces.

Angiotensin II is a potent vasoconstrictor that also stimulates aldosterone and vasopressin synthesis. It also is capable of regulating thirst. Angiotensin II stimulates heart rate and myocardial contractility. It also potentiates the release of epinephrine by the adrenal medulla, increases CRH release, and activates the sympathetic nervous system. It can induce glycogenolysis and gluconeogenesis. The renin-angiotensin system participates in the response to injury by maintaining volume homeostasis.

Insulin Insulin is derived from pancreatic beta islet cells and released on stimulation by certain substrates, autonomic neural input, and other hormones. In normal metabolism, glucose is the major stimulant of insulin secretion. Other substrate stimulants include amino acids, free fatty acids, and ketone bodies. Hormonal and neural influences during stress alter this response. Epinephrine and sympathetic stimulation inhibit insulin release. Peripherally, cortisol, estrogen, and progesterone interfere with glucose uptake. The net result of impaired insulin production and function after injury is stress-induced hyperglycemia, which is in keeping with the general catabolic state.

Insulin exerts a global anabolic effect; it promotes hepatic glycogenesis and glycolysis, glucose transport into cells, adipose tissue lipogenesis, and protein synthesis. In the injured patient, a biphasic pattern of insulin release is observed. The first phase occurs within a few hours after injury and is manifested as a relative suppression of insulin release, reflecting the influence of catecholamines and sympathetic stimulation. The later phase is characterized by a return to normal or excessive insulin production but with persistent hyperglycemia, demonstrating a peripheral resistance to insulin.

Activated lymphocytes express receptors for insulin. Insulin enhances T lymphocyte proliferation and cytotoxicity. Institution of insulin therapy to newly diagnosed diabetics is associated with increased B and T lymphocyte populations.

Glucagon Glucagon is a product of pancreatic alpha islet cells. As with insulin, the release of glucagon also is mediated by its substrates, autonomic neural input, and other hormones. Whereas insulin is an anabolic hormone, glucagon serves more of a catabolic role. The primary stimulants of glucagon secretion are plasma glucose concentrations and exercise. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, which under basal conditions account for approximately 75 percent of the glucose produced by the liver. The release of glucagon after injury is initially decreased but returns to normal 12 h later. By 24 h, glucagon levels are supranormal and can persist for up to 3 days.

IMMUNE RESPONSE TO INJURY

While the classic neuroendocrine response to injury has been extensively investigated, many characteristics of the inflammatory response associated with injury remain unexplained. Even after the normalization of macroendocrine hormone function after the pri-

mary injury, the persistence of systemic inflammation, the progression of organ dysfunction, and even late mortality indicate the presence of other potent mediators influencing the injury response. These mediators usually are small proteins or lipids that are synthesized and secreted by immunocytes. These molecules, collectively referred to as *cytokines*, are indispensable in tissue healing and in the immune response generated against microbial invasions. As mounting evidence suggests, the activities of these cytokine mediators are integrally related to classic hormone function and metabolic responses to injury.

Cytokine-Mediated Response

Patients with injuries or infections exhibit hemodynamic, metabolic, and immune responses partially orchestrated by endogenous cytokines. Unlike classic hormonal mediators such as catecholamines and glucocorticoids, which are produced by specialized tissues and exert their influence predominantly by endocrine routes, cytokines are produced by diverse cell types at the site of injury and by systemic immune cells (Table 1-4). Cytokine activity is exerted primarily locally via cell-to-cell interaction (paracrine).

Cytokines are small polypeptides or glycoproteins that exert their influence at very low concentrations. Most are less than 30 kD in weight, but in their biologically active form, some of these cytokines function as oligomers (e.g., trimeric tumor necrosis factor-alpha) with higher molecular weights. Most cytokines also differ from classic hormones in that they are not stored as preformed molecules. Their relatively rapid appearance after injury reflects active gene transcription and translation by the injured or stimulated cell.

Cytokines exert their influence by binding to specific cell receptors and activating intracellular signaling pathways leading to modulation of gene transcription. By this mechanism, cytokines influence immune cell production, differentiation, proliferation, and survival. These mediators also regulate the production and actions of other cytokines, which may either potentiate (proinflammatory) or attenuate (anti-inflammatory) the inflammatory response. The capacity of cytokines to activate diverse cell types and to incite equally diverse responses underscores the pleiotropism of these inflammatory mediators. There is also a marked degree of overlapping activity among different cytokines.

Cytokines are effector molecules that direct the inflammatory response to infections (bacterial, viral, and fungal) and injury, and they actively promote wound healing. These responses are manifested by fever, leukocytosis, and alterations in respiratory and heart rates. Exaggerated, acute production of proinflammatory

TABLE 1-4
CATALOGUE OF RECOGNIZED CYTOKINES RELEASED IN RESPONSE TO INJURY

TNF-α
↑PMN release from bone marrow
↑PMN activation, migration, degranulation, and superoxide production
↑PMN cytotoxicity against mycotic infections
↑Differentiation (activation) of macrophage
↑Macrophage antiviral/antiparasite activities
↑Acute-phase reactant (APR) production through IL-6 induction
↑Wound healing/remodeling
  ↑Endothelial procoagulant activity and leukocyte adhesion
  ↑Vascular endothelial permeability
  ↑Neovascularization in wounds
  ↑Collagen synthesis/fibroblast proliferation
↑Osteoclast activity in bond healing

IL-1
↑T lymphocyte activation and proliferation
↑TNF, IL-4, and IL-6 production
↑PMN release from bone marrow and functional restoration
↑PMN migration to injured site
↑Differentiation (activation) of macrophage
↑Granulocyte/macrophage colony–stimulating factor (GM-CSF)
↓Pain perception
  ↑β-Endorphin release
  ↑Brain opiatelike receptors
↑Acute-phase reactant (APR) production through IL-6 induction
↑Wound healing/remodeling
↑Osteoclast activity in bone healing
↑Body temperature (fever)

IL-2
↑Overall immunocompetence and gut barrier immunity
↑Lymphokine-activated killers (LAK) production
↑T lymphocyte proliferation
↑Reticuloendothelial system (RES) activity

IL-4
↑Macrophage MHC class II expression and adhesion molecules
↓Macrophage production of IL-1, TNF, IL-6, IL-8, and superoxides

TABLE 1-4
CATALOGUE OF RECOGNIZED CYTOKINES RELEASED IN RESPONSE TO INJURY (CONTINUED)

↑Macrophage programmed cell death
↑Macrophage susceptibility to glucocorticoid effects
↑B lymphocyte proliferation
↑Ig class switching to IgG_4 and IgE

IL-6
↑Fibroblast antiviral activity
↑B lymphocyte differentiation and immunoglobulin production
↑Acute-phase reactant (APR) and prostaglandin production

IL-8
↑Chemotaxis of PMNs, lymphocytes, macrophages to sites of injury
↑PMN degranulation
↑Adhesion molecules CD11/CD18 for PMN-endothelial binding

IL-10
↓Cytokine synthesis by lymphocytes and macrophages
Modulates inflammatory activities of TNF-α, IL-1, IL-6, IL-8, IFN-γ, PGE_2
↑Release of soluble TNFRs
↓Macrophage production of reactive oxygen metabolites
↑B cell immunoglobulin synthesis

IL-12
Stimulates $CD4^+$ and $CD8^+$ T cells
↑Lymphocyte and NK cell proliferation
↓B-lymphocyte immunoglobulin production
↑Hematopoiesis
↑IL-2 and IFN-γ production

IL-13
↑Macrophage MHC class I and II expression
↓Antibody-dependent cytotoxicity
↓Production of IL-1, IL-6, IL-8, IL-10, IL-12, nitric oxide
↑IL-1ra production
↑B cell production of immunoglobulins
No effect on T cells

IFN-γ
↑Macrophage and PMN activation against invading organisms (including viral)

TABLE 1-4
CATALOGUE OF RECOGNIZED CYTOKINES RELEASED IN RESPONSE TO INJURY (CONTINUED)

↑MHC class I and II surface antigen expression
↑Macrophage oxidative and cytotoxic activity
↑Overall lymphocyte proliferation
↑B lymphocyte immunoglobulin production
↑IL-1 and TNF-α activity

GM-CSF
↑Myeloproliferation (macrophages, PMNs, eosinophils)
Partial stimulation of megakaryocyte progenitors
↑Chemotaxis of PMNs and macrophages
↓Apoptosis
↑Cytokine production by macrophages

cytokines is responsible for the hemodynamic instability characteristic of septic shock. Chronic and excessive production of these cytokines is partly responsible for the metabolic derangements of the injured patients, such as debilitating muscle wasting and cachexia. The presence of anti-inflammatory cytokines may serve to attenuate some of these exaggerated responses. The excessive release of anti-inflammatory cytokines, however, may render the patient immunocompromised and increase susceptibility to infections.

Understanding of the pathophysiology of inflammatory cytokine mediators has been derived largely from patients with endotoxemia or sepsis. Inflammatory mediator responses to infections and traumatic injury are not dissimilar, particularly in the temporal sequence of cytokine expression. The cytokine response evidenced by fever, leukocytosis, hyperventilation, and tachycardia commonly seen in injury is referred to as *systemic inflammatory response syndrome* (SIRS), but it is not necessarily the result of an identifiable infectious process. Central to the insult suffered by the host and the subsequent inflammatory response is the activity of the host's immunocyte population, circulating and tissue-fixed.

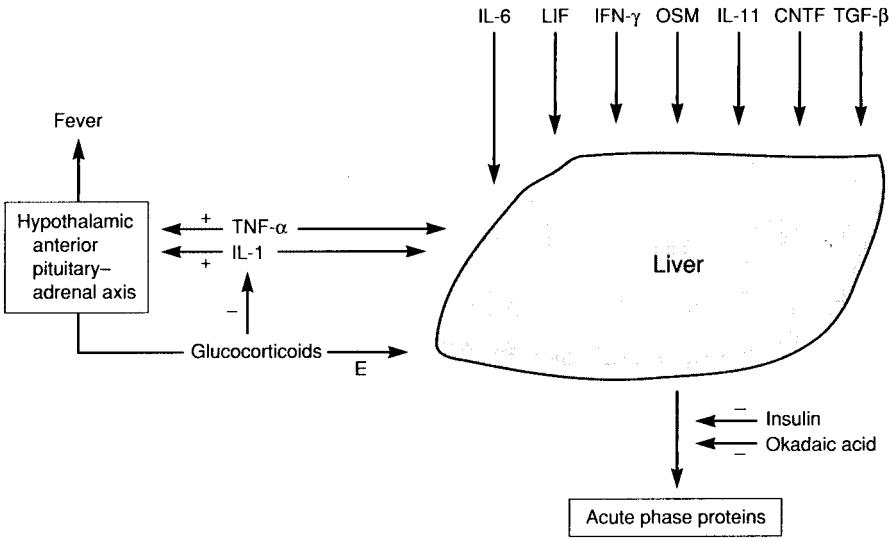
The cytokine cascade activated in response to injury consists of a complex network with diverse effects on all aspects of physiologic regulatory mechanisms. Cytokines are pivotal determinants of the host response after injury, and a proper perspective on their immunobiologic sequelae can have important applications in the comprehensive care of the surgical patient. The number of cytokines

identified has expanded to nearly 30, but their functions and elicited responses, particularly in injury, are incompletely understood largely because of the pleiotropic, redundant, and mutual interactions among these mediators. The cytokines described here represent a limited list of mediators related to injury and the inflammatory response.

Tumor Necrosis Factor-alpha The inflammatory response to severe cross-sectional tissue injury or infectious agents evokes a complex cascade of proinflammatory cytokines. Among these, tumor necrosis factor-alpha (TNF-α) is the earliest and one of the most potent mediators of the subsequent host response. The sources of TNF-α synthesis include monocytes/macrophages and T cells, which are abundant in the peritoneum and splanchnic tissues. Kupffer cells represent the single largest concentrated population of macrophages in the human body. Surgical or traumatic injuries to the viscera may have profound influences on the generation of inflammatory mediators and homeostatic responses such as acute phase protein production (Fig. 1-3).

The release of TNF-α in response to acute injury is rapid and short-lived. Experiments simulating an acute inflammatory response by means of endotoxin challenge in human subjects have demonstrated a monophasic tumor necrosis factor (TNF) appearance curve, peaking at approximately 90 min and followed by a return to undetectable levels within 4 h. Even with a half-life of 15–18 min, the brief appearance of TNF can induce marked metabolic and hemodynamic changes and activate cytokines distally in the cascade. The abbreviated appearance of TNF reflects the presence of effective endogenous modulators that serve to prevent unregulated TNF-α activity. Several natural mechanisms antagonize TNF production or activity. Endogenous inhibitors in the form of cleaved extracellular domains of the transmembrane TNF receptors (soluble TNF receptors, sTNFRs) are readily detectable in the circulation. These receptors may serve a protective role by competitively sequestering excess circulating TNF but are probably only capable of doing so against low levels of TNF activity and for brief periods.

TNF-α also is a major cytokine related to muscle catabolism and cachexia during stress. Amino acids are mobilized from skeletal muscles and shunted toward the hepatic circulation as fuel substrates. Studies have demonstrated that TNF-α–induced muscle catabolism occurs through a ubiquitin-proteasome proteolytic pathway with increased expression of the ubiquitin gene. Other associated functions of TNF-α include activation of coagulation and promotion of the release of prostaglandin E_2 (PGE_2), platelet-activating factor (PAF), glucocorticoids, and eicosanoids.


IL-6
LIF
IFN-γ
OSM
IL-11
CNTF
TGF-β
Fever
Hypothalamic anterior pituitary–adrenal axis
+
TNF-α
+
IL-1
–
Glucocorticoids
E
Liver
–
Insulin
–
Okadaic acid
Acute phase proteins

Complement proteins

C2, C3, C4, C5, C9
Factor B
C1 inhibitor
C4 binding protein

Coagulation proteins

Fibrinogen
von Willebrand factor

Proteinase inhibitors

α1-antitrypsin
α1-antichymotrypsin
α2-antiplasmin
Heparin cofactor II
Plasminogen activator inhibitor I

Metal-binding proteins

Haptoglobin
Hemopexin
Ceruloplasmin
Manganese superoxide dismutase

Other proteins

α_1-acid glycoprotein
Heme oxygenase
Mannose-binding protein
Leukocyte protein I
Lipoprotein (a)
Lipopolysaccharide-binding protein

Negative APRs

Albumin
Pre-albumin
Transferrin
ApoAI
ApoAII
α_2-HS glycoprotein
Inter-α-trypsin inhibitor
Histidine-rich glycoprotein

Major APRs

Serum amyloid A
C-reactive protein
Serum amyloid P component

FIGURE 1-3 Inflammatory mediators that modulate hepatic acute phase reactants synthesis in humans. E = enhancement of activity; OSM = oncostatin M; CNTF = ciliary neurotrophic factor; ApoAI = apolipoprotein AI. (From: *Steel DM, Whitehead AS: The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunol Today 15:81, 1994, with permission.*)

Interleukin-1 TNF-α also induces the biosynthesis and release of IL-1 from macrophages and endothelial cells. There are two known proinflammatory species of IL-1, IL-1α and IL-1β. IL-1α is predominantly cell membrane–associated and exerts its influence via cellular contacts. The more detectable form released in the circulation is IL-1β, which is produced in greater quantities than IL-1α and is capable of inducing the characteristic systemic derangements after injury.

The potency and effects of IL-1 reflect those of TNF-α, eliciting similar physiologic and metabolic alterations. At high doses of IL-1 and TNF-α, these cytokines independently initiate a state of hemodynamic decompensation. At low doses, they can produce the same response only if administered simultaneously. These observations emphasize the synergism of TNF-α and IL-1 in eliciting proinflammatory responses. The half-life of IL-1 is approximately 6 min, which, along with its primary role as a local inflammatory mediator, makes its detectability in acute injury or illness even less likely than that of TNF-α.

Among its effects, IL-1 induces the classic febrile response to injury by stimulating local prostaglandin activity in the anterior hypothalamus. Associated with the hypothalamic activity is the induction of anorexia by an IL-1 effect on the satiety center. This cytokine also augments T-cell proliferation by enhancing the production of IL-2 and also may influence skeletal muscle proteolysis. Attenuated pain perception after surgery can be mediated by IL-1 by promoting the release of β-endorphins from the pituitary gland and increasing the number of central opioid-like receptors. Like TNF, IL-1 is a potent stimulant for ACTH and glucocorticoid release via its actions on the hypothalamus and pituitary gland. A nonagonist IL-1 species, known as *IL-1 receptor antagonist* (IL-1ra), also is released during injury. This molecule effectively competes for binding to IL-1 receptors yet exacts no overt signal transduction. IL-1ra, which is often detectable during inflammation or injury, serves as a potent regulator of IL-1 activity. Distal cytokine mediators, released as part of the inflammatory cascade initiated by TNF-α and IL-1, include IL-2, IL-4, IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF), and interferon-γ (IFN-γ).

Interleukin-2 Although necessary as an inflammatory mediator in promoting T lymphocyte proliferation, immunoglobulin production, and gut barrier integrity, IL-2 has not been readily detectable in the circulation during acute injury. Similar to IL-1, its short half-life of less than 10 min adds to the difficulty in detecting it after injury. IL-2 secretion by lymphocytes is impaired after acute injury

and several disease states, notably cancer and acquired immune-deficiency syndrome (AIDS). Perioperative blood transfusions also are associated with reduced IL-2 production. Attenuated IL-2 expression contributes to the transient immunocompromised state of the surgical patient. A low point in gut barrier IL-2 activity resulting from injuries can predispose the patient to enteric organism activation of the inflammatory cytokine cascade. The combined diminution of lymphocyte survival and IL-2 activity may contribute to the immunocompromised phenotype of the injured patient.

Interleukin-4 IL-4 is a glycoprotein molecule, produced by activated T cells, with diverse biologic effects on hemopoietic cells, including induction of B lymphocyte proliferation. As a potent anti-inflammatory cytokine, IL-4 downregulates several functions associated with activated human macrophages, namely, the effects of IL-1β, TNF-α, IL-6, IL-8, and superoxide production. These anti-inflammatory effects of IL-4 are not seen in resting monocytes. The importance of this cytokine is its capacity to downregulate the response of inflammatory macrophages exposed to stimuli such as bacterial endotoxin or proinflammatory cytokines. IL-4 can induce programmed cell death in inflammatory macrophages. IL-4 also appears to increase macrophage susceptibility to the anti-inflammatory effects of glucocorticoids. IL-13 may share several properties with IL-4.

Interleukin-6 Because of the elevated blood levels of IL-6 often observed during acute injury or stress, it is used frequently as an indicator of the systemic inflammatory response and a predictor of preoperative morbidity. TNF-α and IL-1 are major inducers of IL-6. IL-6 can be produced by virtually all cell types, including the intestines. After injury, IL-6 levels in the circulation are detectable by 60 min, peak at between 4 and 6 h, and can persist for as long as 10 days. The relatively long half-life partially explains its ease of detectability. IL-6 levels appear to be proportional to the extent of tissue injury during an operation rather than the duration of the surgical procedure itself.

IL-6 appears to play a complex role in mediating proinflammatory and anti-inflammatory activities. IL-1 and IL-6 are important mediators of the hepatic acute-phase protein response during injury and appear to enhance C-reactive protein, fibrinogen, haptoglobin, amyloid A, α_1-antitrypsin, and complement production (see Fig. 1-3). IL-6 not only induces PMN activation during injury and inflammation but also may delay the phagocytic disposal of senescent or dysfunctional PMNs during injury. The persistence of inflammatory PMNs after injury might explain the injurious effects on distant tissues, such as the pulmonary or renal system.

IL-6 mediates the anti-inflammatory pathway during injury through different mechanisms. It is capable of attenuating TNF and IL-1 activity while promoting the release of sTNFRs and IL-1ra. Prolonged and persistent expression of IL-6 is associated with immunosuppression and postoperative infectious morbidity.

Interleukin-8 The appearance of IL-8 activity is temporally associated with IL-6 after injury and has been proposed as an additional biomarker for the risk of multiple organ failure. IL-8 does not produce the hemodynamic instability characteristic of TNF-α and IL-1 but rather serves as a PMN activator and potent chemoattractant. IL-8 may be a major contributor to organ injury, such as acute lung injury.

Interleukin-10 IL-10 acts primarily by modulating TNF-α activity. Its appearance in the circulation during endotoxemia closely follows the appearance TNF-α. Neutralization of IL-10 during endotoxemia increases monocyte TNF-α production and mortality, but restitution of IL-10 reduces TNF-α levels and its associated deleterious effects. In addition, IL-10 may be protective during injury-induced inflammation by promoting IL-1ra and sTNFR production. In animal experiments, the sustained systemic production of IL-10 during septic peritonitis modulates the systemic inflammatory response; mortality increases when IL-10 is blocked with an anti-IL-10 antibody. This immunomodulatory effect also may abrogate the proinflammatory response necessary for local clearance of invading organisms.

Interleukin-12 IL-12 can promote the differentiation of T-helper cells and the production of IFN-γ. Thus it is a pivotal molecule in cell-mediated immunity after injury or infection. In mice with fecal peritonitis, survival increases with IL-12 administration. IL-12 also is implicated in preventing programmed cell death (apoptosis) in certain T lymphocyte populations after their activation.

Interleukin-13 IL-13 is a pleiotropic cytokine that shares many of the properties of IL-4. IL-13 is produced during T-helper cell responses. IL-4 and IL-13 modulate macrophage function, but IL-13 has no identifiable effect on T lymphocytes and only has influence on subpopulations of B lymphocytes. IL-13 can inhibit nitric oxide production and the expression of proinflammatory cytokines, and it can enhance the production of IL-1ra. The net effect of IL-13, along with IL-4 and IL-10, is anti-inflammatory.

Interferon-γ Much of IL-12 biology is mediated through the production and activities of IFN-γ. Human T-helper (TH) cells activated by the bacterial antigens IL-2 or IL-12 readily produce

IFN-γ. Conversely, IFN-γ can induce the production of IL-2 and IL-12 by T-helper cells. With its release from activated T cells, IFN-γ is detectable in vivo by 6 h and has a half-life of approximately 30 min. IFN-γ levels peak at 48–72 h and may persist for 7–8 days. Injured tissues, such as operative wounds, also demonstrate the presence of IFN-γ production 5–7 days after injury. IFN-γ has important roles in activating circulating and tissue macrophages. Alveolar macrophage activation mediated by IFN-γ may induce acute lung inflammation after major surgery or trauma.

Granulocyte/Macrophage Colony-Stimulating Factor Granulocyte/macrophage colony-stimulating factor (GM-CSF) production is induced by IL-2 and endotoxin. In vitro studies have demonstrated a prominent role for GM-CSF in delaying apoptosis of macrophages and PMNs. This growth factor is effective in promoting the maturation and recruitment of functional leukocytes necessary for normal inflammatory cytokine response and potentially in wound healing. The mechanisms may be the result of the suppression of IL-10 production. Results of perioperative GM-CSF administration in patients undergoing major oncologic procedures have demonstrated augmentation of neutrophil numbers and function.

Programmed Cell Death

During systemic inflammation, the response mounted by the host to injury and infection manifests the collective activities of circulating and tissue-fixed immunocytes and endothelial cell populations. In the normal host, programmed cell death (apoptosis) is the principal mechanism by which senescent or dysfunctional cells, including macrophages and PMNs, are systematically disposed of without activating other immunocytes or the release of proinflammatory contents. The signals inducing normal apoptosis differ from cell to cell but most likely converge at a common final pathway. These signals arise from the extracellular environment and may include hormonal and paracrine activities.

The inflammatory milieu disrupts the normal apoptotic machinery in dysfunctional or aging cells, consequently delaying the disposal of activated macrophages and PMNs. Several proinflammatory cytokines delay the normal temporal sequence of macrophage and PMN apoptosis in vitro. These include TNF, IL-1, IL-3, IL-6, GM-CSF, granulocyte colony-stimulating factor (G-CSF), and IFN-γ. By contrast, IL-4 and IL-10 accelerate apoptosis in activated monocytes. The prolonged survival of inflammatory immunocytes may perpetuate and augment the inflammatory response to injury and infection, precipitating multiple organ failure and eventual death in severely injured and critically ill patients.

Hormones and Cytokine Interactions

Cortisol/Glucocorticoids Hypercortisolemia differentially influences leukocyte counts and cytokine expression in a temporal fashion. Glucocorticoid administration immediately before or concomitantly with endotoxin infusion in healthy human beings is able to attenuate the symptoms (e.g., fever, tachycardia), catecholamine response, and acute-phase response. It increases IL-10 release, however, which release may contribute to the acute anti-inflammatory effect of glucocorticoids.

Glucocorticoids also can influence the regulation of T-lymphocyte proliferation or programmed cell death. Glucocorticoid-induced apoptosis of T lymphocytes requires elevations of intracellular cAMP. IL-2, IL-4, and IL-10 protects these T lymphocytes from glucocorticoid-induced apoptosis. IL-1, TNF, and IL-6 can activate the hypothalamus-pituitary-adrenal axis and induce the release of CRH and ACTH, leading to increased circulatory glucocorticoid levels. Glucocorticoids, in turn, inhibit endotoxin-induced production of TNF at the level of mRNA translation. Dexamethasone also inhibits neutrophil apoptosis and prolongs their functional responsiveness. This can be detrimental to the patient because the delay in clearance from tissues may perpetuate the injurious effects of activated neutrophils.

Catecholamines Catecholamines inhibit endotoxin-induced macrophage production of TNF-α in vitro. In normal human subjects, short-term preexposure to epinephrine effectively inhibits endotoxin-induced TNF production. Concurrently, short-term preexposure to epinephrine increases the production of the anti-inflammatory cytokine IL-10. Endogenous or exogenous epinephrine may serve to limit excessive proinflammatory effects of the cytokine network during the early phase of systemic infection. Thus the use of catecholamines in treatment may have the potential for influencing immune cell function.

OTHER MEDIATORS OF INJURY RESPONSE

Endothelial Cell Mediators

Endothelial Cell Function In addition to modulating coagulation and vascular tone, mediators elaborated by the vascular endothelium participate in the inflammatory process. In a paracrine fashion, TNF-α, IL-1, endotoxin, thrombin, histamine, and IFN-γ are capable of stimulating or activating the endothelial cell during local tissue injury. In response, the endothelial cell releases several media-

tors, including IL-1, platelet-activating factor (PAF), prostaglandins (PGI_2 and PGE_2), GM-CSF, growth factors, endothelin, nitric oxide, and small amounts of thromboxane A_2 (TxA_2). Activated endothelial cells also release collagenases capable of digesting their own basement membranes. This permits neovascularization and vascular remodeling at sites of injury in order to facilitate adequate oxygen supply and immunocyte transport. Angiotensin-converting enzymes (ACE) convert angiotensin I to angiotensin II on the surface of endothelial cells, making it a potent regulator of vascular tone. Endothelial cell mediators can modulate cardiovascular and renal function and influence the hypothalamus-pituitary-adrenal axis.

The activated endothelial cell upregulates its expression of leukocyte adhesion receptor molecules such as E-selectin (formerly referred to as *endothelial-leukocyte adhesion molecule-1*, ELAM-1), P-selectin, and intercellular adhesion molecules (ICAM-1, ICAM-2). The adhesion of leukocytes and platelets to the endothelial surface occurs early in the endothelial-derived inflammatory process. The expression of E-selectin on endothelial cell surfaces is maximal at 4–6 h. Recovery from the inflammatory process is characterized by internalization of these adhesion molecules within the endothelial cell.

Neutrophil adhesion to the endothelium during injury has important clinical implications for increasing vascular permeability and passage of leukocytes into injured tissues. In the nonstressed state, the endothelium possesses little capacity to recognize and bind circulating leukocytes. Local injuries and inflammatory mediator stimulation promote the margination of circulating PMNs to the endothelial surfaces. These marginated PMNs are deformable and travel along the endothelial surfaces at markedly reduced velocities, which is referred to as *rolling.* Rolling represents a process of transient attachment and detachment between receptors of PMNs and the endothelium. The subsequent development of stronger receptor adhesions, PMN activation by the endothelial mediators, and release of PMN proteinases at endothelial junctions precedes the migration of PMNs out of the vascular compartment, a process referred to as *diapedesis.* Although necessary for local tissue inflammation and eradication of microbes, activated PMNs and the subsequent release of inflammatory mediators and reactive oxygen metabolites are implicated in capillary leakage, acute lung injury, and postischemic injury. The ability to attract leukocytes and produce inflammatory mediators makes endothelial cells important participants in the immune response to injury.

Endothelium-Derived Nitric Oxide Endothelium-derived nitric oxide or relaxing factor (EDNO or EDRF) can be released in

response to acetylcholine stimulation, hypoxia, endotoxin, cellular injury, or mechanical shear stress from circulating blood. Its vasodilatory activity has been demonstrated in large (conduit) arteries and in resistance vessels of most mammalian species, including human beings. Induction of vascular smooth muscle relaxation by EDNO increases cytosolic cyclic guanosine monophosphate (cGMP) within the myocytes. cGMP is present in platelets and can be activated by EDNO. Increased cGMP in platelets is associated with reduced adhesion and aggregation. EDNO induces vasodilation and platelet deactivation. EDNO is a readily diffusible substance with a half-life of a few seconds, and it decomposes spontaneously into nitrate and nitrite. EDNO is formed from oxidation of L-arginine, a process catalyzed by nitric oxide synthase (NO synthase). In addition to the endothelium, this enzymatic activity also is present in PMNs, macrophages, renal cells, Kupffer cells, and cerebellar neurons. In normal vasculature, experiments blocking EDNO activity induce a state of vasoconstriction that is readily reversed with L-arginine administration. This demonstrates that the vasculature is in a constant state of vasodilation because of the continuous basal release of EDNO. Endogenous inhibitors of EDNO have been identified that are autoregulators of endothelial tone. Elevations of EDNO in septic shock and trauma are associated with low systemic vascular resistance.

Prostacyclin Prostacyclin (PGI_2) is an important endothelium-derived vasodilator synthesized in response to vascular shear stress and hypoxia. It has functions similar to those of EDNO. Prostacyclin is derived from arachidonic acid and causes relaxation and platelet deactivation by increasing cAMP. It has been used to reduce pulmonary hypertension, particularly in pediatric patients.

Endothelins Endothelins (ETs) are elaborated by vascular endothelial cells in response to injury, thrombin, IL-1, angiotensin II, arginine vasopressin, catecholamines, and anoxia. ET is a small peptide with potent vasoconstrictor properties. Among the peptides in this family, ET-1 is the most biologically active and potent vasoconstrictor known. It is estimated to be 10 times more potent than angiotensin II. ET receptors are linked to the formation of EDNO and PGI_2, which are negative feedback mechanisms, and the vasoconstrictor activity of ET can be reversed by the administration of acetylcholine, which stimulates EDNO production. Thus both EDNO and ET interact to maintain physiologic tone in vascular smooth muscles. Increased serum levels of ET are correlated with the severity of injury after major trauma, major surgical procedures, and in cardiogenic or septic shock.

Platelet-Activating Factor Another endothelium-derived product is PAF, a phospholipid constituent of cell membranes that can be induced by TNF, IL-1, AVP, and angiotensin II. This inflammatory mediator stimulates production of TxA_2, which is a potent vasoconstrictor. Experimentally, PAF can induce hypotension and increase vascular permeability, hemoconcentration, pulmonary hypertension, bronchoconstriction, primed PMN activity, eosinophil chemotaxis/degranulation, and thrombocytopenia. It induces a general leukocytopenia by way of margination. Administration of antagonists to PAF in experimental human endotoxemia partially attenuates myalgias and rigors, but they do not reverse hemodynamic derangements. PAF alters the shape of endothelial cells, causing them to contract and increase permeability sufficiently to permit the passage of macromolecules, such as albumin, across cell junctions. PAF is a chemotactant for leukocyte adherence to the vascular wall and facilitates migration out of the vascular compartment. The disparity between PAF-induced vascular permeability and PAF-induced vasoconstriction is most likely the result of differences in receptor types and affinity in different vascular segments. Other cells that secrete PAF include macrophages, PMNs, basophils, mast cells, and eosinophils.

Atrial Natriuretic Peptides Atrial natriuretic peptides (ANPs) are released by the central nervous system and by specialized endothelium found in atrial tissues in response to wall tension. ANPs are potent inhibitors of aldosterone secretion and prevent reabsorption of sodium. In rats, myocardial EDNO inhibits the release of ANP, while ET-1 stimulates it. The role of ANP in human response to injury is unknown.

Intracellular Mediators

Heat-Shock Proteins In addition to heat, hypoxia, trauma, heavy metals, and hemorrhage induce the production of intracellular heat-shock proteins (HSPs). These proteins are presumed to protect cells during stress states. HSPs function intracellularly in the assembly, disassembly, stability, and transport of proteins. The classic example of HSP activity is the intracellular transport of steroid molecules. Gene expression occurs in parallel with hormonal activities of the hypothalamus-pituitary-adrenal axis. This response may be ACTH-sensitive, and the production may decline with age. Although HSPs are important intracellular effectors, their relevance in the human response to injury can only be inferred from animal data.

Reactive Oxygen Metabolites Reactive oxygen metabolites (ROMs) are short-lived, highly reactive molecular oxygen species

with an unpaired outer orbit. They cause tissue injury by peroxidation of cell membrane fatty acids. ROMs are produced by complex processes that involve anaerobic glucose oxidation coupled with the reduction of oxygen to superoxide anion. Superoxide anion is a potent ROM. It is metabolized to form other reactive species, such as hydrogen peroxide and hydroxyl radical. Cells are not immune to damage by their own ROMs but are generally protected by oxygen scavengers that include glutathione and catalases. In ischemic tissues, the intracellular mechanisms for production of ROMs become fully activated but are nonfunctional because of a lack of oxygen supply. With restoration of blood flow and oxygen, large quantities of ROMs are produced that can induce reperfusion injury. In response to a stimulus, activated leukocytes are potent generators of reactive oxygen metabolites. ROMs also can induce apoptosis.

Other Inflammatory Mediators

Eicosanoids The eicosanoid class of mediators, which encompasses prostaglandins (PG), thromboxanes (Tx), and leukotrienes (LT), consists of oxidation derivatives of the membrane phospholipid arachidonic acid (eicosatetraenoic acid). The eicosanoids are secreted by virtually all nucleated cells except lymphocytes. The synthesis of arachidonic acid from phospholipids requires enzymatic activation of phospholipase A_2 (Fig. 1-4). There are two subsequent synthetic pathways. Products of the cyclooxygenase pathway include all the prostaglandins and thromboxanes. The lipoxygenase pathway generates the leukotrienes. Initial phospholipase A_2 activation can be achieved by compounds such as epinephrine, angiotensin II, bradykinin, histamine, and thrombin. The synthesis of prostaglandins and thromboxanes is inhibited by nonsteroidal anti-inflammatory drugs and salicylates, which are cyclooxygenase inhibitors. Eicosanoids are not stored in cells but are synthesized rapidly on stimulation by hypoxic and ischemic injury, direct tissue injury, endotoxin, norepinephrine, AVP, angiotensin II, bradykinin, serotonin, acetylcholine, and histamine.

The products of arachidonic acid metabolism are functionally cell/tissue specific. Vascular endothelium primarily synthesizes PGI_2, which causes vasodilation and platelet deactivation. Thromboxane synthetase converts platelet prostaglandins to TxA_2, a potent vasoconstrictor and platelet aggregator. Macrophages are capable of synthesizing cyclooxygenase and lipoxygenase products. Second messengers mediate much of eicosanoid activity.

Eicosanoids have diverse effects systemically on endocrine and immune function, neurotransmission, and vasomotor regulation (Table 1-5). Eicosanoids promote changes in vascular permeability,

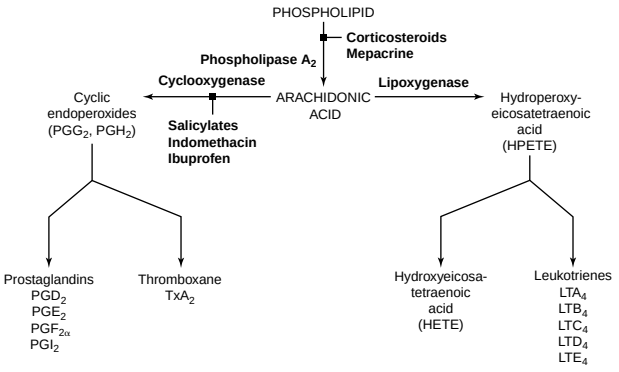


FIGURE 1-4 Arachidonic acid metabolism. Corticosteroids can block the conversion of phospholipids to arachidonic acid. Salicylates can inhibit prostaglandin synthesis. (From: *Robertson RP: Prostaglandins and other arachidonic acid metabolites, in Becker KL, et al (eds): Principles and Practice of Endocrinology and Metabolism, 2d ed. Philadelphia, JB Lippincott 1996, chap 170, with permission.*)

leukocyte migration, and vasodilation after injury. They can potentially contribute to acute lung injury, pancreatitis, and renal failure. Leukotrienes are produced by cells of the lung, connective tissue, smooth muscle, macrophages, and mast cells that mediate the reactions characteristic of anaphylaxis. Leukotrienes promote capillary leakage, leukocyte adherence, neutrophil activation, bronchoconstriction, and vasoconstriction.

Products of the cyclooxygenase pathway inhibit pancreatic beta cell release of insulin, whereas products of the lipoxygenase pathway promote beta cell activity. Hepatocytes also express specific receptors for PGE_2 that, when activated, inhibit gluconeogenesis. PGE_2 inhibits hormone-stimulated lipolysis. Small amounts of PGE_2 suppress proliferation of human T lymphocytes by mitogens, an effect mediated by downregulation of IL-2 production. Enhanced lymphocyte activation can be achieved with the administration of indomethacin, a PGE_2 inhibitor.

Kallikrein-Kinin System Bradykinins are potent vasodilators produced through kininogen degradation by the serine protease kallikrein. Kallikrein exists in blood and tissues in an inactive form and is activated by various chemical and physical factors, such as Hageman factor, trypsin, plasmin, factor XI, glass surfaces, kaolin,

TABLE 1-5
SYSTEMIC STIMULATORY AND INHIBITORY ACTIONS OF EICOSANOIDS

Organ/Function	Stimulator	Inhibitor
Pancreas		
Glucose-stimulated insulin secretion	12-HPETE	PGE_2
Glucagon secretion	PGD_2, PGE_2	
Liver		
Glucagon-stimulated glucose production	PGE_2	
Fat		
Hormone-stimulated lipolysis	PGE_2	
Bone		
Resportion	PGE_2, PGE-m, 6-K-PGE_1, $PGF_{1\alpha}$, PGI_2	
Pituitary		
Prolactin	PGE_1	
LH	PGE_1, PGE_2, 5-HETE	
TSH	PGA_1, PGB_1, PGE_1, $PGE_{1\alpha}$	
GH	PGE_1	

Parathyroid		
PTH	PGE_2	$PGF_{2\alpha}$
Pulmonary		
Bronchoconstriction	$PGF_{2\alpha}$, TXA_2, LTC_4, LTD_4, LTE_4	PGE_2
Renal		
Stimulate renin secretion	PGE_2, PGI_2	
Gastrointestinal		
Cytoprotective effect	PGE_2	
Immune Response		
Suppress lymphocyte activity	PGE_2	
Hematologic		
Platelet aggregation	TxA_2	PGI_2

SOURCE: Modified from Robertson RP: Prostaglandins and other arachidonic acid metabolites, in Becker KL, et al (eds): *Principles and Practice of Endocrinology and Metabolism*, 2d ed. Philadelphia, JB Lippincott 1996, chap 170, with permission.

and collagen. Kinins are rapidly metabolized. One of these enzymes, kinase II, is identical to angiotensin-converting enzyme. The use of angiotensin-converting enzyme inhibitors (ACE inhibitors) in controlling hypertension may serve partially to block kinin degradation in some patients and enhance the kinin-induced injurious effects on the bronchial tree. Kinins increase capillary permeability and tissue edema, evoke pain, and increase bronchoconstriction. They also increase renin formation, which promotes sodium and water retention via the renin-angiotensin system.

Bradykinin release is stimulated by hypoxic and ischemic injury. Increased kallikrein activity and bradykinin levels have been detected after hemorrhage, sepsis, endotoxemia, and tissue injury. These observations are correlated with the magnitude of injury and mortality. Clinical trials using bradykinin antagonists in attempts to reduce the deleterious sequelae of septic shock have demonstrated only modest effects and no overall improvement in survival. Kinins increase glucose clearance by inhibiting gluconeogenesis.

Serotonin The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is a tryptophan derivative that is found in the intestine and in platelets. Patients with midgut carcinoid tumors often secrete excessive 5-HT. This neurotransmitter stimulates vasoconstriction, bronchoconstriction, and platelet aggregation. It also has chronotropic and inotropic effects. Although it is released at sites of injury, its role in the injury response is unclear.

Histamine Histamine is derived from histidine and stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets. There are two receptors for histamine binding. H_1 binding mediates increased uuptake of the histamine precursor, L-histidine, and stimulates bronchoconstriction, intestinal motility, and myocardial contractility. H_2 binding inhibits histamine release. H_1 and H_2 receptor activation induces vasodilation and increases vascular permeability. Histamine administration causes hypotension, peripheral pooling of blood, increased capillary permeability, decreased venous return, and myocardial failure. Histamine is released in hemorrhagic shock, trauma, thermal injury, endotoxemia, and sepsis. Histamine levels are correlated with mortality from septic shock.

METABOLIC RESPONSE TO INJURY

The description of human biochemical responses to injury and the classification of such responses into an ebb and flow phase provide a useful model by which the metabolic response to injury may be

characterized. The ebb phase corresponds to the earliest moments to hours after injury, often in association with hemodynamic instability or reductions in effective circulating blood volume. The metabolic consequences of this phase are less well studied but generally are associated with reductions in total body energy expenditure and urinary nitrogen loss. The ebb phase is associated with neuroendocrine hormone appearance, including catecholamines and cortisol. Less is known about the microendocrine mediator response. It is difficult to separate the immune cell mediator response from responses to fluid or volume resuscitation and tissue reperfusion and reoxygenation.

The flow phase is ushered in by compensatory mechanisms resulting from volume repletion and cessation of initial injury conditions. The metabolic response associated with the flow phase serves to direct energy and protein substrates both to preserve organ function and repair damaged tissues. This includes an increase in whole-body oxygen consumption and metabolic rate, enhancement of enzyme pathways for oxidation of energy substrates such as glucose, and stimulation of the immune system to repair tissue and prevent additional breaks in epithelial barriers. A reprioritization of substrate processing occurs to support the production of acute-phase reactants, immunoreactive proteins, and coagulation factors. Wound healing begins during the early flow phase.

Metabolic Response to Fasting

A comparison between the metabolic physiology of injury and that of unstressed fasting is useful for assessing the physiologic alterations under these widely varying conditions. Factors such as antecedent health status, age, and lean body mass also influence the absolute rates of substrate utilization after fasting and injury.

Substrate Metabolism A healthy adult of 70 kg body weight expends 1700–1800 kcal/day of energy obtained from the oxidation of lipid, carbohydrate, and protein. Obligate glycolytic cells, such as neurons, leukocytes, and erythrocytes, require 180 g of glucose per 24 h for basal energy needs. During acute starvation, glucose is derived from existing storage pools, including approximately 75 g glucose stored as hepatic glycogen. Skeletal muscle cannot directly release free glucose because it lacks the glucose-6-phosphatase necessary for this. The reduction of circulating glucose during prolonged fasting stimulates hormonal release that modulates gluconeogenesis and substrate substitution for those tissues which require glucose for energy. Glucose concentration falls within hours after the onset of fasting in association with decreases in insulin

and increases of circulating glucagon GH, catecholamines, AVP, and angiotensin II. Glucagon and epinephrine enhance cAMP to promote glycogenolysis, and cortisol and glucagon promote gluconeogenesis. Norepinephrine, AVP, and angiotensin II also promote glycogenolysis. Cortisol and epinephrine limit pyruvate use. The effect of these actions is an increase in glucose production. Sustained glucose production depends on the presentation of amino acids, glycerol, and fatty acids to the liver.

The primary gluconeogenic precursors used by the liver and to a lesser extent by the kidney for gluconeogenesis are lactate, glycerol, and amino acids such as alanine and glutamine. Skeletal muscle releases lactate by the breakdown of endogenous glycogen stores and by glycolysis of transported glucose. Lactate is also released by erythrocytes and white blood cells after aerobic glycolysis and release of newly formed lactate into the circulation. This lactate is reconverted to glucose in the liver by the Cori cycle.

The quantity of glucose made from lactate produced by skeletal muscle is not sufficient to maintain glucose homeostasis. Consequently, approximately 75 g of protein must be degraded daily during fasting and starvation to provide gluconeogenic amino acids to the liver. Proteolysis, which results primarily from decreased insulin and increased cortisol, is associated with an increase in urinary nitrogen excretion from the normal 6–8 g/day to approximately 8–11 g within the initial 5 days of fasting. Protein mobilized in starvation is derived primarily from skeletal muscle, but the loss of protein from other organs also occurs. The amino nitrogen load resulting from deamination of amino acids for gluconeogenesis increases urinary ammonia excretion. The renal excretion of ammonium ion becomes the primary route of elimination of alpha-amino nitrogen during starvation because the normally active hepatic enzymes are diminished. Renal gluconeogenesis increases through metabolism of glutamine and glutamate. The kidney may account for up to 45 percent of glucose production during late starvation.

After approximately 5 days, the rate of whole-body proteolysis diminishes to a level of 15–20 g/day, and urinary nitrogen excretion stabilizes at 2–5 g/day for several weeks. This reduction in proteolysis occurs because the nervous system and other previous glucose-utilizing tissues adapt to ketone oxidation as the predominant energy source. Consequently, the amount of protein required for gluconeogenesis is significantly reduced. A reduction in anabolic growth factors such as IGF-1 (formerly somatomedin C) also is observed during the first several days of fasting. This leads to a reduction in transcellular amino acid transport and tissue protein synthesis contemporaneously with reductions in proteolysis.

Energy requirements for gluconeogenesis and basal enzymatic and muscular function, such as neural transmission and cardiac contraction, can be met by the mobilization of approximately 160 g of triglycerides from adipose tissue in the form of free fatty acids and glycerol in a resting, fasting 70-kg subject. Free fatty acid release is stimulated by a reduction in the serum insulin concentration. Increased glucagon may participate in this alteration, as do catecholamines. The free fatty acids and ketone bodies generated by the liver are used as a source of energy by tissues such as the heart, kidney, muscle, and liver. Lipid stores provide up to 40 percent of the caloric expenditure during starvation. Lipid oxidation during starvation diminishes the absolute glucose requirement to sustain tissue and body energy expenditure. Fatty acid use occurs at a rate that is proportional to serum fatty acid concentration. Ketone bodies inhibit pyruvate dehydrogenase and spare glucose. The use of fat as a main fuel source decreases the amount of mandatory glycolysis, which diminishes the requirements for gluconeogenesis and protein degradation.

Whole-body energy expenditure decreases during prolonged fasting. This reduction in resting energy expenditure is a consequence of decreased sympathetic nervous system activity and reduced skeletal muscle activity, as well as reduced secretory enzyme production and intestinal energy needs.

Metabolism after Injury

The metabolic consequences of injury differ in many fundamental ways from those of simple starvation. Well-defined changes in hormone levels and associated substrates accompany injury. These changes can reflect the degree of underlying injury. It is the sustained activities of macroendocrine hormones in conjunction with immune cell activation that provide the signals that differentiate injury metabolism from unstressed starvation.

Energy Balance Injury of any magnitude is associated with increases in energy expenditure and oxygen consumption that vary directly with the severity of injury or burn surface area. The increase in energy expenditure results initially from the increased activity of the sympathetic nervous system and increased circulating concentrations of catecholamines.

Lipid Metabolism Lipolysis is enhanced by the immediate elevations in ACTH, cortisol, catecholamines, glucagon, and growth hormone, reduction in insulin, and increased sympathetic nervous system activity. Lipolysis observed during the ebb phase results in

elevated levels of plasma free fatty acids and glycerol. Acidosis, hyperglycemia, and anesthetic agents can alter lipid mobilization early after injury. During the flow phase, net lipolysis continues, as reflected by increased concentrations and clearance of plasma free fatty acids. In the presence of oxygen, the released fatty acids can be oxidized by cardiac and skeletal muscle to produce energy. The roles of cytokines, such as TNF, IL-1, and PGE, in fat metabolism are not fully understood. The high concentrations of intracellular fatty acids and the elevated concentration of glucagon during the ebb and flow phases inhibit fatty acid synthesis. Ketogenesis is variable and is inversely correlated with the severity of injury. Ketogenesis is decreased after major injury, severe shock, and sepsis. It is suppressed by increases in levels of insulin and other energy substrates, by increased uptake and oxidation of free fatty acids, and by an associated counterregulatory hormone response. After minor injury or mild infection, ketogenesis increases but to a lesser extent than that seen during nonstressed starvation. Injuries that are associated with minor ketone body formation also appear to be associated with a small or absent increase in plasma free fatty acid concentrations.

Carbohydrate Metabolism Glucose intolerance is well documented in injured patients. By contrast, basal insulin levels are elevated by several times during the early flow phase, indicating a state of relative insulin resistance. A 50–60 percent increase in net splanchnic glucose output is observed in septic patients, and a 50–100 percent increase is noted in thermally injured patients. The associated macroendocrine hormone milieu contributes to this net gluconeogenic response and is believed to be largely under the active control of glucagon with permissive requirement for cortisol. The precise contributions of other macroendocrine hormones are unclear. Proinflammatory mediators such as IL-6 also may exert an influence on hepatic glucose production. Definable acute changes in substrate turnover are associated with the proinflammatory mediator activity induced by endotoxin administration or TNF infusion.

Increases in plasma glucose levels are proportional to the severity of injury and to some extent are correlated with survival. With the presence of hyperglycemia, resulting largely from increased hepatic production, a ready source of substrate is provided to tissues such as those of the nervous system, wound, and red blood cells, which do not require insulin for glucose transport. Elevated concentrations of glucose and of some amino acids may be necessary for leukocyte energy requirements in inflamed tissues and in defense of epithelial barriers or other sites of microbial invasion.

Insulin resistance is of teleologic benefit to the host in that the accompanying neuroendocrine hormone response precludes the adaptation to ketone body production. To a large extent, the deprivation of glucose to nonessential organs such as skeletal muscle and adipose tissues is mediated by catecholamines and cortisol. Mechanisms for reduced glucose oxidation are not fully understood. Reduction of skeletal muscle pyruvate dehydrogenase activity diminishes the conversion of glucose to acetyl CoA and subsequent entry into the tricarboxylic acid cycle. The consequent accumulation and shunting of three carbon skeletons to the liver provides substrate for gluconeogenesis.

Glucose must be provided to inflammatory and healing cells in the wound. Glucose uptake and lactate production in wounded tissue are significantly increased. Wound inflammatory cells require glucose as an energy substrate, and glucose uptake in wounded tissue is correlated with the inflammatory cellular infiltrate.

Protein and Amino Acid Metabolism The intake of protein for a healthy young adult is approximately 80–120 g, or 13–20 g of nitrogen per day. Daily fecal and urinary excretion of nitrogen is 2–3 g and 13–20 g, respectively. After injury, daily nitrogen excretion in the urine increases to 30–50 g as urea nitrogen and represents net proteolysis. The increased excretion of urea after injury also is associated with the urinary loss of sulfur, phosphorus, potassium, magnesium, and creatinine, which indicates breakdown of intracellular compounds and a loss of lean tissue. Skeletal muscle is depleted, while visceral tissues, such as liver and kidney, are relatively preserved. The mechanisms for this visceral protein preservation are unclear. The net changes in catabolism and synthesis depend on the severity of the injury. Elective operations and minor injuries result in decreased protein synthesis and normal rates of protein breakdown. Severe trauma, burns, and sepsis are associated with increased whole-body protein turnover and increased net protein catabolism (Table 1-6). Accelerated proteolysis and gluconeogenesis persist after major injury and during sepsis. The rise in urinary nitrogen and negative nitrogen balance begin shortly after injury, reach a peak about the first week, and may continue for 3–7 weeks. The magnitude of nitrogen loss also is related to the age, sex, and physical condition of the patient. Young, healthy males lose more protein in response to an injury than do women or the elderly, presumably because they have a higher lean body mass than the latter two patient subsets.

The amino acid composition of normal human beings varies according to tissue origin. After trauma, substrate cycling occurs between skeletal muscle, liver, and the wound. Increases by several

TABLE 1-6
SUBSTRATE TURNOVER IN RESPONSE TO LPS AND TNF ADMINISTRATION

	Energy Expenditure (% of basal)	Glucose Turnover Rate (μmol/kg/min)	Free Fatty Acid Turnover Rate (μmol/kg/min)	Protein Turnover Rate (μmol/kg/min)
Control	100	11.8 $\pm$ 0.5	3.8 $\pm$ 0.6	1.28 $\pm$ 0.02
Tumor necrosis	134	13.1 $\pm$ 0.6	7.4 $\pm$ 1.4	N/A
Lipopolysaccharide	131	12.7 $\pm$ 0.4	N/A	1.46 $\pm$ 0.05

SOURCE: Adapted from Fong Y, Moldawer LL, et al: Cachectin/TNF or IL-1 alpha induces cachexia with redistribution of body proteins. *Am M Physiol* 256:R659, 1989, with permission.

times in the splanchnic uptake of alanine and glutamine in conjunction with similar trends for peripheral tissue efflux are observed after injury. Although the precise mechanisms for the net increase in skeletal muscle protein breakdown remain unclear, the combined extracellular hormonal milieu of relative insulin resistance, cortisol excess, and proinflammatory cytokine activity exert a synergistic influence. The intracellular muscle concentrations of several essential amino acids decrease at the same time that net efflux is occurring from skeletal muscle. The release of glutamine and alanine is greater than can be predicted from their relative abundance in muscle tissue protein, indicating their net synthesis in muscle before release. Glutamine is a major energy source for lymphocytes, fibroblasts, and the GI tract, especially during conditions of increased stress. Glutamine may act as a conditionally essential amino acid during periods of catabolism, since depletion of this substrate has pronounced negative effects on enterocytes and mucosal integrity and since administration of glutamine reverses these effects.

NUTRITION IN THE SURGICAL PATIENT

Most patients undergoing elective surgical operations withstand the brief period of catabolism and starvation without noticeable difficulty. Maintaining adequate nutrition may be of critical importance, however, in managing seriously ill patients, especially those with preexisting weight loss. Between these two extremes are patients for whom nutritional support is not essential for life but may serve to shorten the postoperative recovery phase and minimize complications. It is essential that the surgeon have a sound grasp of the fundamental metabolic changes associated with surgery, trauma, and sepsis and an awareness of the methods available to reverse or ameliorate these events.

Surgery, Trauma, Sepsis

In contrast to energy and protein conservation during unstressed starvation, the injured patient manifests increases in energy expenditure and nitrogen loss (Fig. 1-5). While the extent and duration of this response to injury are modified by a variety of factors, including the adequacy of resuscitation, infection, and medication, the inability to downregulate body energy expenditure and nitrogen losses may rapidly deplete labile and functional energy stores. The postinjury metabolic environment precludes the efficient oxidation of fat and production of ketones, thereby promoting continued

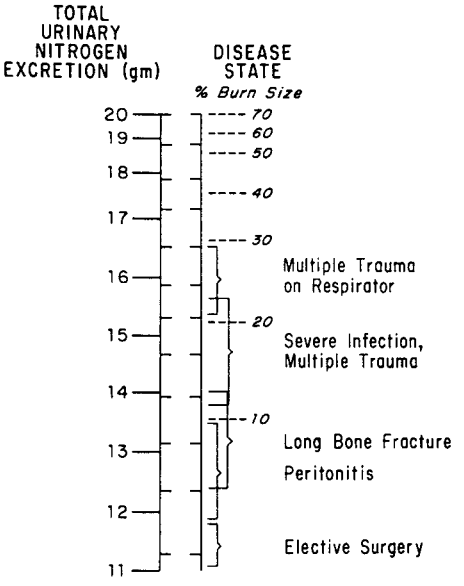


FIGURE 1-5 The minimum anticipated daily urinary nitrogen excretion of adult patients in relation to the injury stimulus. These losses may be modulated by a number of variables, including the age and nutritional status of the patient. (Adapted from: *Grant JP: Handbook of Total Parenteral Nutrition. Phialdelphia, WB Saunders, 1980, with permission.*)

erosion of protein. If unchecked, this enhanced net protein catabolism may lead to organ failure.

The sequence of flow phase metabolic and endocrine events occasioned by injury may be divided into several phases. The magnitude of the changes and the duration of each phase vary considerably and are directly related to the severity of the injury. The benefits of exogenous nutritional support in each of these recovery phases are controversial. Based on the current understanding of endocrine and immune system interactions, tissue restoration and substrate-dependent immune competence should be facilitated during periods of attenuated mediator activity. This does not preclude a rationale for earlier efforts at nutritional intervention, but it provides a biologic basis for reasonable expectations of therapy.

Catabolic Phase Once patients have received initial resuscitation and stabilization of wounds, the earliest definable metabolic response is one of catabolism. This phase has been termed the *adrenergic-corticoid phase* because it corresponds to the period during which changes induced by adrenergic and adrenal corticoid hormones are most striking. It is also likely that components of the micromediator systems exert significant influences during this phase. To variable degrees, rates of gluconeogenesis, acute-phase protein production, and immune cell activity are all altered during the catabolic phase. The administration of moderate amounts of glucose to these individuals produces little or no change in the rate of protein catabolism. Provision of sufficient nonprotein calories and amino acids may reduce the rate of protein breakdown. In the catabolic phase, glucose turnover is increased, whereas Cori cycle activity is stimulated and three-carbon intermediates are converted back to glucose in the liver. Lipolysis also is stimulated by this hormonal milieu, and an obligatory oxidation of fatty acids is evident.

Efforts directed at interruption of afferent neurogenic stimuli by extradural anesthesia have met with partial success in attenuating some of these abnormalities of energy substrate turnover. The impact of such therapy on nitrogen loss has been far less dramatic, suggesting that circulating or tissue paracrine factors other than classic neuroendocrine hormones are of major importance in early postinjury metabolic responses. Blockade of TNF and IL-1 activities during conditions of human endotoxinemia does not prevent the characteristic increase in metabolic rate and glucose or protein turnover.

Early Anabolic Phase The transition from a catabolic to an anabolic phase may occur within 3–8 days after uncomplicated elective surgery. It may be delayed for weeks, however, in patients with extensive cross-sectional tissue injury, sepsis, or ungrafted thermal injury. This turning point, also known as the *corticoid-withdrawal phase*, is characterized by a sharp decline in nitrogen excretion and restoration of appropriate potassium-nitrogen balance. This phase is also biochemically characterized by a reprioritization of acute-phase reactants, as early inflammatory response proteins are supplanted by tissue repair and anabolic factors such as IGF-1. Clinical manifestations of this transition period are brief and coincide with initial diuresis of retained water and renewed interest in oral nutrition. The early anabolic phase may last from a few weeks to a few months depending on the capacity to ingest adequate nutrition and the extent to which erosion of protein stores has occurred. Nitrogen balance is positive, indicating synthesis of proteins, and there is a rapid and progressive gain in weight and muscular strength. Positive

nitrogen balance reaches a maximum of approximately 4 g/day, which represents the synthesis of approximately 25 g of protein and the gain of over 100 g of lean body mass per day. The total amount of nitrogen gain ultimately equals the amount lost during the catabolic phase, although the rate of gain will be much slower than the rate of initial loss.

Late Anabolic Phase The final period of convalescence, or the late anabolic phase, may last from several weeks to several months after a severe injury. This phase is associated with the gradual restoration of adipose stores as the previously positive nitrogen balance declines toward normal. Weight gain is much slower during this phase because of the higher caloric content of fat and can be realized only if intake is in excess of caloric expenditure. In most individuals, the phase ends with a gradual return to the previously normal body weight. The patient who is partially immobilized during this period of time, however, may exhibit a marked gain in weight as a result of decreased energy expenditure.

Assessment and Requirements

Nutritional homeostasis assumes that proper timing and administration of nutrients have a favorable impact on the outcome of therapy. Nutritional assessment is undertaken to determine the severity of nutrient deficiencies or excesses and to aid in predicting nutritional requirements. Important information is obtained by determining the presence of weight loss and of chronic illnesses or dietary habits influencing the quantity and quality of food intake prior to injury. Physical examination seeks to assess loss of muscle and adipose tissues, organ dysfunction, and subtle change in skin, hair, or neuromuscular function reflecting an impending nutritional deficiency. Anthropometric data (weight change, skin-fold thickness, and arm circumference muscle area) and biochemical determinations (levels of creatinine excretion, albumin, and transferrin) can be used to substantiate the patient's history and physical findings. It is imprecise to rely on any single or fixed combination of these findings to assess nutritional status or morbidity. Appreciation for the stresses and natural history of the disease process, in combination with nutritional assessment, is the basis for identifying patients in acute or anticipated need of nutritional support.

The caloric and nitrogen requirements necessary to maintain an individual in balance after severe injury depend on the extent of injury, the source and route of administered nutrients, and to some extent, the degree of antecedent malnutrition. A fundamental goal of nutritional support is to meet the energy requirements for meta-

bolic processes, core temperature maintenance, and tissue repair. Failure to provide adequate nonprotein energy sources leads to dissolution of lean tissue stores. The requirements for energy may be measured by indirect calorimetry or estimated from urinary nitrogen excretion, which is proportional to resting energy expenditure. Basal energy expenditure (BEE) also can be estimated by the equations of Harris and Benedict:

$$\text{BEE (men)} = 66.47 + 13.75W + 5.0H - 6.76A \text{ kcal/day}$$

$$\text{BEE (women)} = 655.1 + 9.56W + 1.85H - 4.68A \text{ kcal/day}$$

where W is weight (kg), H is height (cm), and A is age (years). These equations are suitable for estimating energy requirements in at least 80 percent of hospitalized patients. Nonprotein calories are supplied in excess of energy expenditure because the use of exogenous nutrients is decreased and energy substrate demands are increased after traumatic or septic insult. Appropriate nonprotein caloric needs are 1.2–1.5 times resting energy expenditure (REE) during enteral nutrition and 1.5–2.0 times REE during intravenous nutrition. It is seldom, if ever, appropriate to exceed this level of nonprotein energy intake during the height of the catabolic phase.

The second objective of nutritional support is to meet the substrate requirements for protein synthesis. Maintenance of protein synthesis depends on many factors, including the nature and degree of the insult, the source and amount of exogenous protein, and previous nutritional status. Consequently, no single nutritional formulation is appropriate for all patients. An appropriate calorie-nitrogen ratio (150–200 : 1) should be maintained, but evidence suggests that increased protein intake (and a lower calorie-nitrogen ratio) may be efficient in selected hypermetabolic patients. In the absence of severe renal or hepatic dysfunction precluding the use of standard nutritional regimens, approximately 0.25–0.35 g of nitrogen per kilogram of body weight should be provided daily. Specialized nutritional formulations designed to improve nitrogen use in organ dysfunction such as acute renal and hepatic failure are targeted either to supplement deficiencies associated with the disease process or to correct characteristic amino acid abnormalities.

Vitamins usually are not given in the absence of preoperative deficiencies. Patients maintained on elemental diets or parenteral hyperalimentation require complete vitamin and mineral supplementation. The commercial defined-formula enteral diets contain varying amounts of essential minerals and vitamins. It is necessary to ensure that adequate replacement is available in the diet or by supplementation. Commercial vitamin preparations often do not contain vitamin K, and some do not provide vitamin B_{12} or folic

acid. Supplemental trace minerals may be given intravenously. Essential fatty acid supplementation also may be necessary. Patients receiving intravenous feeding require all the preceding micronutrients to prevent the development of deficiencies.

Indications and Methods for Nutritional Support

The ability to provide nutritional support to stressed patients and to attenuate nitrogen losses in catabolic states is an important adjunct to surgical care. The need for nutritional support should be assessed during the preoperative and postoperative courses of all but the most routine cases. Most surgical patients, however, tolerate a brief period of starvation (up to 1 week) well and do not require special nutritional regimens. If the patient has a relatively uncomplicated postoperative course and resumes normal oral intake at the end of this period, defined-formula diets or parenteral alimentation is unnecessary and inadvisable because of the associated risks. During the early anabolic phase, the patient needs an adequate caloric intake, a high calorie-to-nitrogen ratio (approximately 150 kcal/g nitrogen), and an adequate supply of vitamins and minerals for maximum anabolism.

For other surgical patients, an adequate nutritional regimen can be of critical importance for a successful outcome. These include patients who are chronically debilitated preoperatively from their diseases or from malnutrition and patients who have suffered trauma, sepsis, or surgical complications. In many cases the need for nutritional therapy during the early catabolic phase is apparent. This most certainly includes patients for whom there is a high expectation of prolonged hospitalization and diminished capacity for voluntary nutrient intake, such as patients with extensive burns or those with other severe injuries and incipient or overt organ failure. Despite the intuitively obvious decision to initiate nutritional support in such populations, documentation of nutrition-specific benefits or improvements in outcome are generally lacking. Nevertheless, such highly stressed and at-risk patients should receive consideration of nutritional support early.

The dilemma more commonly presented to the clinician is the identification of other patients in whom a reasonable expectation of benefit from nutritional intervention can be met. Prospective, randomized trials have significantly narrowed the populations in whom this expectation might be met. In general, the indications for preoperative nutritional support, at least in hospitalized patients, appear largely confined to patients with clinical evidence of erosion of lean body mass and adipose tissue stores. It is also possible that nutritional support in the ambulatory setting might benefit those

with evidence of organ failure or immunosuppression before elective surgery.

Specialized nutritional support can be given enterally or enterally with supplements via peripheral vein or by central venous routes. The enteral route always should be used when possible because it is considered to be more economical and well tolerated, even in patients who have had recent abdominal surgery. Nasopharyngeal, gastrostomy, and jejunostomy tube feedings may be considered for alimentation in patients who have a relatively normal GI tract but cannot or will not eat. Elemental diets may be administered by similar routes when bulk and fat-free nutrients requiring minimal digestion are indicated. Parenteral alimentation may be used for supplementation in the patient with limited oral intake or, more commonly, for complete nutritional management in the absence of oral intake. Clinical studies demonstrate that parenteral feeding potentially enhances the magnitude of endocrine and cytokine responses. While the mechanisms for this observation in parenterally fed subjects remain to be fully elucidated, a loss of intestinal barrier function permitting acute or chronic host exposure to luminal toxins has been proposed. In human beings, it has not been clearly determined whether parenteral nutrition significantly alters intestinal barrier function instead of intracellular and intercellular anatomy. While several studies suggest a higher incidence of infectious complications in parenterally fed subjects compared with an enterally fed cohort, this observation is largely confined to traumatically injured populations.

Despite the failure to document clinical differences between the enteral and parenteral feeding routes for exogenous nutrients, the GI tract serves a number of synthetic and immunologic functions that bear consideration in the design of nutritional support regimens. A number of approaches for preserving GI mucosal integrity and gut mass, including luminal stimulation by digestible or nondigestible substrates and infusion of critical intestinal fuel sources such as glutamine or short-chain fatty acids, are undergoing clinical trials. To date, these products have not been clearly documented to improve outcome in the majority of populations studied.

The patient's ability to tolerate and absorb enteral feedings is determined by the rate of infusion, the osmolality, and the chemical nature of the product. Enteral feedings often are begun at a rate of 30–50 mL/h and are increased by 10–25 mL/h per day until the optimal volume is delivered. After full volume is attained, the concentration of the solution is increased slowly to the desired strength. If esophageal or gastric feedings are given, residual gastric volume should be monitored to reduce the risk of a major aspiration episode. If abdominal cramping or diarrhea occurs, the rate of administration or the concentration of the solution should be decreased. All

feeding tubes should be thoroughly irrigated clear of solutions if feedings are interrupted or medications are given by this route.

Parenteral alimentation involves the continuous infusion of a hyperosmolar solution containing carbohydrates, proteins, fat, and other necessary nutrients through an indwelling catheter inserted into the superior vena cava. In order to obtain the maximum benefit, the ratio of calories to nitrogen must be adequate (at least 100–150 kcal/g nitrogen), and the two materials must be infused simultaneously. These nutrients can be given in quantities considerably greater than basal caloric and nitrogen requirements, and this method has proved highly successful in achieving growth and development, positive nitrogen balance, and weight gain in a variety of clinical situations.

Indications for the Use of Intravenous Feedings It is difficult to demonstrate that parenteral feeding significantly alters the clinical course or outcome in most nonsurgical patient populations. Preoperative nutritional support may benefit some surgical patients, particularly those with preexisting malnutrition. Evidence of benefit from the use of nutritional support in the elective postoperative setting is lacking. The routine use of parenteral alimentation in the critical care environment has yet to be adequately assessed, and so it is currently used intuitively.

The principal indications for parenteral alimentation are found in seriously ill patients suffering from malnutrition, sepsis, or trauma when use of the GI tract for feedings is not possible. In some instances, intravenous nutrition may be used to supplement inadequate oral intake. The safe and successful use of this regimen requires proper selection of patients with specific nutritional needs, experience with the technique, and an awareness of the associated complications. The fundamental goals are to provide sufficient calories and nitrogen substrate to promote tissue repair and to maintain the integrity or growth of lean tissue mass. Listed below are situations in which parenteral nutrition has been used in an effort to achieve these goals. Indications 1 and 2 below usually are used exclusively for intravenous nutrition. Indications 3 to 13 might be appropriate for enteral or parenteral nutrition.

1. Newborn infants with catastrophic GI anomalies such as tracheoesophageal fistula, gastroschisis, omphalocele, or massive intestinal atresia
2. Infants who fail to thrive nonspecifically or secondarily to GI insufficiency associated with the short-bowel syndrome, malabsorption, enzyme deficiency, meconium ileus, or idiopathic diarrhea

3. Adult patients with short-bowel syndrome secondary to massive small-bowel resection or enteroenteric, enterocolic, enterovesical, or enterocutaneous fistulas
4. Patients with high alimentary tract obstructions without vascular compromise secondary to achalasia, stricture, or neoplasia of the esophagus, gastric carcinoma, or pyloric obstruction
5. Surgical patients with prolonged paralytic ileus after major operations, multiple injuries, or blunt or open abdominal trauma or patients with reflex ileus complicating various medical diseases
6. Patients with normal bowel length but with malabsorption secondary to sprue, hypoproteinemia, enzyme or pancreatic insufficiency, regional enteritis, or ulcerative colitis
7. Adult patients with functional GI disorders such as esophageal dyskinesia after cerebrovascular accident, idiopathic diarrhea, psychogenic vomiting, or anorexia nervosa
8. Patients who cannot ingest food or who regurgitate and aspirate oral or tube feedings because of depressed or obtunded sensorium after severe metabolic derangements, neurologic disorders, intracranial surgery, or central nervous system trauma
9. Patients with excessive metabolic requirements secondary to severe trauma such as extensive full-thickness burns, major fractures, or soft tissue injuries
10. Patients with granulomatous colitis, ulcerative colitis, and tuberculous enteritis in whom major portions of the absorptive mucosa are diseased
11. Paraplegics, quadriplegics, or debilitated patients with indolent decubitus ulcers in the pelvic areas, particularly when soilage and fecal contamination are a problem
12. Patients with malignancy, with or without cachexia, in whom malnutrition might jeopardize successful delivery of a therapeutic option
13. Patients with potentially reversible acute renal failure, in whom marked catabolism results in the liberation of intracellular anions and cations, inducing hyperkalemia, hypermagnesemia, and hyperphosphatemia

Contraindications to hyperalimentation include the following:

1. Lack of a specific goal for patient management or when, instead of extending a meaningful life, inevitable dying is prolonged
2. Periods of cardiovascular instability or severe metabolic derangement requiring control or correction before attempting hypertonic intravenous feeding

3. Feasible GI feeding (In the vast majority of instances, this is the best route by which to provide nutrition.)
4. Patients in good nutritional status, in whom only short-term parenteral nutrition support is required or anticipated
5. Infants with less than 8 cm of small bowel, since virtually all have been unable to adapt sufficiently despite prolonged periods of parenteral nutrition
6. Patients who are irreversibly decerebrate or otherwise dehumanized

For a more detailed discussion, see Lin E, Lowry SF, and Calvano SE: The Systemic Response to Injury, chap. 1 in *Principles of Surgery,* 7th ed.

CHAPTER

2

FLUID AND ELECTROLYTE MANAGEMENT OF THE SURGICAL PATIENT

ANATOMY OF BODY FLUIDS

Total Body Water

Water constitutes 50 to 70 percent of the total body weight. At 1 year of age, the total body water averages 65 percent of body weight. The figure for the average adult male is 60 percent of body weight, and for adult females, it is 50 percent of body weight.

The water of the body is divided into three functional compartments, intracellular and extracellular, which is further divided into intravascular and interstitial. The intracellular fluid varies between 30 and 40 percent of the body weight because of the body's diverse cell population. The extracellular water represents 20 percent of body weight, with approximately one-third of this being intravascular fluid.

The chemical composition of the intracellular fluid includes potassium and magnesium as the principal cations. Phosphates and proteins are the principal anions. In the extracellular fluid, sodium is the principal cation and chloride and bicarbonate are the principal anions. Because plasma has a higher protein content (organic anions), its concentration of cations is higher and it has fewer inorganic anions than interstitial fluid. In any given solution, the number of milliequivalents of cations present is balanced by precisely the same number of milliequivalents of anions.

The differences in ionic composition between intracellular and extracellular fluid are maintained by the semipermeable cell membrane. Although the total osmotic pressure of a fluid is the sum of the partial pressures contributed by each of the solutes in that fluid, the effective osmotic pressure depends on those substances which fail to pass through the pores of the semipermeable membrane. The dissolved proteins in the plasma are primarily responsible for effective osmotic pressure between the plasma and the interstitial fluid compartments, also known as the *oncotic pressure.* While

sodium, as the principal cation of the extracellular fluid, contributes a major portion of the osmotic pressure, it is the intravascular proteins that do not penetrate the cell membrane freely that constitute the oncotic pressure.

Because cell membranes are completely permeable to water, the effective osmotic pressures in the intracellular and extracellular compartments is maintained by redistribution of water between the compartments. Fluid shifts between the intracellular, intravascular, and interstitial fluid compartments are triggered by changes in the volume, concentration, or composition of the extracellular fluid.

NORMAL EXCHANGE OF FLUID AND ELECTROLYTES

Optimal care of the patient undergoing major surgery requires a working knowledge of the basic principles governing the internal and external exchanges of water and salt. Homeostasis of the body's fluid environment, normally maintained by the kidneys, may be compromised by surgical stress, abnormal hormonal controls, or injuries to the lungs, skin, or gastrointestinal tract.

The normal individual consumes an average of 2000–2500 mL of water per day, in the form of liquids and solid food. The daily losses average 250 mL in stool, 800–1500 mL in urine, and approximately 600 mL as insensible losses through the skin and lungs. The mandatory minimum urine output to excrete nitrogenous wastes is approximately 500 mL/day. Fever increases the insensible losses through the skin. Hyperventilation increases the insensible losses through the lungs.

Daily salt intake varies from 50–90 mEq as sodium chloride. The kidneys usually excrete the excess salt. Sweat represents a hypotonic loss of fluids of 15–60 mEq/L. Insensible fluid losses from the skin and lungs do not contain salt.

The volume and composition of various gastrointestinal secretions are shown in Table 2-1. Excessive gastrointestinal losses should be replaced by an isotonic salt solution.

CLASSIFICATION OF BODY FLUID CHANGES

Disorders of fluid balance may be classified in three categories: disturbances of volume, concentration, and composition.

TABLE 2-1
COMPOSITION OF GASTROINTESTINAL SECRETIONS

Type of Secretion	Volume (mL/24 h)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO^3 (mEq/L)
Salivary	1500	10	26	10	30
	(500–2000)	(2–10)	(20–30)	(8–18)	0
Stomach	1500	60	10	160	0
	(100–4000)	(9–116)	(10–32)	(8–154)	
Duodenum		140	5	104	0
	(100–2000)				
Ileum	3000	140	5	104	30
	(100–9000)	(80–150)	(2–8)	(43–137)	
Colon		60	30	40	0
Pancreas		140	5	75	115
	(100–800)	(113–185)	(3–7)	(54–95)	
Bile		145	5	100	35
	(50–800)	(131–164)	(3–12)	(89–180)	

Volume Changes

Volume deficit or excess usually is diagnosed by clinical examination of the patient. The blood urea nitrogen (BUN) level rises with an extracellular deficit. The serum creatinine level usually does not increase proportionally in those with healthy kidneys, and this discrepancy often is used to differentiate between prerenal and renal azotemia. The hematocrit increases with extracellular fluid deficit and decreases with an extracellular excess. The serum sodium concentration is not related to the volume status of extracellular fluid; a severe volume deficit may exist with a normal, low, or high serum sodium level.

Volume Deficit Extracellular fluid volume deficit is the most common fluid disorder in the surgical patient. The most common causes include loss of gastrointestinal fluids from vomiting, nasogastric suction, diarrhea, and fistula drainage. Other common causes include sequestration of fluid in soft tissue injuries, infection, tissue inflammation, peritonitis, intestinal obstruction, and burns. Acute, rapid losses result in central nervous system (CNS) and cardiovascular signs, but slower, more insidious losses are well tolerated until severe extracellular volume deficit exists. Thermal

regulation may become a problem in the hypovolemic patient, and body temperature actually may vary with environmental temperature. The febrile response to illness may be suppressed in hypovolemic patients. Severe volume depletion depresses all body systems and interferes with clinical evaluation of a patient.

Volume Excess Extracellular fluid volume excess is an iatrogenic condition or may be secondary to renal insufficiency, cirrhosis, or congestive heart failure. In the healthy young adult, the signs of circulatory overload, manifested primarily in the pulmonary circulation, are well tolerated. In the elderly patient, congestive heart failure with pulmonary edema may develop quickly with even a moderate volume excess.

Concentration Changes

Sodium is the ion primarily responsible for the osmolarity of the extracellular fluid space. Hypo- and hypernatremia can be diagnosed on clinical grounds when the rate of change in extracellular sodium concentration is rapid. Slower changes in concentration should be noted early by laboratory tests and corrected promptly.

Hyponatremia Acute symptomatic hyponatremia is characterized by CNS signs of increased intracranial pressure (ICP). The excessive intracellular water associated with hyponatremia may lead to increased ICP. Oliguric renal failure may develop with severe hyponatremia if replacement of sodium salts is delayed. Hyponatremia is not universally caused by administration of hypotonic solutions. Many hypovolemic conditions result in hyponatremia when sodium loss is in excess of free water losses.

Hypernatremia Acute symptomatic hypernatremia results in CNS and tissue signs except when hypertonic sodium solutions have been administered. Hypernatremia is universally associated with intravascular volume depletion. While volume changes occur frequently without any change in serum sodium concentration, the reverse is not true.

Mixed Volume and Concentration Abnormalities Mixed volume and concentration abnormalities may develop as a consequence of the disease stage or as a result of inappropriate parenteral fluid therapy. One of the more common mixed abnormalities is an extracellular fluid deficit in hyponatremia. This occurs when a patient continues to drink water while losing large volumes of

gastrointestinal fluids. In the postoperative period, when gastrointestinal losses are replaced with a hypotonic sodium solution, a similar condition exists.

Normally functioning kidneys can minimize these changes and compensate for many of the imprecise replacements associated with parenteral fluid administration. Patients who have an extracellular volume deficit or who have oliguric or anuric renal failure are prone to develop mixed volume and osmotic concentration abnormalities. Fluid and electrolyte management in these patients therefore must be precise. Mild volume deficits in elderly patients with borderline renal function may result in significant fluid and electrolyte abnormalities. These changes usually are reversible with prompt correction of the extracellular fluid volume deficit.

Composition Changes

Disorders of acid-based balance and changes in the concentration of K^+, Ca^{2+}, and Mg^{2+} are common in surgical patients.

Acid-Base Balance The pH of body fluids is usually maintained within narrow limits despite the large load of acid produced as a by-product of cellular metabolism. These acids are neutralized efficiently by several buffering systems and subsequently eliminated by the lungs and the kidneys. The most important buffers include proteins, phosphates, and the bicarbonate–carbonic acid system. The four types of acid-base disturbances include respiratory acidosis and alkalosis and metabolic alkalosis and acidosis. A primary respiratory disturbance may result in a compensatory metabolic change in an attempt to maintain pH homeostasis. A metabolic disturbance often results in a more rapid respiratory compensatory disturbance in a similar fashion. A thorough knowledge of pH, bicarbonate concentration, and $PaCO_2$ allows an accurate diagnosis of most acid-base disturbances. Clinical interpretation must be made in association with the patient's clinical history.

Respiratory Acidosis This condition is associated with retention of CO_2 secondary to decreased alveolar ventilation in surgical patients, acute problems resulting in inadequate ventilation including airway obstruction, atelectasis, pneumonia, pleural effusion, pain from an upper abdominal incision, abdominal distention, or excessive use of narcotics. Management involves prompt correction of the pulmonary defect, endotracheal intubation, and mechanical ventilation if necessary. Strict attention to tracheobronchial hygiene in the postoperative period is important.

Respiratory Alkalosis This condition usually is caused by apprehension, pain, hypoxia, CNS injury, and iatrogenic assisted ventilation. In the acute phase, the serum bicarbonate concentration is normal, and the alkalosis develops as a result of a rapid decrease in the $PaCO_2$. The dangers associated with severe respiratory alkalosis are related to hypokalemia and ventricular tachyarrhythmias. Other complications include a disadvantageous shift in the oxyhemoglobin dissociation curve, limiting the ability of hemoglobin to unload oxygen to the tissues. Treatment is directed at correcting the underlying problem, including appropriate sedation, analgesia, proper use of a mechanical ventilator, and correction of preexisting potassium deficits.

Metabolic Acidosis This disorder results from the retention or gain of acids or the loss of bicarbonate. The most common causes include renal failure, diarrhea, small bowel fistula, diabetic ketoacidosis, and lactic acidosis. The initial compensation is an increase in minute ventilation and depression of the $PaCO_2$. Even with normal kidneys, metabolic acidosis may develop when excessive amounts of chloride ion are used in replacement crystalloid solutions. The "anion gap" is a useful tool in delineating the etiology of metabolic acidosis. The gap is calculated from a sum of serum chloride and bicarbonate levels subtracted from the serum sodium concentration. The anion gap is a laboratory anomaly because routine chemistry tests include Na, K, Cl, and HCO_3. The unmeasured anions therefore account for the gap and include sulfate, phosphate, lactate, and other organic anions.

The most common cause of an elevated anion gap is shock or inadequate tissue perfusion resulting in lactic acidosis. Diabetic ketoacidosis, starvation, ethanol intoxication, and poisoning by methanol, ethylene glycol, or excessive amounts of aspirin also produce increased anion gaps. Treatment of the metabolic acidosis should be directed toward correction of the underlying disorder. Bicarbonate therapy should be reserved only for the treatment of severe acidosis and only after the advantages of a compensatory respiratory alkalosis are used. The use of sodium bicarbonate after cardiac arrest should be guided by serial measurements of pH and $PaCO_2$.

Metabolic Alkalosis This disorder results from the loss of fixed acids or the gain of bicarbonate and is aggravated by hypokalemia. The pH and serum bicarbonate concentration are elevated. Respiratory compensation is small and usually not detected. Primary compensation for metabolic alkalosis is usually by renal mechanisms. A common problem in the surgical patient is a hypo-

chloremic, hypokalemic metabolic alkalosis resulting from extracellular volume deficits. Ordinarily, the urinary excretion of bicarbonate increases to compensate for the alkalosis. However, in the volume-depleted patient, aldosterone-mediated sodium resorption results in reabsorption of bicarbonate in an attempt to improve volume status. The removal of bicarbonate from the glomerular filtrate results in a paradoxical aciduria and a self-perpetuating metabolic alkalosis. Prompt management with an isotonic sodium chloride solution and replacement of the usual potassium depletion are indicated. Occasionally, severe metabolic alkalosis with excessive gastrointestinal fluid losses requires the infusion of acidic solutions such as ammonium chloride, arginine hydrochloride, or 0.2 *N* hydrochloric acid. Correction of the alkalosis should be gradual over a 24-h period with frequent measurements of pH, $PaCO_2$, and serum electrolytes.

POTASSIUM ABNORMALITIES

Ninety-eight percent of the potassium in the body is located within the intracellular compartment. At a concentration of 150 mEq/L, it is the major cation of intracellular water. The small amount of extracellular potassium is critical to cardiac and neuromuscular function in maintaining transmembrane gradients required for transmission of an electrical impulse. Rapid shifts of potassium into and out of cells are designed to maintain a critical transmembrane gradient and are easily affected by acidosis and cellular injury. When renal function is normal, dangerous hyperkalemia is encountered rarely.

Hyperkalemia Significant hyperkalemia results in cardiovascular signs including bradyarrhythmias, heart blocks, and cardiac arrest. Gastrointestinal symptoms including nausea, vomiting, colic, and diarrhea are associated with disturbances in muscular dysfunction. Treatment includes withholding exogenous potassium, administering intravenous calcium, or administering bicarbonate, glucose, and insulin to promote cellular uptake of potassium. In severe hyperkalemia, enteral administration of cation exchange resins, such as Kayexalate, or hemodialysis is required.

Hypokalemia This is a more common problem in surgical patients. The etiologies include excessive renal excretion, intracellular shift of extracellular potassium, excessive administration of potassium-free parenteral fluids, and losses in gastrointestinal secretions. Chronic potassium losses associated with diuretic use may result in a diminished ability to shift potassium into and out of cells to correct acid-base disorders. Gradual replacement of total body potassium stores is required.

The signs of potassium deficit include cardiac tachyarrhythmias and abnormal contractility of skeletal and smooth muscle and flaccid paralysis. Treatment should be intravenous replacement with no more than 40 mEq/L of intravenous fluid and should not exceed 40 mEq/h.

CALCIUM ABNORMALITIES

Most of the 1000 g of calcium in the average-sized adult is found in bone in the form of phosphate and carbonate salts. Normal daily intake is 1–3 g, most of which is excreted by the gastrointestinal tract. The normal serum level is 8.5–10.5 mg/dL, half of which is bound to albumin and plasma proteins. The fraction of calcium that is ionized changes in relationship to the pH. Acidosis causes an increase in the ionized fraction.

In the routine postoperative course, disturbances of calcium metabolism are infrequent. In the critically ill patient with large fluid shifts and capillary leak, ionized calcium levels usually are low but unpredictable, and replacement therapy should be guided by serial determinations.

Hypocalcemia The symptoms of hypocalcemia include numbness and tingling of the circumoral region and the tips of the fingers and toes. The signs of hypocalcemia include hyperactive tendon reflexes, positive Chvostek's sign, muscle cramps, tetany with carpopedal spasm, seizures, and electrocardiographic (ECG) changes.

The most common causes include acute pancreatitis, massive soft tissue infections, renal failure, pancreatic and small bowel fistulas, and hypoparathyroidism. Transient hypocalcemia is a frequent occurrence after removal of parathyroid adenomas. Hypocalcemia also is associated with severe hypomagnesemia.

Treatment of hypocalcemia is directed toward correcting the underlying cause and repletion. Acute symptoms usually are treated with intravenous calcium chloride or gluconate. Chronic losses may be supplemented orally, with or without vitamin D.

Hypercalcemia The early manifestations of hypercalcemia include fatigue, lassitude, weakness, anorexia, nausea, vomiting, and weight loss. With severe hypercalcemia, lassitude gives way to somnambulism, stupor, and coma. The two major causes of hypercalcemia are hyperparathyroidism and cancer with bony metastases.

A serum calcium concentration of 15 mg/dL or higher requires emergency treatment. Vigorous volume repletion with salt solutions dilutes the calcium level and increases urinary calcium excretion. Once the extracellular volume deficit has been corrected, increased renal clearance can be augmented by furosemide administration.

The use of oral and intravenous inorganic phosphate also lowers the serum calcium level by inhibiting bone resorption. If administered too quickly, intravenous phosphorous can cause an abrupt fall in calcium with the formation of calcium phosphate complexes and may result in tetany, hypotension, and acute renal failure. Intravenous sodium sulfate also lowers the serum calcium level by increasing urinary excretion of calcium.

Corticosteroids decrease resorption of calcium from bone and reduce the intestinal absorption of vitamin D. They are useful in treating hypercalcemic patients with sarcoidosis, myelomas, myolymphomas, and leukemias, although the reduction in serum calcium level may not be apparent for 1–2 weeks. Mithramycin, a cytotoxic drug, effectively lowers the serum calcium level in 24–48 h by direct action on bone. Calcitonin induces a moderate decrease in the serum calcium level, but the effect is diminished with repeated administration. The definitive treatment of acute hypercalcemic crisis in patients with hyperparathyroidism is immediate surgery.

MAGNESIUM ABNORMALITIES

The total body content of magnesium in the average adult is approximately 2000 mEq, about half of which is incorporated in the bone. The distribution of magnesium is similar to that of potassium, primarily intracellular. Serum magnesium concentration normally ranges from 1.5–2.5 mEq/L. The normal dietary intake of magnesium is approximately 20 mEq. Most is excreted in feces and some in urine.

Magnesium Deficiency Magnesium deficiency occurs with starvation, malabsorption syndromes, large losses of gastrointestinal fluid, large-volume crystalloid resuscitation with magnesium-free solutions, and during total parenteral nutrition with inadequate quantities of magnesium replacement. Other causes include acute pancreatitis, diabetic ketoacidosis, primary aldosteronism, chronic alcoholism, amphotericin B therapy, and a protracted course after thermal injury.

The magnesium ion is essential for proper function of most enzyme systems. The signs and symptoms are similar to those of calcium deficiency. A concomitant calcium deficiency occasionally is noted and is refractory to treatment in the absence of magnesium repletion.

The diagnosis of magnesium deficiency depends on an awareness of the syndrome and occasionally clinical recognition of the symptoms. Laboratory confirmation is available but may not be reliable because the syndrome may exist in the presence of a normal serum magnesium level. The surgical patient who is maintained on

parenteral fluids in the long term deserves routine magnesium administration.

Treatment of magnesium deficiency is by parenteral administration of magnesium sulfate or magnesium chloride. With normal renal function, as much as 2 mEq of magnesium per kilogram of body weight per day can be administered in the face of severe depletion. The intravenous route is preferable for initial treatment, and large doses should be administered over a 4-h period. Acute magnesium toxicity should be avoided, and monitoring of vital signs and continuous ECG monitoring should be routine for doses larger than 40 mEq. Calcium chloride or calcium gluconate should be available to counteract any adverse effects of hypermagnesemia.

To replete the intracellular compartment may take 1–3 weeks, and the asymptomatic patient may require intramuscular or oral replacement with magnesium sulfate or magnesium oxide, respectively.

Magnesium should not be given to the oliguric patient or in the presence of hypovolemia unless actual magnesium depletion has been demonstrated. Considerably smaller doses should be used in the patients with renal insufficiency.

Magnesium Excess Symptomatic hypermagnesemia is rare but usually is seen in patients with severe renal insufficiency. Serum magnesium levels tend to parallel changes in potassium concentration in these patients. Retention and accumulation of magnesium occur in any patient with impaired glomerular or renal tubular function. The problem is compounded with acidosis or when the patient takes magnesium-containing antacids or laxatives. Other causes include early thermal injury, massive trauma, severe extracellular volume deficit, and severe acidosis.

The early signs and symptoms of magnesium excess include lethargy, weakness, and interference with cardiac conduction and resemble those seen in hyperkalemia. Somnolence leading to coma and muscular paralysis occur in the later stages. Treatment consists of replenishing any preexisting extracellular volume deficit, correcting acidosis, and withholding exogenous magnesium. Acute symptoms may be alleviated with intravenous administration of calcium. Peritoneal dialysis or hemodialysis is indicated for chronically elevated levels.

FLUID AND ELECTROLYTE THERAPY

Parenteral Solutions

Many different electrolyte solutions, with various compositions, are available for parenteral administration. The choice of a particular

fluid depends on the patient's volume status and electrolyte balance.

The ideal isotonic salt solution for replacing gastrointestinal losses and extracellular fluid volume deficits, in the absence of gross abnormalities of concentration and composition, is lactated Ringer's solution. It contains 130 mEq of sodium balanced by 109 mEq of chloride and 28 mEq of lactate. Lactate is readily converted to bicarbonate by the liver and is used instead of bicarbonate because is it more stable in storage. Concern about the ability of the liver to metabolize lactate is unwarranted even when infusing large quantities of lactated Ringer's solution to patients in hemorrhagic shock.

Isotonic sodium chloride is the intravenous fluid best used for initial correction of an extracellular fluid volume deficit in the presence of hypernatremia, hypochloremia, and metabolic alkalosis. It contains 154 mEq of sodium and 154 mEq of chloride per liter. The high concentration of chloride above the normal serum concentration of 103 mEq/L may not be rapidly excreted by the kidneys, and a dilutional acidosis may develop. The kidneys should easily excrete the excess chloride.

In the postoperative period, 0.45% sodium chloride in 5% dextrose solution is used to provide free water for insensible losses and some sodium for renal adjustment of the serum concentration. With added potassium, this is a reasonable solution to use for maintenance requirements in patients with an uncomplicated course requiring only a short period of parenteral fluids.

Preoperative Fluid Therapy

Preoperative evaluation and correction of existing fluid disorders are an integral part of surgical care. Determination of a particular fluid disorder is facilitated by categorizing the abnormalities as volume, concentration, and compositional changes. Although some disease states produce characteristic changes in fluid balance, each disturbance should be regarded as a separate entity. Volume changes cannot be predicted accurately from a knowledge of the serum sodium level because an extracellular volume deficit or excess may exist with a normal, low, or high sodium concentration. Similarly, any of the four primary acid-based disturbances may be associated with any combination of volume and concentration abnormalities. Close observation and frequent evaluation of the clinical situation are the most rewarding approach.

CORRECTION OF VOLUME CHANGES

Changes in the extracellular fluid volume are the most frequent and important abnormalities encountered in the surgical patient. The

diagnosis of volume changes is made almost entirely on clinical grounds. The signs exhibited by an individual patient depend not only on the relative or absolute quantity of extracellular fluid lost but also on the rapidity with which it is lost.

Volume deficits may result from external loss of fluids or from an internal redistribution of extracellular fluid into a nonfunctional compartment. Whereas external losses may be witnessed or easily measured, internal distribution is more difficult to evaluate and quantify. Although the concept of a "third space" is not new, it is usually considered in patients with massive ascites, burns, or crush injuries. Perhaps more important is the third-space loss into the peritoneum, the bowel wall, and other tissues with inflammatory lesions of the intraabdominal organs. Realizing that the peritoneum has approximately 2 m^2 of surface area, the magnitude of these losses may be substantial. Swelling of the bowel wall and mesentery and secretion of fluid into the lumen of the bowel can cause loss of several liters of fluid. Similar deficits may occur with massive infection of the subcutaneous tissues (necrotizing fascitis) or with severe crush injury.

These third-space losses are sometimes referred to as "parasitic" because they remain part of the extracellular fluid space and equilibrate very slowly. The term *nonfunctional* is used because the fluid is no longer able to participate in the normal function of the extracellular fluid compartment. The patient with ascites may have an enormous total extracellular fluid volume, but the functional component is severely depleted. This patient will evoke the signs and symptoms of an extracellular fluid volume deficit without changes in weight or obvious compositional changes.

Exact quantification of these deficits is impossible and probably unnecessary. Acute losses of fluid from the extracellular compartment are more likely to result in cardiovascular signs. Gradual or chronic losses are better tolerated but insidious.

Upon diagnosis of a volume deficit, prompt fluid replacement with a balanced salt solution should be initiated. Clinical observation of the reversible signs of the volume deficit and establishment of an hourly urine output of 30–50 mL are used as general guidelines indicating the adequacy of resuscitation. Usually a reliable index of volume replacement, the hourly urine output can be misleading. An osmotic diuresis as a result of hyperglycemia in critically ill patients and patients with chronic renal disease may cause inappropriately high urinary volumes. Reliance on a formula or a single clinical sign is perilous in determining when adequate fluid replacement has occurred.

Rate of Fluid Administration The rate of fluid administration varies depending on the severity and type of fluid disturbance, the

presence of continuing losses, and the cardiac status of the patient. The most severe volume deficits may be replaced safely with isotonic solution at rates up to 2000 mL/h. Constant observation by the physician is mandatory, and the rate of replacement should be reduced as the fluid status improves. Elderly patients with associated cardiovascular disorders require slower, more careful correction with constant monitoring of the cardiopulmonary system. If urinary output is not restored promptly, measurements of central filling pressures and cardiac output may be required to prevent renal injury from underresuscitation and congestive heart failure from excessive volume restoration.

CORRECTION OF CONCENTRATION CHANGES

If symptomatic hyponatremia or hypernatremia complicates volume loss, prompt correction of the concentration abnormality to relieve symptoms is necessary. Volume replenishment should be accomplished with slower correction of the remaining concentration abnormality. For immediate correction of severe hyponatremia, 5% sodium chloride or molar sodium lactate is used. The sodium deficit is estimated by multiplying the decrease in serum sodium concentration below normal by the total body water. The patient should be reevaluated before complete correction of the concentration disorder. Although most of the sodium is found in extracellular fluid, the estimate is based on total body water because the effective osmotic pressure in the extracellular compartment cannot be increased without proportionately increasing it in the intracellular compartment. In treated moderate hyponatremia with an associated volume deficit, volume replacement can be started immediately with normal saline. Should a concomitant metabolic acidosis exist, M/6 sodium lactate (167 mEq/L each of sodium and lactate) may be used.

Treatment of hyponatremia associated with volume excess is by restriction of water. In the presence of severe symptomatic hyponatremia, a small amount of hypertonic salt solution may be infused initially to alleviate symptoms.

For the correction of severe symptomatic hypernatremia with an associated volume deficit, 5% dextrose in water should be infused until symptoms are relieved. If the correction is too rapid, convulsions and coma may result. Correction of hypernatremia concomitant with repletion of the volume deficit by half-normal saline or half-strength lactated Ringer's solution is safer.

COMPOSITION AND MISCELLANEOUS CONSIDERATIONS

Correction of existing potassium deficits should be started only after an adequate urine output is obtained. Should the patient have a concomitant metabolic alkalosis, less potassium may be required with shifting of the potassium out of the intracellular compartment

as the alkalosis is corrected. Calcium and magnesium rarely are needed during preoperative resuscitation but should be given as necessary.

Prevention of volume depletion in the preoperative period is important. Prolonged periods of fluid restriction or the use of cathartics and enemas for preparation of the bowel may cause significant acute losses of extracellular fluid. Recognition and treatment of these losses will minimize complications during the operative period.

Intraoperative Fluid Management

If preoperative replacement of extracellular fluid volume has been incomplete, hypotension may develop promptly with the induction of anesthesia. Compensation for a mild volume deficit in the awake patient may be revealed when these compensatory mechanisms are abolished with anesthesia.

In addition to blood losses during operation, there may be extracellular fluid losses during procedures requiring extensive dissection, evaporative losses from the open abdomen or chest, edema of the bowel wall, or collections within the lumen of the bowel and the peritoneal cavity. Replacement of these losses in the form of the balanced salt solution markedly reduces postoperative oliguria. Administration of blood should be used to maintain an acceptable red blood cell mass. The addition of albumin to intraoperative blood and fluid replacement is not necessary and potentially harmful. Balanced crystalloid solutions should be administered at a rate of 0.5–1 L/h during major abdominal operations, unless there are other measurable losses.

Postoperative Fluid Management

IMMEDIATE POSTOPERATIVE PERIOD

Evaluation of the patient in the recovery room, determination of the amount of fluid lost or gained during the operation, and a review of the preoperative fluid status should precede orders for postoperative fluids. Correction of any existing deficit should be prompt, and maintenance fluids for the remainder of the day should be ordered initially. Frequent assessments of the vital signs and urinary output facilitate appropriate fluid management in the first 24 h after operation.

Postoperative hypotension and tachycardia require prompt investigation and appropriate therapy. Smaller volume deficits are less noticeable, and evaluation of the level of consciousness, pupillary size, breathing patterns, skin warmth and color, body temper-

ature, and urine output are recommended. Operative blood loss usually is underestimated by the operating surgeon by 15–40 percent. Serial laboratory studies of the hematocrit, electrolytes, and blood gases may be helpful. Ongoing signs and symptoms of volume deficit, despite "adequate" volume replacement, should lead one to suspect that there is continuing losses of blood or other extracellular fluids.

LATER POSTOPERATIVE PERIOD

The problem of volume management during the postoperative convalescent phase is one of accurate measurement and replacement of all losses. The measured sensible losses, usually of gastrointestinal origin, should be replaced with an isotonic salt solution. The insensible losses, as a result of increased hypermetabolism, hyperventilation, and fever, should be replaced with 5% dextrose in water. In individuals with normal renal function, the specific crystalloid solution and electrolyte concentration are less important. The determination of serum electrolyte levels in patients with an uncomplicated postoperative course often is unnecessary. A prolonged period of parenteral replacement or excessive losses, either sensible or insensible, or some degree of renal insufficiency warrants daily determinations of serum electrolytes and possibly nutritional supplementation.

SPECIAL CONSIDERATIONS IN THE POSTOPERATIVE PATIENT

Volume Excesses Administration of isotonic salt solutions in excess of volume losses may result in overexpansion of the extracellular fluid space. The kidneys may be able to excrete the additional sodium, but after several days, the signs and symptoms of overload may be noted. The earliest sign of volume overload is weight gain. Edema, tachypnea, and fatigue are early signs of volume overload. Circulatory and pulmonary signs of overload represent a massive overload or even moderate overload in patients without significant cardiopulmonary reserve. Excessive total extracellular fluid with a concomitant depletion of the intravascular circulating volume may coexist and represent a significant challenge in postoperative care.

Hyponatremia When hypotonic solutions are used to replace sensible measured losses, hyponatremia can develop. Insidious hyponatremia can develop if the patient has good kidney function. Excessive losses of sodium through the urine may develop in elderly patients with salt-losing kidneys. Neurologic deficits also may develop. This problem may be avoided by administering isotonic solutions in the early postoperative period.

In the presence of hyperglycemia, pseudohyponatremia may develop. The osmotic effect of glucose in the extracellular compartment may cause the transfer of cellular water into the extracellular compartment, diluting the sodium. This problem may be addressed by correcting the hyperglycemia.

Hypernatremia Hypernatremia is uncommon but dangerous in the postoperative period. Invariably, in the surgical patient, hypernatremia results from excessive water losses. Insensible losses should be replaced with 5% dextrose in water. Occasionally, osmotic diuretics such as mannitol and urea also can result in losses of water in excess of sodium, resulting in hypernatremia. Again, 5% dextrose in water should be used to correct the serum sodium level, and the osmotic diuretics should be discontinued and/or removed by dialysis.

ACUTE RENAL FAILURE

Acute renal insufficiency after trauma or surgical stress is a lethal complication. Acute renal failure is classified according to its cause as prerenal, renal, or postrenal. The most common cause in the postoperative period is shock from volume depletion or cardiac failure. The most common intrarenal causes include endotoxemia, trauma, drugs, and myoglobin. Postrenal causes are mechanical obstruction of the ureter, bladder, or urethra.

Therapy of acute renal failure begins with removal of the cause. Correcting the volume deficit or removing the nephrotoxic agent is mandatory. Postrenal obstructions should be addressed appropriately.

Maintaining homeostasis during acute renal failure involves removing organic acids produced by intermediary metabolism. Additional indications for dialysis include hyperkalemia, azotemia with complications, fluid overload, hyperkalemia, and the need to remove other waste products of metabolism.

Predisposing Factors The most common predisposing factors to renal failure include trauma, sepsis, cardiopulmonary bypass, renal transplantation, urologic surgery, vascular disease, preexisting renal disease, radiographic contrast agents, and drugs. The evaluation of patients with acute renal failure requires urine chemistry and urine hematology, inspection of the urine sediment, and thoughtful analysis of the development of azotemia in relationship to various interventions during the care of the patient.

Management of the Patient with Established Acute Renal Failure Disorders of fluid and electrolytes require initial atten-

tion. The oliguric or anuric patient represents a special challenge because the administration of various solutions becomes more important. The use of dialysis is governed by the severity of the electrolyte and fluid disorders exhibited by the patient. The four forms of dialysis for acute renal failure include hemodialysis, peritoneal dialysis, continuous arteriovenous hemodialysis, and continuous venovenous ultrafiltration.

High-Output Renal Failure Uremia occurring without oliguria is a more frequent but less well recognized disorder than acute renal insufficiency. Clinical experience and laboratory experiments suggest that high-output renal failure represents a less severe renal injury than that required to produce oliguric renal failure. The primary danger of high-output renal failure is the delay in recognition because of normal urine output. Inappropriate administration of various medications and potassium can cause significant problems. The disorder usually is self-limiting.

For a more detailed discussion, see Shires GT III, Barber A, and Shires GT: Fluid and Electrolyte Management of the Surgical Patient, chap. 2 in *Principles of Surgery,* 7th ed.

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CHAPTER

3

HEMOSTASIS

BIOLOGY OF HEMOSTASIS

Hemostasis is a complex process that prevents or terminates blood loss from the intravascular space, provides a fibrin network for tissue repair, and ultimately, removes the fibrin when it is no longer needed. Four major physiologic events participate in this process (Fig. 3-1).

Vascular Constriction

This is the initial response to injury, even at the capillary level. Vasoconstriction begins prior to platelet adherence as a reflex response to various stimuli. It is subsequently linked to platelet plug and fibrin formation. The vasoconstrictors thromboxane A_2 (TXA_2) and serotonin are released during platelet aggregation. Local physical factors, including the extent and orientation of injury to the blood vessel, also may influence the degree of bleeding.

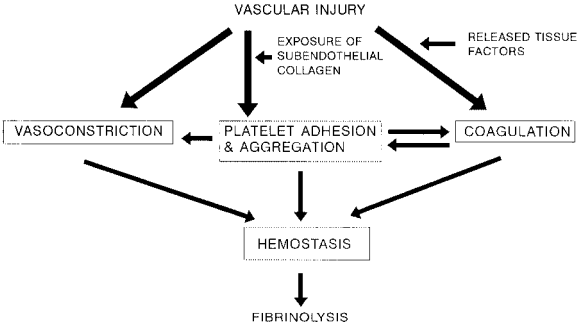

FIGURE 3-1 Simplified view of the process involved in hemostasis.

Platelet Function

Platelets normally number 150,000–400,000/mm^3, with an average life span of 10 days. They contribute to hemostasis by two processes. *Primary hemostasis* is a reversible process that is not affected by heparin administration. Platelets adhere to the subendothelial collagen of disrupted vascular tissue. This process requires von Willebrand factor (vWF), a protein congenitally absent in von Willebrand disease. The platelets expand and initiate a release reaction, recruiting additional platelets. The resulting aggregate forms a plug, sealing the disrupted vessel. ADP, TXA_2, and serotonin are the prominent mediators in this process. Opposing these mediators are prostacyclin, endothelium-derived relaxing factor (EDRF), and prostaglandin E_2 (PGE_2), which are vasodilators and inhibit aggregation. The second process by which platelets act, which is irreversible, involves *fibrinogen-dependent degranulation.* Platelet factor 3 is released, acting at several points in the coagulation cascade. Platelet-derived mediators also influence the subsequent fibrinolytic process.

Coagulation

Coagulation refers to a cascade of zymogen activation that ultimately results in the cleavage of fibrinogen to insoluble fibrin that stabilizes the platelet plug. The *intrinsic* pathway is initiated by exposure of coagulation factors to subendothelial collagen at the site of vascular damage. The *extrinsic* pathway is activated by tissue factors (glycoproteins). The two pathways converge at activated factor X (Xa), which, in turn, cleaves prothrombin to thrombin. All the coagulation factors except thromboplastin, factor VIII, and Ca^{2+} are synthesized in the liver. Factors II, VII, IX, and X are dependent on vitamin K (Fig. 3-2).

Fibrinolysis

The patency of blood vessels is maintained by lysis of fibrin deposits and by antithrombin III (which neutralizes several of the proteases in the complement cascade). Fibrinolysis depends on plasmin, which is derived from the precursor plasma protein plasminogen. Plasmin lyses fibrin, the fragments of which interfere with platelet aggregation.

TESTS OF HEMOSTASIS AND BLOOD COAGULATION

The most valuable part of this assessment is a careful history and physical examination. Specific questions should be asked to determine if there was a prior history of transfusion, untoward bleeding

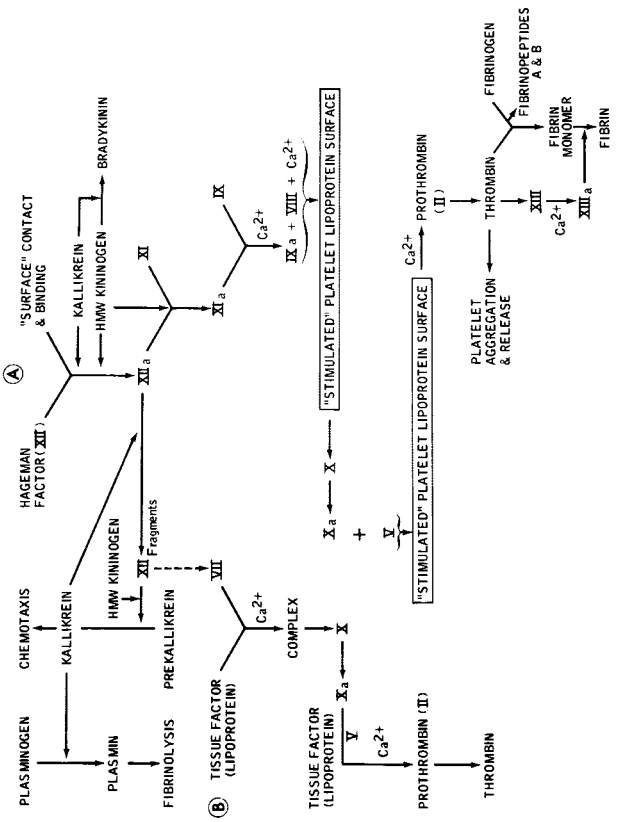

FIGURE 3-2 Outline of the intrinsic (*A*) and extrinsic (*B*) pathways of fibrin formation.

during a major surgical procedure, any bleeding after a minor operation, any spontaneous bleeding, or any family history of bleeding difficulties.

The history should include a list of medications and underlying medical disorders (e.g., malignancy, liver or kidney disease) that may affect normal hemostasis. Laboratory studies also provide important clues of hemostatic ability.

Platelet Count Spontaneous bleeding rarely occurs with a platelet count of greater than 50,000/mm^3. Platelet counts in this range are usually adequate to provide hemostasis following trauma or surgical procedures if other hemostatic factors are normal.

Bleeding Time This assesses the interaction between platelets and a damaged blood vessel and the formation of a platelet plug. Deficiencies in platelet number, platelet function, or some coagulation factors will yield a prolonged bleeding time.

Prothrombin Time (PT) This test measures the extrinsic pathway of blood coagulation. Thromboplastin, a procoagulant, is added with calcium to an aliquot of citrated plasma, and the clotting time is determined. The test will detect deficiencies in factors II, V, VII, and X or fibrinogen.

Partial Thromboplastin Time (PTT) A screen of the intrinsic clotting pathway, the PPT will determine abnormalities in factors VIII, IX, XI, and XII. This test has a high sensitivity; only extremely mild deficiencies in factor VIII or IX will be missed. The PTT, used in conjunction with the PT, can help place a clotting defect in the first or second stage of the clotting process.

Thrombin Time (TT) This screen detects abnormalities in fibrinogen and will detect circulating anticoagulants and inhibitors of anticoagulation.

Tests of Fibrinolysis Fibrin degradation products (FDPs) can be measured immunologically. Falsely positive results (>10 mg/mL) may be seen in liver disease, kidney disease, thromboembolic disorders, and pregnancy.

EVALUATION OF THE SURGICAL PATIENT AS A HEMOSTATIC RISK

Preoperative Evaluation of Hemostasis

Rapaport has suggested four levels of concern (given the patient's history and the proposed operation) that should dictate the extent of preoperative testing.

Level I: The history is negative, and the procedure is relatively minor (e.g., breast biopsy or hernia repair). No screening tests are recommended.

Level II: The history is negative and a major operation is planned, but significant bleeding is not expected. A platelet count, blood smear, and PTT are recommended to detect thrombocytopenia, circulating anticoagulant, or intravascular coagulation.

Level III: The history is suggestive of defective hemostasis, and the patient is to undergo a procedure in which hemostasis may be impaired, such as operations using pump oxygenation or cell savers. This level also applies to situations where minimal postoperative bleeding could be detrimental, such as intracranial operations. A platelet count and bleeding time should be done to assess platelet function. A PT and PTT should be used to evaluate coagulation, and the fibrin clot should be checked to screen for abnormal fibrinolysis.

Level IV: These patients have a known hemostatic defect or a highly suggestive history. The same tests suggested for level III should be checked, and a hematologist should be consulted. In case of an emergency, assessment of platelet aggregation and a TT are indicated to detect dysfibrinogenemia or a circulating anticoagulant.

Patients with liver disease, obstructive jaundice, kidney failure, or malignancy should have the platelet count, PT, and PTT checked preoperatively.

CONGENITAL DEFECTS IN HEMOSTASIS

Classical Hemophilia (Factor VIII Deficiency)

Classical hemophilia (hemophilia A) is a sex-linked recessive disorder in which there is a failure to synthesize normal factor VIII. The incidence is approximately 1 in 10,000 to 1 in 15,000 persons. Spontaneous mutations account for almost 20 percent of cases. Clinical expression of the disease is highly variable.

The severity of the clinical manifestations is related to the degree of factor deficiency. Spontaneous bleeding and severe complications are the rule when virtually no factor VIII activity can be detected. Concentrations of approximately 5 percent of normal may produce no spontaneous bleeding, yet there may be severe bleeding with trauma or surgical therapy.

Significant bleeding is usually first noted when the subject is a toddler. At that time the child may be subject to bleeding into joints, epistaxis, and hematuria. Intracranial bleeding, associated with trauma in half the cases, accounts for 25 percent of deaths.

Hemarthrosis is the most characteristic orthopedic problem. Retroperitoneal bleeding or intramural intestinal hematoma also may occur, causing nausea, vomiting, or crampy abdominal pain. Upper gastrointestinal examination may demonstrate uniform thickening of mucosal folds ("picket fence" or "stack of coins" appearance).

Treatment The plasma concentration of factor VIII necessary to provide hemostatic integrity is normally quite small (as little as 2–3 percent). Once serious bleeding begins, however, much higher levels (30 percent) of activity are required to achieve hemostasis. The half-life of factor VIII is 8–12 h; after an initial transfusion, its half-life is approximately 4 h. One unit of factor VIII is considered to be the amount present in 1 mL normal plasma. Cryoprecipitate concentrates of factor VIII contain 9.6 units/mL. The amount of activity suggested to be repleted varies according to the severity of the lesion. To calculate the amount of factor VIII needed: 1 unit/kg of body weight will yield approximately a 2 percent rise in activity. Half this amount is subsequently administered every 4–6 h to maintain a safe level.

Wet-frozen cryoprecipitate is preferred for replacement in patients with mild hemophilia, since it provides the lowest risk of viral hepatitis. Factor VIII concentrates are preferred in severe disease. In mild hemophilia A and mild von Willebrand disease, dDAVP, a synthetic derivative of vasopressin, has been used to produce a dose-dependent increase in all factor VIII activities and release plasminogen activator. Following major surgical treatment of a hemophiliac, transfusion replacement of factor VIII should be continued for at least 10 days. Even relatively minor procedures should be supplemented with factor VIII to achieve levels above 25–30 percent.

Christmas Disease (Factor IX Deficiency)

Factor IX deficiency is clinically indistinguishable from factor VIII deficiency. It is also inherited as an X-linked recessive disease with variable expression. The clinically severe form of the disease has a level of less than 1 percent of normal activity. Half the patients belong to this group.

Treatment All patients require substitution therapy when major or minor surgery is performed. Current therapy involves the administration of factor IX concentrate. The initial half-life is shorter than that of factor VIII; its steady-state half-life is much longer

(18–40 h). A number of factor IX concentrates are available. Konyne contains 10–60 units/mL of factor IX but has been associated with thromboembolic complications. Newer preparations have had additional clotting factors removed, and the incidence of thromboembolic events is lower. During severe hemorrhage, treatment should be directed to achieving levels of 20–50 percent of normal for the first 3–5 days and then maintaining a plasma level of 20 percent for approximately 10 days. Plasma activity should be monitored during the course of therapy. The development of antibodies occurs in about 10 percent of patients.

von Willebrand Disease

von Willebrand disease occurs in approximately 1 in 1000 individuals. The clinically severe form of the disease occurs much less frequently. This disorder is usually transmitted as an autosomal dominant trait, but recessive inheritance may occur. The disease is characterized by abnormal vWF and a decrease in the level of factor VIII:C (procoagulant) activity, which corrects the clotting abnormality in hemophilia A. Characteristically, patients with this disease have a prolonged bleeding time, but this is less consistent than the factor VIII:C reduction. A given patient may have an abnormal bleeding time on one occasion and a normal bleeding time on another. Ristocetin fails to cause platelet aggregation in about 70 percent of patients with this disease.

Clinical Manifestations Clinical manifestations are usually minimal until trauma or surgery makes them apparent. Spontaneous bleeding is often limited to the skin or mucous membranes. Epistaxis and menorrhagia are relatively common. Serious bleeding following minor surgery is not uncommon.

Treatment Treatment is directed at correcting the bleeding time and factor VIII R:vWF (the von Willebrand factor). Only cryoprecipitate is effective (10–40 units/kg q12h). Replacement therapy should start 1 day before surgery, and the duration of therapy should be the same as that described for classic hemophilia.

ACQUIRED HEMOSTATIC DEFECTS

Platelet Abnormalities

Thrombocytopenia, the most common abnormality of hemostasis in the surgical patient, may be due to massive blood loss, medications, or a variety of disease processes. Heparin-induced thrombocytopenia

is notable for being reported in 0.6 percent of patients receiving heparin and is thought to be immune mediated. The lowest platelet counts occur after 4–15 days of initial therapy and after 2–9 days in patients receiving subsequent courses.

Abnormalities in platelet number also may be accompanied by abnormalities in function. Uremia affects bleeding time and platelet aggregation. Defects in platelet aggregation and secretion occur in patients with thrombocytopenia, polycythemia, or myelofibrosis.

Treatment A count greater than 50,000/mm^3 requires no specific therapy. Thrombocytopenia due to acute alcoholism, drug effect, or viral infection generally will correct within 1–3 weeks. Severe thrombocytopenia may be due to vitamin B_{12} or folate deficiency. This condition is usually responsive to the appropriate nutrient therapy. In patients with idiopathic thrombocytopenia or lupus erythematosus, a platelet count of less than 50,000/mm^3 may respond to steroid therapy or plasmapheresis. Splenectomy alone should not be performed to correct thrombocytopenia associated with splenomegaly due to portal hypertension.

Prophylactic platelet administration is not routinely required following massive blood transfusions. One unit of platelets contains approximately 5.5×10^5 platelets and would be expected to increase the circulating platelet count by 10,000/mm^3 in a 70-kg man. In patients refractory to standard platelet transfusion, the use of human leukocyte antigen (HLA)–compatible platelets has proved effective.

Acquired Hypofibrinogenemia-Defibrination Syndrome (Fibrinogen Deficiency)

This is rarely an isolated defect because deficiencies in factors II, VI, and VIII and platelets usually accompany this state. Most patients with acquired hypofibrinogenemia suffer from disseminated intravascular coagulation (DIC). DIC is caused by the introduction of thromboplastic material into the circulation. This syndrome has been seen with a retained dead fetus, separation of the placenta, and amniotic fluid embolism. Defibrination has been observed in association with extracorporeal circulation, disseminated carcinoma, lymphoma, and a variety of infections (including both gram-negative and gram-positive sepsis).

It is difficult to distinguish DIC from secondary fibrinolysis because both show prolongation in the TT, PTT, and PT. The combination of a low platelet count, a positive plasma protamine test, re-

duced fibrinogen, and increased FDPs (taken in the context of the patient's underlying disease) is highly suggestive of the syndrome.

The prime consideration in treatment is relieving the underlying medical problem. The use of intravenous fluids is indicated to maintain volume. If there is active bleeding, hemostatic factors should be replaced with fresh frozen plasma, cryoprecipitate, and platelet concentrates as needed. Most studies show that heparin is not indicated in acute forms of DIC but is indicated for purpura fulminans or venous thromboembolism. Fibrinolytic inhibitors may be used to block the accumulation of FDPs. They should not be used without prior effective antithrombotic treatment with heparin.

Fibrinolysis

The acquired hypofibrinogenemic state in the surgical patient also may be due to pathologic fibrinolysis. This can be seen in patients with metastatic prostatic carcinoma, shock, sepsis, hypoxia, neoplasia, cirrhosis, and portal hypertension. A reduction in fibrinogen and factors V and VIII is seen, since they all are substrates for the enzyme plasmin. Thrombocytopenia is not an accompaniment of the purely fibrinolytic state. Treatment of the underlying disorder (if identified) is warranted. ϵ-Aminocaproic acid (EACA), an inhibitor of fibrinolysis, also may be useful.

Myeloproliferative Diseases

Thrombocytopenia can be treated by standard therapy for the underlying disease. Ideally, the hematocrit should be kept below 48 percent and the platelet count less than 400,000/mm^3. In a study with polycythemic patients undergoing major surgical procedures, 46 percent had complications perioperatively, including a 16 percent mortality (in 80 percent of whom the disease was not under control). Hemorrhage is the most common complication in this group, followed by thrombosis and infection. Preoperative use of antiplatelet agents (e.g., aspirin, dipyridamole) and anticoagulants has been suggested in these patients.

LIVER DISEASE

Advanced liver disease may result in decreased synthesis of the coagulation factors II, V, VII, X, and XIII. Also, there may be increased fibrinolysis due to the failure of the liver to clear plasminogen activators.

ANTICOAGULATION AND BLEEDING

Spontaneous bleeding may be a complication of anticoagulant therapy, with an incidence proportional to the degree of anticoagulation. Surgical therapy may be necessary in patients receiving anticoagulant therapy. The risk of thrombotic complications is increased when anticoagulant therapy is suddenly discontinued and may be due to a "rebound phenomenon." When the clotting time is less than 25 min in the heparinized patient or when the PT is less than 1.5 times control, reversal of anticoagulant therapy may not be necessary. If an emergent surgical procedure is necessary, anticoagulation can be reversed. Heparin can be reversed with protamine sulfate (1 mg protamine per 1000 units heparin). Bleeding is infrequently related to hypoprothrombinemia if the prothrombin concentration is greater than 15 percent. Warfarin can be discontinued several days before surgery. If emergency surgery is required, parenteral vitamin K_1 can be used. Reversal may take up to 6 h, so fresh frozen plasma may be needed.

LOCAL HEMOSTASIS

The goal of local hemostasis is to prevent the flow of blood from incised or transected blood vessels. The techniques may be classified as mechanical, thermal, or chemical.

Mechanical

The oldest mechanical device to effect closure of a bleeding point or to prevent blood from entering an area of disruption is digital pressure. The finger has the advantage of being the least traumatic means of hemostasis. Diffuse bleeding from multiple transected vessels may be controlled by mechanical techniques, including direct pressure over the bleeding area, pressure at a distance, or generalized pressure. Direct pressure is preferable and is not attended by the danger of tissue necrosis associated with a tourniquet. Gravitational suits have been used to create generalized pressure.

The hemostat represents a temporary mechanical device to stem bleeding. Ligature replaces a hemostat as a permanent method of hemostasis of a single vessel.

Thermal

Cautery effects hemostasis by denaturation of proteins, which results in coagulation of large areas of tissue. Cooling also has been

applied to control bleeding and acts by increasing the local intravascular hematocrit and decreasing the blood flow by vasoconstriction. Cryogenic surgery uses temperatures between −20 and −180°C.

Chemical

Some chemicals act as vasoconstrictors, others are procoagulants, and others have hygroscopic properties that aid in plugging disrupted blood vessels. Epinephrine is a vasoconstrictor, but because of its considerable absorption and systemic effects, it is generally used only on areas of mucosal oozing. Local hemostatic materials include gelatin foam, cellulose, and micronized collagen.

TRANSFUSION

Approximately 14 percent of all inpatient operations include blood transfusions. Blood provides transportation of oxygen to meet the body's metabolic demands and removes carbon dioxide.

Replacement Therapy

Banked whole blood is stored at 4°C and has a storage life of up to 35 days. Up to 70 percent of transfused erythrocytes remain in the circulation 24 h after transfusion; 60 days after transfusion, approximately 50 percent of the cells will survive. Banked blood is rarely indicated.

Banked blood is a poor source of platelets. Factors II, VII, IX, and XI are stable in banked blood. Factor VIII rapidly deteriorates during storage. During the storage of whole blood, red cell metabolism and plasma protein degradation result in chemical changes in the plasma, including increases in lactate, potassium, and ammonia and a decrease in pH.

Typing and Crossmatching Serologic compatibility is routinely established for donor and recipient A, B, O, and Rh groups. As a rule, Rh-negative recipients should be transfused only with Rh-negative blood. In the patient receiving repeated transfusions, serum drawn less than 48 h before cross-matching should be used. Emergency transfusion can be performed with group O blood. If it is known that the prospective recipient is group AB, group A blood is preferable.

Fresh Whole Blood This term refers to blood given within 24 h of its collection.

Packed Red Cells and Frozen Red Cells Packed cells have approximately 70 percent of the volume of whole blood. Use of frozen cells markedly reduces the risk of infusing antigens to which the patients have previously been sensitized. The red cell viability is improved, and the ATP and 2,3-diphosphoglycerate (2,3-DPG) concentrations are maintained.

Platelet Concentrates Platelet transfusions should be used for thrombocytopenia due to massive blood loss replaced with stored blood, thrombocytopenia due to inadequate production, and qualitative platelet disorders. Isoantibodies are demonstrated in about 5 percent of patients after 1–10 transfusions, 20 percent after 10–20 transfusions, and 80 percent after more than 100 transfusions. HLA-compatible platelets minimize this problem.

Fresh Frozen Plasma and Volume Expanders Factors V and VIII require plasma to be fresh or freshly frozen to maintain activity. The risk of hepatitis is the same as that of whole blood or packed red cells. In emergency situations, lactated Ringer's solution can be administered in amounts two to three times the estimated blood loss. Dextran or lactated Ringer's solution with albumin can be used for rapid plasma expansion.

Concentrates Antihemophilic concentrates are prepared from plasma with a potency of 20–30 times that of fresh frozen plasma. The simplest factor VIII concentrate is plasma cryoprecipitate. Albumin also may be used as a concentrate (25 g has the osmotic equivalent of 500 mL), with the advantage of being hepatitis-free.

INDICATIONS FOR REPLACEMENTS OF BLOOD OR ITS ELEMENTS

Volume Replacement The most common indication for blood transfusion in the surgical patient is the restoration of circulating blood volume. The hematocrit can be used to estimate blood loss, but up to 72 h is required to establish a new equilibrium after a significant blood loss.

In the normal person, reflex mechanisms allow the body to accommodate up to moderate-size blood losses. Significant hypotension develops only after about a 40 percent loss of blood volume.

Loss of blood during operation may be estimated by weighing the sponges (representing about 70 percent of the true loss). In pa-

TABLE 3-1
BLOOD REPACEMENT RECOMMENDATIONS

Percentage of Total Blood Volume Loss	Replacement
20	Crystalloid solutions
20–50	Crystalloids and red cell concentrates (RBCs)
Above 50	Crystalloids, RBCs, and albumin or plasma
Continued bleeding above 50	Crystalloids, RBCs, fresh frozen plasma, and albumin or plasma

tients who have normal preoperative blood values, replacement recommendations are shown in Table 3-1.

Improvement in Oxygen-Carrying Capacity Transfusion should be performed only if treatment of the underlying anemia does not provide adequate blood counts for the patient's clinical condition. In general, raising hemoglobin levels above 7–8 g/dL provides little additional benefit. A whole blood substitute, Fluosol-DA, provides oxygen-carrying capacity in the absence of blood products.

Replacement of Clotting Factors Supplemental platelets or clotting factors may be required in the treatment of certain hemorrhagic conditions. Fresh frozen plasma is used in the treatment of a coagulopathy in patients with liver disease, but its efficacy is very low. The rigid use of PT and PTT to anticipate the effect of fresh frozen plasma is not justified. If fibrinogen is required, a plasma level greater than 100 mg/dL should be maintained.

Massive Transfusion This term refers to a single transfusion of greater than 2500 or 5000 mL over a 24-h period. A number of problems may accompany the use of massive transfusion, including thrombocytopenia, impaired platelet function, deficiency in factors V, VIII, and XI, and the increased acid load of stored blood products.

With large transfusions, a heater may be used to warm the blood, since hypothermia may result in decreased cardiac output and an acidosis.

Complications (Table 3-2)

Hemolytic reactions from blood group incompatibilities are usually manifest by a sensation of warmth and pain along the site of transfusion, flushing in the face, pain in the lumbar region, and constricting pain in the chest. The patient additionally may experience chills, fever, and respiratory distress. In anesthetized patients, two signs of reaction are abnormal bleeding and continued hypotension in the face of adequate replacement. The morbidity and mortality of hemolytic reactions are high and include oliguria, hemoglobinuria, hypotension, jaundice, nausea, and vomiting. The transfusion should be stopped immediately if a transfusion reaction is suspected. Samples of the recipient and donor blood should be sent for comparison with pretransfusion samples. Renal function should be monitored following a suspected transfusion reaction. Renal toxicity is affected by the rate of urinary excretion and the pH. Alkalinization of the urine prevents precipitation of hemoglobin.

Febrile and Allergic Reactions These occur in approximately 1 percent of transfusions. They appear as urticaria and fever oc-

TABLE 3-2
COMPLICATIONS OF TRANSFUSION

Complication	Risk per Unit Blood Product
Infectious	
Hepatitis C	1:3300
Human immunodeficiency virus	1:40,000–1:225,000
Human T-lymphocyte virus (I and II)	1:50,000
Hepatitis B	1:200,000
Immunologic	
Fever, chills, urticaria	1:50–1:100
Hemolytic reaction	1:1000
Fatal hemolytic reaction	1:100,000

curring within 60–90 min of the start of the transfusion. Occasionally, the allergic reaction is severe enough to cause anaphylactic shock. Treatment consists of antihistamines, epinephrine, and steroids, depending on the severity of the reaction.

Transmission of Disease Posttransfusion viral hepatitis is the most common fatal complication of blood transfusion. Other viral illnesses may be transmitted (e.g., cytomegalovirus, human immunodeficiency virus, etc.), as well as several bacterial species.

Additional, less frequent complications include

Embolism: Intravenous volumes of less than 200 mL are generally well tolerated by normal adults.

Volume overload: The patient's risk is related to underlying cardiac reserve.

Bacterial sepsis: Gram-negative organisms and *Pseudomonas* predominate. *Thrombophlebitis:* More commonly seen with prolonged infusions.

For a more detailed discussion, see Schwartz SI: Hemostasis, Surgical Bleeding, and Transfusion, chap. 3 in *Principles of Surgery*, 7th ed.

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CHAPTER

4

SHOCK

Shock is a pathophysiologic condition clinically recognized as a state of inadequate tissue perfusion. There are four distinct categories: hematogenic, neurogenic, vasogenic, and cardiogenic. It is clear that shock is a systemic disorder that disrupts vital organ function as the eventual result of a variety of causes. Whereas hemorrhagic or traumatic shock is characterized by global hypoperfusion, septic shock may be associated with hyperdynamic circulation resulting in a maldistribution of regional or intraorgan blood flow.

CIRCULATORY HOMEOSTASIS

Preload Most of the blood volume at rest is contained within the venous system. The effect of the return of this venous blood to the heart produces ventricular end-diastolic wall tension, a major determinant of cardiac output. Gravitational shifts in blood volume distribution are rapidly compensated for by active and passive alterations in venous capacity. In the normal heart, most changes in cardiac output are a reflection of alterations in preload. Changes in position, intrathoracic pressure, intrapericardial pressure, and circulating blood volume produce major changes in cardiac output.

The normal circulating blood volume is maintained within narrow limits by balancing salt and water intake with external losses by the kidney's ability to respond to alterations in hemodynamics and the hormonal effects of renin, angiotensin, and antidiuretic hormone. In the acute setting, the changes in the venous tone, systemic vascular resistance, and intrathoracic pressure come into use. In addition, the net effect of preload on the ventricle also responds to the cardiac determinants of ventricular function, including coordinated atrial contraction, which augments ventricular diastolic filling, and tachycardia, which drops the effect of preload on the ventricle by compromising diastolic filling time.

Ventricular Contraction The Frank-Starling curve describes the varying force of ventricular contraction as a function of its preload.

A number of disease states, including myocardial injury, valve dysfunction, and cardiac hypertrophy, may alter the mechanical performance of the heart. Septic, hemorrhagic, and traumatic shock deteriorate intrinsic cardiac function. While the mechanisms of these alterations in myocardial performance are unclear, their effect on the evaluation and management of global perfusion in clinical shock may be assessed by Swan-Ganz catheterization that measures preload indirectly as end-diastolic pressure, thermodilution cardiac output, and estimations of calculated vascular resistance.

Afterload Afterload is the force acting to resist myocardial work during contraction. Arterial pressure is the major component of afterload that influences the ejection fraction. The decreased effective circulating volume in shock states prevents this compensatory maintenance of cardiac output.

PATHOPHYSIOLOGY OF HYPOVOLEMIC SHOCK

Hypovolemic shock results from a decrease in the circulating or effective intravascular volume. As intravascular volume is lost, an increase in peripheral vascular resistance occurs to defend the blood pressure in compensation for falling cardiac output. Differential increases in peripheral resistance in regional arteriolar beds, particularly in the skin, gut, and kidney, further defend pressure at the cost of further decreasing organ flow. The pale, cool skin noted on examination and the blanching of the bowel with decreased pulses in the mesentery are gross signs seen at the bedside and at laparotomy. A decrease in circulating blood volume also results in tachycardia in response to decreased stroke volume from inadequate preload. Orthostatic testing may unmask cardiovascular instability.

Compensatory Responses

The following compensatory responses occur during hypodemic shock:

1. Increased vascular tone, which elevates peripheral vascular resistance and results in a redistribution of blood flow among the organ systems of the body
2. Increased sympathetic activity, greater myocardial contractility, and enhanced venous return
3. Decreased capillary hydrostatic pressure and mobilization of the interstitial fluid pool into the intravascular space

4. Tissue extraction of oxygen, which is enhanced in hemorrhagic shock by the presence of acidosis and elevated levels of erythrocyte 2,3-diphosphoglycerate (2,3-DPG)
5. Arteriolar constriction and loss of circulating volume, which diminish renal blood flow
6. Release of epinephrine and norepinephrine, which produce vasoconstriction and tachycardia, resulting in increased cardiac output and blood pressure
7. Stimulation of adrenocorticotropic hormone (ACTH) release
8. Decreased insulin secretion, which augments the mobilization of glucose, amino acids, and fat stores
9. Increased antidiuretic hormone (ADH) secretion, which increases water permeability and passive sodium transport, allowing increased water resorption and splanchnic vasoconstriction

Activation of the renin-angiotensin system occurs. Angiotensin II is a powerful arterial and arteriolar vasoconstrictor that stimulates renal prostaglandin production as well as the release of aldosterone and ACTH.

Increased aldosterone secretion occurs. This represents the principal mechanism by which the kidney may excrete the accumulated by-products of anaerobic metabolism and cellular damage.

Prostaglandins, particularly prostaglandin E_2 (PGE_2), and kallikreins, produced in the kidney, function locally to dilate renal vessels and increase renal blood flow. Thromboxane A_2 results in splanchnic and cutaneous vasoconstriction and may promote cardiovascular dysfunction. The leukotrienes, produced by activated mast cells, also are potent vasoconstrictors that promote muscle catabolism and amino acid release.

Pulmonary Derangements in Shock

Accompanying successful fluid resuscitation is the emergence of pulmonary dysfunction in 1–2 percent of the survivors of shock. This occurs in some patients without lung injury per se. Acute respiratory distress syndrome (ARDS) is characterized by hypoxia (despite oxygen therapy), decreased pulmonary compliance, diffuse or patchy infiltrates on chest x-ray, and noncardiac pulmonary edema.

Etiology A number of injuries can trigger a final common pathway, resulting in the symptom complex known as ARDS. These include direct pulmonary injury, as seen in aspiration, inhalation injury, pulmonary contusion, and near drowning, and seemingly

unrelated disorders, as seen in multiple transfusions and trauma such as fractures. Common to all these disorders is the initiation of inflammatory mediators. These result in increases in microvascular permeability and subsequent proteinaceous fluid deposition in the alveolar epithelial and pulmonary capillary endothelial interface. Resulting from this disruption are abnormal ventilation and perfusion relationships and hypoxia. Diuretics and fluid restriction have no impact on this pathophysiology and are not useful. Colloid administration also has not been shown to effectively decrease extravascular lung water because the normal barrier is disrupted and is permeable to large molecules such as albumin (Fig. 4-1).

Diagnosis The diagnosis of ARDS begins with clinical suspicion and is based on documentation of hypoxia, an abnormal chest x-ray, and a measured decreased lung compliance.

Therapy for ARDS The therapeutic goal is to maintain tissue oxygenation. Supplemental oxygen is supplied to maintain a PaO_2 of 65 mmHg or more. Hemoglobin concentration should be maintained at 12 g/dL or higher, with buffering of pH to allow optimal

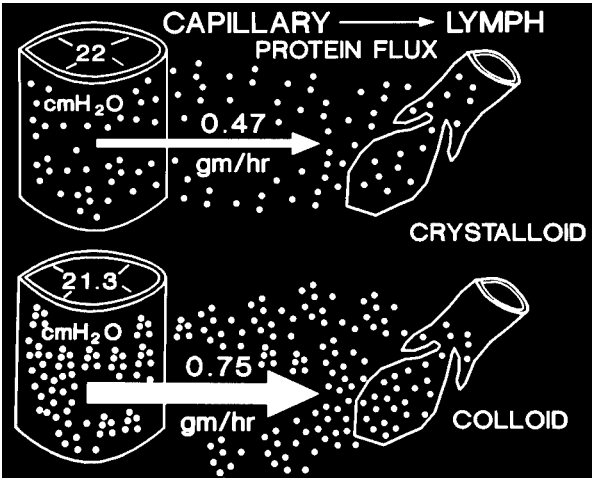

FIGURE 4-1

oxygen transport. A pulmonary artery catheter is desirable to monitor central volumes and mixed venous saturations. Standard pulmonary management includes the use of a volume ventilator in the mandatory mode with tidal volume and rate set to allow adequate carbon dioxide exchange. This usually can be accomplished with rates of 10–12 breaths per minute and tidal volumes of 10–12 mL/kg of dry weight. Positive end-expiratory pressure (PEEP) is initiated at 5 cmH_2O to approximate glottic pressure. PEEP is used to maintain oxygenation at nontoxic levels (50 percent or less) of oxygen. In managing the patient with ARDS, the ventilator is set at 100 percent oxygen, and the optimal level of PEEP is identified. This level is found by increasing PEEP by increments of 2.5 cmH_2O, allowing at least 30 min for equilibration and measuring arterial and mixed venous blood gases, pulmonary capillary wedge pressure, and cardiac output. PEEP is increased to as much as 20 cmH_2O, and optimal settings (highest oxygenation without compromise of cardiac output) are identified. PEEP is then set at this level, and oxygen is decreased incrementally to maintain a PaO_2 of 65 mmHg, with a goal of 50 percent inspired oxygen or less. PEEP can then be decreased, if oxygenation is maintained, by increments of 2.5 cmH_2O every 12 h.

Volume loading to ensure adequate filling pressures before PEEP is applied is beneficial in interpreting changes in wedge pressure and cardiac output that may occur after use of PEEP. Increased intrathoracic pressure and decreased venous return can cause depression of cardiac output. Lowering of PEEP is necessary if cardiac output becomes compromised. Pneumothorax can occur at high pressures ($>$ 20 cmH_2O) and can be catastrophic. Peak airway pressures should be monitored carefully.

Trials of early application of PEEP in patients at high risk for ARDS failed to show any benefit in overall mortality or complications. The course of ARDS has been relatively unaffected in trials of anti-inflammatory drugs such as ibuprofen and sepsis trials using anticytokine therapy.

THERAPY FOR SHOCK

Hypovolemic Shock

Initial care of the injured patient should follow the guidelines from the advanced trauma life support procedures of the American College of Surgeons Committee on Trauma. Therapy for shock is aimed at replacement of preexisting deficits through the rapid infusion of isotonic fluid solutions and blood. Initial therapy should

be with lactated Ringer's solution run through two large-bore intravenous (IV) lines. If shock persists, blood should be infused while a source for the hemorrhage is defined. The development of acidosis during resuscitation from shock merely indicates inadequate resuscitation and should be treated with additional fluids, not bicarbonate. There appears to be no advantage to the use of "colloid" solutions such as albumin over that of crystalloid. Hypotension is treated through continued fluid replacement. Vasopressors do not have a role in the therapy of hypovolemic shock because they serve only to further constrict an already highly vasoconstricted state and further worsen peripheral perfusion. There appeared to be early support for the use of vasodilators to improve peripheral perfusion during shock, but their clinical usefulness in patients has not been proved. Although early studies suggested that there is adrenocorticoid depletion in hemorrhagic shock, in the normal patient, steroids have no place during resuscitation.

FLUID RESUSCITATION

Lactated Ringer's Solution This equilibrates rapidly throughout the extracellular compartment, restoring the extracellular fluid deficit associated with blood loss. Concern that the lactate content of Ringer's solution might aggravate the lactic acidosis coexisting with hemorrhagic shock is unwarranted.

Colloid Solutions Colloidal substances such as albumin raise the intravascular colloidal pressure, leading to intravascular influx of interstitial fluid. Because colloids remain briefly in the intravascular space, a lower total volume of resuscitative fluid is required to attain hemodynamic stability than when crystalloid solutions are used. Colloid solutions are more expensive and may bind and decrease the ionized fraction of serum calcium, decrease circulating levels of immunoglobulins, decrease the immune reaction to tetanus toxoid, and decrease endogenous production of albumin. A meta-analysis of colloid versus crystalloid fluid resuscitation concluded that crystalloid is superior to colloid for resuscitation after trauma in human beings, with a 12 percent reduction in mortality after crystalloid infusion.

Hypertonic Saline A small volume of hypertonic saline can be an effective initial resuscitative solution. Hypertonic saline resuscitation results in a lower water load than equivalent resuscitation with balanced salt solutions. In view of the need for electrolyte monitoring and lack of definition of the volumes appropriate for infusion, long-term benefits have not been established.

Hetastarch Hydroxyethyl starch (hetastarch) is an artificial colloid derived from amylopectin that has colloidal properties similar to those of albumin. It is less expensive than albumin, and because of its larger molecular weight and need for enzymatic degradation, it has a longer plasma half-life than albumin. As with any colloidal solution, hetastarch restores intravascular volume at the further expense of the already compromised interstitial space when used in resuscitation during shock. Mild and transient coagulopathies have been noted in patients resuscitated with hetastarch.

Dextran Dextran, in 40- and 70-kD solutions, also has been used as a plasma expander. Although dextran has a shorter half-life than hetastarch, it also approximates the colloidal activity of albumin when given by intravenous infusion. Dextran use is associated with a greater risk of anaphylaxis than is hetastarch or albumin and has produced coagulation defects and immunoglobulin depression.

Blood Substitutes Stroma-free hemoglobin (SFH) has been used to provide oxygen-carrying capacity, but problems with the use of SFH for resuscitation remain. Perfluorochemical compounds have enhanced abilities to dissolve gases, particularly oxygen and carbon dioxide. Potential adverse effects include acute pulmonary edema, activation of complement and the coagulation cascade, acute respiratory failure, and depression of the reticuloendothelial system.

ADJUVANT THERAPY

Vasopressors Treatment with vasopressors during shock may elevate blood pressure but at the expense of further increased peripheral resistance and diminished tissue perfusion. Vasopressor therapy also may worsen the plasma volume deficit associated with hemorrhage, and the use of such agents in place of adequate fluid resuscitation is inadvisable.

Positioning Elevating both legs while maintaining the head, trunk, and arms in the supine position is the preferred position for the treatment of hypovolemic shock.

MAST Garment When applied to the extremities with modest pressures, the MAST garment functions well as a splint and may control some venous bleeding. When applied at high pressures, the resulting increase in total peripheral resistance may elevate the systemic pressure while decreasing cardiac output and peripheral perfusion. Additionally, inflation of the abdominal bolster may

compress the inferior vena cava, impairing venous return to the heart by further increasing the venous resistance. The MAST garment may be of value when used occasionally as specific treatment of bleeding pelvic fractures. Its use must not delay the immediate repletion of intravascular and extravascular volume or rapid transport of the injured patient.

Pulmonary Support Breathing high oxygen concentrations probably is of little value during a period of hypotension. Nevertheless, in the small but significant group of patients in hypovolemic shock in whom the oxygen saturation is not normal, the initial use of increased oxygen concentrations may be extremely important. This can occur in patients with preexisting defects, such as chronic obstructive pulmonary disease. Although oxygen is not administered routinely to patients in shock, if any doubt exists as to the adequacy of oxygenation of arterial blood, the initial administration of oxygen until the injuries to the patient have been diligently assessed is certainly justified.

Antibiotics The use of broad-spectrum antibiotics is advisable as a preventive measure in the severely injured patient. Cefoxitin 2 g IV has proved to be a safe and effective single agent in multiorgan abdominal injuries.

Analgesics Treatment of pain in the patient with hypovolemic shock is rarely a problem. However, if the causative injury produces severe pain, e.g., fracture, peritonitis, or injury to the chest wall, control of pain becomes mandatory. Small doses of narcotics should be given intravenously for the management of pain in patients with shock.

Steroids Steroid depletion with hypovolemic shock may occur in the elderly patient or in patients with specific adrenocortical diseases, such as incipient Addison's disease, postadrenalectomy patients, or patients who have had adrenal suppression with exogenous adrenocortical steroids. In these specific instances, the IV administration of hydrocortisone is desirable. In the trauma patient with hypovolemic shock, administration of adrenocorticoids is not indicated.

Monitoring Continuous bedside monitoring of circulatory efficacy, including assessment of the heart rate, arterial blood pressure, urinary output, and peripheral perfusion, remains the cornerstone for resuscitation. Adequate resuscitation is indicated when adequate cerebral function and urinary output are restored. In the patient

with multiple injuries, central venous pressure (CVP) monitoring is useful. The use of a balloon-tipped Swan-Ganz catheter allows measurement of pulmonary artery and pulmonary wedge pressures as well as thermodilution cardiac output determinations. Early use of the Swan-Ganz catheter rarely is necessary in the initial emergency department treatment for hemorrhagic shock.

Cardiogenic Shock

Cardiogenic shock occurs when the heart is unable to generate sufficient cardiac output to maintain adequate tissue perfusion. Cardiogenic shock is manifested by hypotension in the face of adequate intravascular volume.

Pathophysiology Myocardial failure may result from a variety of diseases, including valvular heart disease, cardiomyopathy, and direct myocardial contusion. Acute myocardial infarction is the most frequent cause of cardiogenic shock, which is often fatal when 40 percent of the left ventricular mass has been lost. Papillary muscle dysfunction, ischemic ventricular septal defects, massive left ventricular infarction, and arrhythmias are complications of acute myocardial infarction that may lead to cardiogenic shock.

The initial compensatory response to diminished myocardial contraction is tachycardia, in an attempt to maintain cardiac output, despite a decreased left ventricular ejection fraction, at the expense of increasing myocardial oxygen consumption. As the cardiac index falls below 2 L/min/m^2, hypotension produces reflex sympathetic vasoconstriction. An increase in afterload further impairs left ventricular function and increases myocardial work. The combination of increased myocardial oxygen demand, hypotension, and shortened diastole amplifies the mismatch between coronary arterial oxygen delivery and myocardial oxygen demand, extending the zone of infarction in the patient who does not receive prompt intervention.

Treatment Although the goal of medical management of cardiogenic shock has been to enhance ventricular performance and improve global perfusion, the traditional management with fluids and inotropic drugs continues to yield a mortality of 80–90 percent. Initial therapy includes optimizing ventricular preload by manipulating filling pressure, decreasing afterload in the patient with adequate systolic pressure, correcting arrhythmias, and improving contractility to sustain vital organ perfusion.

Monitoring and Volume Management Supplemental oxygen, pain relief and sedation, and continuous electrocardiographic (ECG)

monitoring should be initiated early. A Foley catheter is inserted for monitoring urine output. Cutaneous oximetry and automated arterial blood pressure cuff measurements can be used in place of an intraarterial catheter for continuous arterial pressure monitoring and blood gas determinations. Placement of a Swan-Ganz catheter for measurement of cardiac output and pulmonary artery wedge pressure is crucial to therapeutic decision-making in these critically ill patients. If any pulmonary complications evolve, early intubation and mechanical ventilation will decrease the myocardial oxygen demand as a consequence of the increased work of breathing.

Inotropic Agents The $beta_1$-adrenergic receptors of the myocardium respond to exogenous sympathomimetic drugs by increasing contractility and improving cardiac output. These effects are obtained at the cost of increasing myocardial oxygen demand in the setting of already compromised myocardial perfusion, but IV infusion of dopamine may promptly reverse life-threatening hypotension and restore mean arterial pressure to about 80 mmHg. The dopaminergic effects of splanchnic, coronary, and renal vasodilatation at low doses (2–5 μg/kg/min) are augmented by adrenergic-mediated increases in contractility and heart rate as dosages rise to 5–8 μg/kg/min. At higher doses, alpha-adrenergic receptor effects predominate, and central arterial pressure can increase while coronary artery constriction further decreases coronary blood flow. Dopamine also causes a variable increase in heart rate and can precipitate other arrhythmias, which underscores the need to titrate the lowest acceptable dose. Dobutamine, a synthetic catecholamine with predominantly inotropic effect, appears to be less arrhythmogenic and may redistribute cardiac output to the coronary circulation. Studies appear to favor dobutamine over dopamine for treating cardiogenic shock after cardiopulmonary bypass or myocardial infarction.

Vasodilator Agents Some patients with low cardiac output and high filling pressures have near-normal arterial blood pressure in the setting of profoundly decreased perfusion by clinical assessment. In these circumstances, systolic ventricular wall stress is high, and reducing afterload should increase cardiac output and decrease myocardial work. An agent such as sodium nitroprusside should be used with extreme caution in hypotensive patients because redistribution of an already depressed cardiac output away from the coronary and cerebral circulation can occur, and any decrease in systemic diastolic pressure would further depress coronary perfusion pressures.

Mechanical Support Despite significant associated morbidity, successful mechanical cardiac support will maintain organ perfu-

sion while decreasing myocardial oxygen demand by unloading the left ventricle and reducing myocardial work. The intraaortic balloon counterpulsation device has been used most widely. It can be inserted at the bedside and fulfills the criteria of elevating diastolic blood pressure, which increases pulmonary perfusion, while decreasing myocardial work, by increasing cardiac output distal to the ventricle.

Arrhythmias Rapid ventricular rates can depress cardiac output to shock levels. Cardiac output falls because stroke volume cannot be compensated for by the rapid heart rate. Digoxin is the drug of choice for atrial fibrillation or atrial flutter, but electrical cardioversion should be undertaken promptly for tachycardia that produces hypotension and hypoperfusion. Resistant sinus tachycardia, while well tolerated by the normal heart, may produce a low-flow state in the diseased heart. Verapamil has been useful in treating tachyarrhythmias of atrial origin, and propranolol slows sinus tachycardia. Beta blockade can further decrease cardiac output in this setting. Immediate nonsynchronized direct-current electric shock is mandatory treatment for ventricular fibrillation or ventricular flutter that has caused cardiogenic shock with loss of consciousness. In the patient with acute myocardial injury, premature ventricular complexes may lead to ventricular tachyarrhythmias. IV lidocaine usually is the initial treatment and also is given after cardioversion to prevent recurrent ventricular fibrillation. Bretylium tosylate has been useful in treating life-threatening ventricular tachyarrhythmias that are unresponsive to lidocaine or class Ia agents, such as procainamide.

Low cardiac output with ventricular rates less than 70 beats/min may occur in patients with impaired cardiac performance. Stroke volume cannot increase to compensate for the pathologic bradycardia. Electrical pacing of the heart at a rate of 80–100 beats/min can restore sufficient cardiac output whether the underlying mechanism is sinus bradycardia, atrial fibrillation with slow ventricular rate, or atrioventricular dissociation.

Neurogenic Shock

Neurogenic shock is the form of shock that occurs after serious interference with the balance of vasodilator and vasoconstrictor influences to the arterioles and venules. This is the shock that is seen with clinical syncope. Neurogenic shock often is observed with serious paralysis of vasomotor influences, as in high spinal anesthesia or injury to the spinal cord. The reflex interruption of nerve impulses also occurs with acute gastric dilatation.

The clinical picture of neurogenic shock is quite different from that classically seen in hypovolemic shock. While the blood

pressure may be extremely low, the pulse rate usually is slower than normal and is accompanied by dry, warm, and even flushed skin. Measurements made during neurogenic shock indicate a reduction in cardiac output, but this is accompanied by a decrease in resistance of arteriolar vessels and a decrease in venous tone. There appears to be a normovolemic state with a greatly increased reservoir capacity in the arterioles and venules, thereby inducing a decreased venous return to the right side of the heart and hence a reduction in cardiac output.

Treatment Treatment of neurogenic shock usually is obvious. Gastric dilatation can be treated rapidly with nasogastric suction. Shock due to high spinal anesthesia can be treated effectively with administration of fluids and a vasopressor such as ephedrine or phenylephrine (Neo-Synephrine). With the milder forms of neurogenic shock, such as fainting, simply removing the patient from the stimulus, relieving the pain, and elevating the legs is adequate therapy while the vasoconstrictor nerves regain the ability to maintain normal arteriolar and venous resistance. In uncomplicated neurogenic shock, central venous pressure should be slightly low, with a near-normal cardiac output. Fluid administration without vasopressors in this form of hypotension may produce a gradually rising arterial pressure and cardiac output without elevation of central venous pressure by gradually "filling" the expanded vascular pool. Slight volume overextension is much less deleterious than excessive vasopressor administration. Balance is best obtained by maintaining a normal central venous pressure that rises slightly with rapid fluid administration (ensuring adequate volume) and using a vasopressor such as phenylephrine judiciously to support arterial pressure.

Septic Shock

Although any agent capable of producing infection, including viruses, parasites, and fungi, may generate septic shock, the most frequent causative organisms in the antibiotic era are gram-negative bacteria and, occasionally, gram-positive bacteria. The initial infectious process appears to be only a stimulus for a series of host responses that may culminate in death, even in the absence of infection at the time of death. Overall mortality exceeds 30 percent, with mortalities over 80 percent in complicated cases with associated multiple organ system failure.

The most common source of gram-negative infection is the genitourinary system. The second most frequent site of origin is the respiratory system, followed by the alimentary system, including

the biliary tract. Increasing and prolonged use of indwelling catheters for monitoring and hyperalimentation is responsible for many bloodstream infections.

Clinical Manifestations Gram-negative infections frequently are heralded by the onset of chills and temperature elevations above 38°C. The patient may rapidly progress to evidence of altered organ function, most often renal and pulmonary in nature. Unlike most other forms of shock, the patient who is normovolemic has hypotension despite an increased cardiac output and a reasonable filling pressure. The peripheral resistance is low and produces the paradoxical "warm shock" with pink, dry extremities. The high cardiac output often is associated with a decrease in oxygen use and a narrowed arteriovenous oxygen difference.

In a patient who is initially hypovolemic or persists in the shock state, a hypodynamic pattern emerges that is characterized by a falling cardiac output, low central pressures, and increased peripheral resistance with more typical cold, pale extremities consistent with global hypoperfusion. Early volume replacement frequently increases cardiac output and produces a hyperdynamic circulation, while the patient later in shock is unresponsive to volume replacement and has a low cardiac output with increasing metabolic acidosis.

Concomitant laboratory tests usually show an elevation in the white blood cell count, but leukopenia may be present in immunosuppressed and debilitated patients or those with overwhelming white cell consumption from sepsis. Thrombocytopenia may be an early indicator of gram-negative sepsis, particularly in pediatric and burn patients. Mild hypoxia with compensatory hyperventilation and respiratory alkalosis are common early findings, despite clinical or radiologic evidence of intrinsic pulmonary disease.

Pathophysiology At the organ level, cardiovascular response to systemic infection, in the absence of hypovolemia, is the development of a hyperdynamic state. A number of vasoregulatory mediators combine to produce a net decrease in systemic vascular resistance. Despite an increased cardiac index and decreased oxygen extraction, no direct evidence for cellular hypoxia has been detected. Myocardial depressant factor, although poorly characterized biochemically, appears to be a reasonable explanation for documented decreases in left ventricular ejection fraction despite acceptable filling pressures.

Interleukin-1 (IL-1) is an endogenous mediator of infection. Cellular dysfunction accompanying acute hemorrhagic shock is associated with a reduction in the transcellular membrane potential. Tumor necrosis factor-alpha (TNF-α) is capable of inducing

membrane depolarization and decreasing skeletal muscle membrane potential and extremity lactate efflux, similar to that seen in sepsis. TNF-α is an important mediator of septic shock.

TNF-α induces the synthesis and secretion of a variety of secondary mediators, including other cytokines, prostaglandins, leukotrienes, platelet-activating factor, complement components, and activation of the clotting cascade, that possess toxic properties capable of causing widespread tissue damage if liberated systemically. In addition, lipopolysaccharide (LPS) may synergize with TNF-α to induce many of the toxic effects mediated by TNF-α. The TNF-α–induced release of these factors may be responsible for pathologic changes seen in the lungs, liver, bowel, and kidneys in response to sepsis and septic shock.

Therapy The control of infection by antibiotic treatment and early surgical debridement or radiologically guided drainage represent definitive therapy. Other recommended measures include fluid therapy and the use of vasoactive drugs. It is essential that a prompt search for the source of infection be made as soon as infection becomes evident. If the infectious process requires drainage, operation should be performed as soon as possible after the patient has been stabilized, because some conditions, such as septic shock secondary to ascending cholangitis, will respond only briefly to adjunctive measures.

Antibiotic treatment should be based on the results of cultures and sensitivity tests when possible, but in the absence of these data, broad-spectrum antibiotics should be started, including coverage for anaerobic organisms such as *Bacteroides* species or fungi, if clinically indicated. Antibiotic therapy should be adjusted when culture and sensitivity reports become available.

Correction of preexisting fluid deficits is essential using pulmonary capillary wedge pressure and cardiac output as a guide. Monitoring is essential, because fluid requirements may be massive in these patients. Resuscitation requirements in excess of 10 L of lactated Ringer's solution are common. The only indications for steroid treatment in patients with septic shock are hypoadrenalism and for stress coverage in patients taking steroids (or who recently completed a course of steroids) for immunosuppression or anti-inflammatory purposes.

Future clinical use of anti-TNF antibodies, protein C, or other antimediator treatment regimens probably will depend on early recognition of the sepsis syndrome for success unless used prophylactically in a population of patients at high risk.

Pharmacologic Support Dopamine is the initial inotropic agent used. Dobutamine often increases cardiac input with less tachycardia and arrhythmia than dopamine. The use of vasodilators in septic shock is limited by low systemic pressure or decreased cardiac filling pressures. More potent vasopressors, despite their obvious detrimental effect on peripheral perfusion, may be transiently unavoidable in patients who have persistent life-threatening hypotension despite optimal fluid and dopamine infusions. Norepinephrine is a potent alpha-receptor agonist that usually is effective in raising pressure in patients for whom the measures described earlier have failed. Epinephrine, a catecholamine with potent alpha- and beta-adrenergic activity, may support the blood pressure in patients who do not respond to norepinephrine.

Manipulations of Humoral Responses Given the obviously complex and ill-defined interactions among a large number of mediators, therapy directed at any single agent is probably ineffective. Carefully tailored multidrug or serial antimediator therapy eventually may allow modulation of the deleterious systemic effects of the necessary host responses to injury and infection. Initial trials of steroids, fibronectin, and naloxone were disappointing. Treatment with HA-1A improved survival and organ function in the presence of gram-negative bacteremia with or without shock. The E5 trial was beneficial in patients with gram-negative bacteremia only in the absence of shock. None of the antibodies directed at lipid A or other epitopes of the core lipopolysaccharide are established therapeutic modalities.

The naturally occurring IL-1 receptor antagonist has been manufactured by recombinant technology. IL-1ra failed to show efficacy in human sepsis. Monoclonal antibodies to TNF also are available and appear promising in patients with septic shock. The use of anticoagulants such as anti–thrombin III in the treatment of sepsis that is unassociated with shock is under investigation.

For a more detailed discussion, see Barber A, Shires GT III, and Shires GT: Shock, chap. 4 in *Principles of Surgery,* 7th ed.

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CHAPTER

5

SURGICAL INFECTIONS

GENERAL CONSIDERATIONS

Surgical infections can be defined conveniently as infections that require operative treatment or result from operative treatment. Infections that require operative treatment include (1) necrotizing soft tissue infections, (2) body cavity infections such as peritonitis, suppurative pericarditis, and empyema, (3) confined tissue, organ, or joint infections such as abscess and septic arthritis, and (4) prosthetic device–associated infections. With the possibility of patient-to-surgeon and surgeon-to-patient spread of viral infections such as from the human immunodeficiency virus (HIV) and hepatitis viruses, infections in health care workers also have become of interest to surgeons.

Infections that result from operative treatments include wound infections, postoperative abscesses, postoperative (tertiary) peritonitis, other postoperative body cavity infections, prosthetic device–related infections, and other hospital-acquired infections, among which are pneumonias, urinary tract infections, and vascular catheter–related infections. Immunocompromised patients are subject to viral and fungal infections that seldom cause infection in the normal host.

Principles of Therapy

The patient's own host defenses and antibiotic therapy are adequate to overcome most infections. Nonoperative treatments can assist recovery from some infections. Chest physiotherapy is useful in patients with pneumonia, especially those with thickened secretions. Increasing fluid intake and thus increasing urine flow is helpful in patients with urinary tract infections. Immobilization and elevation can relieve pain and reduce the swelling of an extremity afflicted with cellulitis or lymphangitis.

Operative treatment generally is required when host defenses cannot function properly or when there is continuing contamination with microorganisms: Infected fluid collections must be drained,

infected necrotic tissue must be debrided, and infected foreign bodies must be removed. Infected fluid collections such as abscesses must be drained because phagocytic cells cannot function properly with the metabolic conditions usually present. Antibiotics are not very effective against bacteria in abscesses because they penetrate abscesses poorly and because antibiotics work best on actively dividing bacteria—and most bacteria in abscesses are not actively dividing. Drainage also is salutary because necrotic tissue and foreign bodies inhibit the proper functioning of host defenses.

Defects in the gastrointestinal (GI) tract provide a continuing source of bacteria that rapidly overwhelms host defenses. Operation is required to end this source by closing the defect in the GI tract or by bringing the defect to the outside as an ileostomy or colostomy.

Determinants of Infection

The development of surgical infection depends on several factors: (1) microbial pathogenicity and number, (2) host defenses, (3) the local environment, and (4) surgical technique (for postoperative infections).

Microbial Pathogenicity The ability of a microbe to cause infection is a balance between host defenses and microbial pathogenicity. Some microbes that have no ability to cause infection in the normal host can cause lethal infection in an individual with compromised host defenses.

Many bacteria (*Streptococcus pneumoniae, Klebsiella pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Salmonella typhi*) and fungi (*Histoplasma capsulatum, Candida albicans, Cryptococcus neoformans*) have thick capsules that make them resistant to phagocytosis (see Surgical Microbiology, below). Other microbes (*Mycobacterium tuberculosis, Aspergillus flavus, Toxoplasma gondii*) resist intracellular killing after they have been phagocytosed when lysosomes that contain enzymes that digest microbes do not fuse with the phagosome. Other microbes successfully resist digestion by lysosomal enzymes.

Some bacteria can elaborate toxins, many of which are enzymes that injure or kill cells or promote spread within tissues. Exotoxins play an important role in the pathogenicity of *Clostridium* species, *Staph. aureus,* and *Strep. pyogenes.* Other bacteria (*Clostridium tetani, C. botulinum*) elaborate neurotoxins that alter normal neural transmission.

Endotoxins are lipopolysaccharide-protein complexes that are normal constituents of the cell wall of gram-negative bacteria. These molecules activate many biologic pathways, including the

complement and coagulation systems, and cause release of cytokines and other biologic mediators from macrophages, release of hormones, and alterations in metabolism.

Host Defenses Local host defenses are important in preventing microbial penetration into the tissues. Systemic host defenses are needed to rid the tissues of microbes once penetration has occurred.

Local Host Defenses Tissues are protected from microbial invasion by a layer of epithelium. The epithelium of the skin, nasopharynx, oral cavity, esophagus, and genitourinary tract are multilayered. At other sites (the tracheobronchial tree, GI tract, and eye), a single layer of epithelium protects the underlying tissues. Each site also provides a local environment that is not conducive to microbial attachment and growth. Among these local environmental features may be lack of moisture (skin), the flushing action of tears and urine, cilia (trachea, bronchi), peristalsis, mucus, pH (GI tract), and local immunity (IgA).

Systemic Host Defenses Host defenses consist of phagocytic cells, the immune system, and other molecular cascades such as the complement system, the coagulation system, and the kinin system. Phagocytic cells that can ingest and kill microbes include polymorphonuclear leukocytes (PMNs) and tissue macrophages (monocytes in the blood). Through a complex set of interactions of microbes with complement and other activation molecules, PMNs adhere to vascular endothelium, migrate across the endothelium and move in the direction of the microbes (chemotaxis), attach to the microbes (which may involve immunoglobulins or other opsonins), and phagocytose the microbes. Finally, lysosomes containing a variety of enzymes fuse with the phagosome, and the microbe is rapidly digested. The initiation of this process and its attendant chemical, cellular, and physiologic changes result in inflammation.

Macrophages are phagocytic cells found throughout the body tissues: in liver (Küpffer cells), spleen, lymphoid tissue, lung (alveolar microphages), brain (glial cells), connective tissue (histiocytes), and pleura and peritoneum. Macrophages also can move toward microbes in response to chemotactic agents and phagocytose and kill them. In addition, macrophages are important in initiating the immune response and can elaborate cytokines, tissue necrosis factor, interferon, and other biologically active molecules. Humoral and cellular immunity are important systemic host defense mechanisms for many microbial agents. The complement system, clotting system, kinin system, leukotrienes, cytokines, and

other biologically active molecules also are activated by microbial agents and have an important role in host defenses.

Host defenses are altered in malnourished individuals, trauma patients, postoperative patients, burn patients, patients with malignant neoplasms, and patients receiving drugs such as cancer chemotherapeutic agents, immunosuppressive agents to prevent transplant rejection, steroids, or other agents that have immunosuppressive effects.

Local Environmental Factors Some environmental factors inhibit systemic host defenses from being fully effective. A traumatic wound that normally would heal without infection has a greatly increased likelihood of becoming infected if the trauma has resulted in devitalization of tissue or if foreign bodies have been deposited in the wound. Phagocytic cells do not function effectively in the presence of devitalized tissue or foreign bodies. A suture can reduce the number of *Staph. aureus* required to produce a subcutaneous infection. Fluid collections and edema also increase the likelihood of infection because they inhibit phagocytosis.

Peripheral vascular disease and shock contribute to soft tissue infection by preventing blood and the systemic host defenses that it contains from reaching the site of microbial contamination. Vascular disease and shock, by lowering tissue oxygen tension (PO_2), inhibit the function of phagocytic cells and promote the growth of anaerobes.

Surgical Technique Surgeons can decrease the likelihood of postoperative infection by handling tissues gently; removing devitalized tissues, blood, and other substances that promote the growth of microbes; and using drains appropriately (and avoiding inappropriate use).

TYPES OF SURGICAL INFECTIONS

Soft Tissue Infections

Infection of the soft tissues—skin, subcutaneous fat, fascia, and muscle—usually can be treated by antibiotics unless an abscess has formed or tissue necrosis has developed.

CELLULITIS AND LYMPHANGITIS

Cellulitis is a spreading infection of the skin and subcutaneous tissues. There may or may not be evidence of injury to the skin. It is characterized by local pain and tenderness, edema, and erythema. The border between infected and uninvolved skin usually is indis-

tinct. *Erysipelas*, which is caused by *Strep. pyogenes*, is characterized by intense erythema with a sharp line of demarcation between involved and uninvolved skin. Cellulitis may be accompanied by systemic manifestations such as fever, chills, malaise, and toxic reaction.

Cellulitis can be caused by numerous bacteria in addition to *Strep. pyogenes*, such as *Staph. aureus*, *Strep. pneumoniae*, other streptococci, *Hemophilus influenzae*, and aerobic and anaerobic gram-negative bacteria. *Lymphangitis*, inflammation of the lymphatic channels in the subcutaneous tissues, presents as visible red streaks. Bacteria may reach the lymph nodes and cause lymphadenitis.

Cellulitis and lymphangitis can be treated by antibiotics alone, but surgery may be needed to treat the source. Treatment includes immobilization and elevation to reduce pain and swelling.

SOFT TISSUE ABSCESS

Surgical treatment usually is required when soft tissue infection results in abscess or tissue necrosis. Furuncles and carbuncles (boils), breast abscesses, and perirectal abscesses require surgical incision and drainage and usually antibiotic therapy. A *carbuncle* is a subcutaneous abscess usually formed by a confluent infection of multiple contiguous hair follicles. A *felon* is a purulent collection in the distal phalanx of the fingers that causes intense pain and pressure in that compartment. Swelling may be minimal because of the fibrous bands between the skin and bone. Treatment requires incision and drainage. A lateral incision is used to avoid a painful scar on the fingertip. Breast abscess usually is caused by *Staph. aureus* but can be a result of gram-negative bacteria as well. It frequently occurs in nursing mothers. Treatment consists of incision and drainage and antibiotics. Perirectal abscess begins as an infection of one of the crypt glands that then extends into the perirectal space and may present subcutaneously near the anus. It is caused by aerobic and anaerobic gram-negative bacteria that are normal residents of the colon. Incision and drainage and antibiotic therapy are the appropriate initial treatment. Up to 50 percent of perirectal abscesses may result in a fistula communicating with the anal crypt and may require later treatment.

NECROTIZING SOFT TISSUE INFECTIONS

Soft tissue infections that cause necrosis are more serious because of their propensity for extensive tissue destruction and high mortality rates. Terms such as *necrotizing fasciitis, streptococcal gangrene, gas gangrene, bacterial synergistic gangrene, clostridial myonecrosis*, and *Fournier's gangrene* are used commonly. Necrotizing

fasciitis rarely is limited to fascia, and myonecrosis frequently is not limited to muscle.

Most necrotizing soft tissue infections are caused by mixed aerobic and anaerobic gram-negative and gram-positive bacteria. *Clostridium* species, of which *C. perfringens*, *C. novyi*, and *C. septicum* are the most common, cause infections with rapid progression, early toxic conditions, and high mortality rates. The term *gas gangrene* has become synonymous with clostridial infection. However, the presence of gas in tissue simply means that anaerobic bacterial metabolism has produced insoluble gases such as hydrogen, nitrogen, and methane. Both facultative and obligate anaerobes are capable of such metabolic activity. Aerobic bacteria also can produce gas.

Diagnosis is not difficult when skin necrosis or bullae are present, but occasionally the clinical findings are subtle until extensive necrosis has occurred. The presence of cutaneous necrosis, bullae, or crepitus strongly suggests a necrotizing infection, and surgical exploration is warranted.

Surgical treatment requires debridement of all necrotic tissue. Amputation may be required for myonecrosis of the extremities. The wound must be inspected daily until the surgeon can be sure that there is no further necrosis. The goal of treatment is to remove all necrotic tissue. Initially, broad-spectrum antibiotics including penicillin should be administered. A Gram stain of the tissue and fluid should be done to look for gram-positive rods (*Clostridium* species) or cocci (*Streptococcus* species). The use of hyperbaric oxygen to treat necrotizing soft tissue infections is controversial.

TETANUS

Tetanus is caused by *Clostridium tetani*, a large gram-positive spore-forming bacillus. Currently, there are approximately 50 cases of tetanus reported per year. *C. tetani* usually is acquired by implantation of the organisms into tissues by means of breaks in the mucosal or skin barriers. Tetanus can appear after surgical wounds, injections, and in patients who have no apparent injury at all. Organisms have virtually no capacity for causing an invasive infection. Clinical tetanus is as much an intoxication as an infection.

The median incubation period for both fatal and nonfatal cases of tetanus is 7–8 days. Tetanus usually appears in generalized form but occasionally appears as localized tetanus with increased muscle tone and spasms confined to muscles near the wound and without systemic signs.

Some patients have symptoms of restlessness, headache, or a stiff neck. In other patients the first symptoms are muscle spasms with vague discomfort in the neck, lumbar region, and jaws. Spasm

of the pharyngeal muscles makes swallowing difficult. Progressively, other muscle groups become involved until the spasms become generalized. Generalized convulsions are frequent, exhausting, and unpredictable. Any slight external stimulus and internal stimuli (e.g., cough, swallow, or distended bladder) may trigger generalized convulsions. These convulsions may involve the laryngeal and respiratory muscles and result in fatal acute asphyxia. Throughout these spasms the patient remains mentally alert. The pulse is elevated, and there is profuse perspiration. Fever may or may not be present. Diagnosis of tetanus is based on the clinical picture associated with no prior history of immunization. Even with adequate treatment, the mortality rate can exceed 50 percent.

Initially therapy consists of administration of tetanus immune globulin (TIG) 500–10,000 units as soon as the diagnosis is made. Nursing care must be provided constantly in an intensive care unit setting. Patients may require tracheostomy if they need a respirator for a prolonged period. Pulmonary emboli can be a problem in patients who have minimal movement. Cardiac exhaustion and circulatory disruption can occur from sympathetic overstimulation. Hyperbaric oxygen treatment is not recommended because it is ineffective.

The wound must be treated to remove as much of the *C. tetani* and nonviable tissue as possible. Debridement of all necrotic tissue should be done. Penicillin G should be administered.

Active immunization with tetanus toxoid is a safe and effective way of preventing tetanus (Table 5-1). One month after the diagnosis of tetanus is made, tetanus toxoid immunization should be begun. The amount of tetanus toxin released during an infection is so small that the patient does not make antibody.

Body Cavity Infections

PERITONITIS AND INTRAABDOMINAL ABSCESS

Primary peritonitis is caused by a single organism and occurs most commonly in young children and in adults with ascites or with renal failure that is being treated by peritoneal dialysis. Primary peritonitis can be treated with antibiotics and other medical measures.

Secondary bacterial peritonitis usually is the result of a defect in the GI tract and requires operative intervention. The goals of surgery are to control the source of contamination, to remove bacteria and adjuvant materials from the peritoneal cavity, and to prevent postoperative abscess or recurrent peritonitis. Antibiotics effective against aerobic and anaerobic enteric bacteria have an important role in treating patients with secondary bacterial peritonitis but should not replace operative intervention. Peritonitis

TABLE 5-1
SUMMARY OF IMMUNIZATION PRACTICES ADVISORY COMMITTEE RECOMMENDATIONS FOR TETANUS PROPHYLAXIS IN ROUTINE WOUND MANAGEMENT

	Clean Minor Wounds		All Other Wounds[a]	
History of Adsorbed Tetanus Toxoid (Doses)	Td[b]	TIG	Td[b]	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
≥3 doses[c]	No[d]	No	No[e]	No

[a]Such as, but not limited to, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, or frostbite.

[b]For children < 7 years of age, diphtheria, pertussis, and tetanus (DPT) immunization is used [or diptheria and tetanus (DT) if pertussis vaccine is contraindicated]. For persons ≥ 7 years of age, Td is preferred to tetanus toxoid alone. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) may be used instead of DTP for the fourth and fifth doses.

[c]If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given. (More frequent boosters are not needed and can accentuate side effects.)

[d]Yes, if > 10 years since last dose.

[e]Yes, if > 5 years since last dose.

Td = tetanus-diphtheria toxoid (adult).

TIG = tetanus immune globulin.

SOURCE: Reproduced from Centers for Disease Control: Tetanus Surveillance—United States, 1989 and 1990. *MMWR* 41(SS-8):1, 1992.

occurring (or persisting) after initial operation for secondary peritonitis is persistent peritonitis. Tertiary peritonitis is a peritonitis-like syndrome occurring late as a result of a disturbance in the host's immune response and is characterized by peritonitis without evidence of pathogens or peritonitis caused by fungi or low-grade pathogenic bacteria. Percutaneous or operative drainage along with antibiotic therapy is necessary for the treatment of intraabdominal abscesses.

EMPYEMA

Empyema usually is a result of pneumonia. Other causes include pulmonary infarction, septic emboli to the lung, tracheal or bronchial fistula, leaking esophageal anastomosis, hepatic abscess, subphrenic abscess, trauma, leaking bronchial closure, infected hemothorax, and paravertebral abscess.

Empyema may be encapsulated and localized or may involve the entire pleural cavity. Initially the fluid in the chest is thin, but with increasing numbers of PMNs and fibrin deposition, the fluid becomes thicker, and the visceral peritoneum and parietal peritoneum adhere to each other. The clinical manifestations of empyema initially resemble those of pneumonia, with pleuritic chest pain and fever. Chronic empyema can be manifested by dyspnea, fatigue, anemia, debility, and clubbing of the fingers.

Treatment of empyema is aimed at evacuation of the empyema contents and expansion of the lung. Most empyemas can be treated by tube thoracostomy, especially in early empyema when the fluid is thin, and antibiotic therapy. The tube may be converted to open drainage after 2–3 weeks when the visceral and parietal pleura have become adherent so that the lung does not collapse. Open drainage should be used if there are multiple pus pockets, if the pus is very thick, or if the empyema is inadequately drained by tube thoracostomy. In some cases a decortication procedure may be necessary to reexpand the lung, or if a bronchopleural fistula is present, a thoracoplasty may be required.

OTHER CLOSED-SPACED INFECTIONS

Purulence in closed spaces usually requires drainage and tetanus toxoid immunization and antibiotic therapy. Antibiotic therapy alone may be sufficient to treat early septic arthritis. If the diagnosis is delayed, surgical treatment is required to preserve joint function and to eradicate the infection.

Antibiotic therapy alone may be sufficient to treat some early cases of pericarditis, but operative therapy is usually required once suppuration has occurred.

PROSTHETIC DEVICE–ASSOCIATED INFECTIONS

Infections in prosthetic devices, such as cardiac valves, pacemakers, vascular grafts, and artificial joints, are associated with great morbidity. Although intensive antibiotic therapy alone occasionally can cure the infection, frequently it can be eradicated only by complete removal of all foreign material and antibiotic therapy. Vascular grafts have been salvaged occasionally without graft removal by treatment with debridement, povidone-iodine–soaked dressings, and antibiotic therapy when the suture line has not been infected.

Infected prosthetic joints and pacemakers have been salvaged occasionally by antibiotic irrigation of the joint or pacemaker.

HOSPITAL-ACQUIRED (NOSOCOMIAL) INFECTIONS

Each year in the United States there are an estimated 2 million hospital-acquired infections that result in 150,000 deaths. Hospital-acquired infections add an average of 1.5 days to the hospital stay of patients who develop lymphangitis, 14.8 days for patients with septicemia, and 16.6 days for patients who have infections at multiple sites. Infection rates were greatest on the surgical service, at 44.3 per 1000 discharges. On surgical services, urinary tract infections are most common, followed by wound infections, lower respiratory infections, bacteremia, and cutaneous infections. Vascular catheter–related infections are frequently classified under bacteremia or cutaneous infections.

WOUND INFECTIONS

Classification Wounds have been classified into four categories according to the theoretical number of bacteria that contaminate wounds: clean, clean-contaminated, contaminated, and dirty. Wound infection rates in large series are approximately 1.5–3.9 percent for clean wounds, 3.0–4.0 percent for clean-contaminated wounds, and approximately 8.5 percent for contaminated wounds. Dirty wounds generally are left open, but wound infection rates for dirty wounds of 28 and 40 percent have been reported. Wound infections encompass infections of the wound that occur above the fascia (superficial wound infections) and those which occur below the fascia (deep wound infections).

Definition of Surgical Wound Infection An incisional (superficial) wound infection occurs at an incision site within 30 days after operation and involves skin or subcutaneous tissue above the fascial layer and any of the following:

1. There is purulent drainage from the incision or a drain located above the fascial layer.
2. An organism is isolated from culture of fluid that has been aseptically obtained from a wound that was closed primarily.
3. The wound is opened deliberately by the surgeon, unless the wound is culture-negative.

Deep surgical wound infection occurs at the operative site within 30 days after operation if no prosthesis was permanently placed and within 1 year if an implant was placed, and infection in-

volves tissues or spaces at or beneath the fascial layer and any of the following:

1. The wound spontaneously dehisces or is deliberately opened by the surgeon when the patient has a fever (>38°C) and/or there is localized pain or tenderness, unless the wound is culture-negative.
2. An abscess or other evidence of infection directly under the incision is seen on direct examination, during operation, or by histopathologic examination.
3. The surgeon diagnoses infection.

Bacteria can gain entrance to the wound from endogenous or exogenous sources. Most infections in clean-contaminated and contaminated wounds and also in the majority of clean wounds are caused by endogenous bacteria present on the skin or mucosal surfaces.

PROPHYLAXIS

Operating Room Environment Air-handling systems are designed to reduce the number of airborne microbes. Special laminar flow systems with high-efficiency particulate air (HEPA) filters frequently are used when prosthetic joints are implanted to reduce the likelihood of airborne contamination.

Instruments and Drapes If drapes become wet, bacteria can move from underneath the drapes to the surgical field by capillary movement. Disposable drapes with plastic liners and cloth drapes with tighter weaves are designed to minimize this type of bacterial contamination. Adhesive plastic drapes do not lower the incidence of wound infection.

Hand Washing Hand washing with soap and an antiseptic agent reduces the number of microbes on the skin. Although tradition calls for scrubbing for 10 min and using two brushes, washing for 5 min and using one brush accomplishes equal reduction in skin bacterial counts. Hexachlorophene, povidone-iodine, and chlorhexidine are the antiseptics most commonly used for hand washing.

Gloves Thirty percent of gloves have defects in them by the end of the operation. Surgeons are potentially exposed to infectious agents harbored by their patients when blood enters through these holes and gets onto their skin. Some advocate wearing two pairs of gloves to reduce the likelihood of exposure to patient's blood.

Other Barriers Caps prevent hair and skin scales (and adherent bacteria) from falling into the patient's wound, masks prevent droplets produced during speaking or coughing from entering the patient's wound, and gowns prevent desquamated skin and other particles from entering the patient's wound. There are no data that demonstrate unequivocally that wearing these barriers lowers the wound infection rate.

Preoperative Stay Patients who have longer preoperative hospitalizations are more likely to develop postoperative wound infections.

Preoperative Shower Cruse reported that the infection rate was 1.3 percent for patients who took a preoperative shower with soap containing hexachlorophene, 2.1 percent for those who took a shower with ordinary soap, and 2.3 percent for those who did not shower. However, another study of 5536 patients found no reduction in wound infection rates in patients who had a preoperative shower with 4% chlorhexidine detergent.

Remote Infections Remote infections can triple the rate of wound infection. Elective operations generally should be delayed until the infection has been eliminated. Elective operations should be delayed until the dermatitis is treated, especially if the skin incision is near or through such regions.

Hair Removal Nicks and cuts caused by shaving are sites where bacteria can proliferate.When shaving is done the night before operation, there is ample time for bacterial proliferation in any nicks or cuts, and the wound infection rate is higher than when shaving is done in the operating room immediately before operation. When hair is removed by clipping with an electric clipper, the wound infection rate can be reduced further.

Skin Preparation Painting the operation site with an alcohol solution of povidone-iodine, which can be accomplished in less than 1 min, is as effective as a 5-min scrub with povidone-iodine followed by painting with povidone-iodine solution.

Reduction of Colonic Bacteria Colon procedures potentially expose the wound to numerous bacteria. Colonic bacteria can be greatly reduced by cleansing the colon of feces. A variety of enemas or cathartics such as magnesium citrate solution or electrolyte solutions in polyethylene glycol can be used. These agents should be used before all elective colon surgery. Oral antibiotics can fur-

ther reduce the number of colonic bacteria. A combination of neomycin and erythromycin base is used most commonly, but other antibiotics also are effective.

Improving Host Defenses Any malnutrition should be corrected to restore the patient's resistance to infection toward normal. Weight reduction lowers the risk of wound infection and pulmonary complications. Uremia and diabetes should be corrected as far as possible. Patients who smoke should cease smoking before the operation.

Surgical Technique The incision should be made in such a way to injure as little tissue as possible and to prevent the accumulation of agents that facilitate bacterial growth or inhibit host defense such as devitalized tissue, foreign bodies, blood, and serum. Blood in the incision provides a good environment for bacterial growth.

There is no solid evidence that local antibiotics lessen the likelihood of infection. There are no definitive studies that provide data on whether subcutaneous sutures affect the risk of wound infection. If the surgeon is concerned about the possibility of a wound seroma such as might occur in the subcutaneous tissue of an extremely obese patient, a closed-suction drain should be used. Latex rubber (Penrose) drains should not be used because bacteria can enter the wound through the drain tract. All devitalized tissue and foreign bodies should be removed from traumatic wounds. Irrigation with saline solution can facilitate the removal of small particles. When complete removal of devitalized tissue and foreign bodies cannot be ensured, or when the wound is heavily contaminated with bacteria, it can be left open and closed secondarily.

Prophylactic Antibiotics Prophylactic antibiotic therapy should be directed against the bacteria likely to contaminate the wound. For clean operations for which antibiotic prophylaxis is appropriate, *Staph. aureus, Staph. epidermidis*, and gram-negative enteric bacteria are the most likely bacteria to cause wound infections. Gram-negative enteric bacteria are the most likely causes of wound infection after gastroduodenal and biliary tract procedures, colorectal surgery, appendectomy, and gynecologic surgery.

The antibiotics usually should be given intravenously 30–60 min before operation so that adequate blood and tissue levels are present at the time that the skin incision is made. The antibiotic dose should be repeated if the operation lasts longer than 4 h or twice the half-life of the antibiotic or if blood loss has been great. With many operations now being performed on patients who are not in a hospital before surgery, oral antibiotic prophylaxis also

may be suitable. Prophylactic antibiotics should not be continued beyond the day of operation. The most commonly violated principle is giving the antibiotic longer than is actually needed, which increases costs and the likelihood of antibiotic resistance among hospital strains of bacteria.

Cephalosporins are the most commonly used antibiotics for prophylaxis because of their broad antibacterial spectrum, which provides activity against gram-positive pyogenic cocci and gram-negative enteric bacteria, and because of their low toxicity. Cefazolin, a first-generation cephalosporin, is an effective antibiotic prophylaxis for indicated clean gastroduodenal, biliary tract, and head and neck operations and traumatic wounds. Vancomycin can be substituted in patients who are allergic to penicillins or cephalosporins. For colorectal procedures, oral neomycin plus erythromycin base and/or cefoxitin or cefotetan provides effective coverage. First- or second-generation cephalosporins provide effective prophylaxis for gynecologic surgery and cesarean section.

Indications Prophylactic antibiotics are indicated when bacterial contamination of the wound is likely or for patients having clean operations in which a prosthetic device is placed. Studies indicate that prophylactic antibiotics can lower the incidence of all infectious complications in clean surgery (hernia and breast surgery), but the incidence of wound infection is not reduced. The bacteria in the stomach are increased in patients who have gastric outlet obstruction, decreased gastric acidity (achlorhydria, antacid or H_2-receptor blocker therapy), or gastric cancer, and prophylactic antibiotics are indicated for these patients. Jaundice, bile duct obstruction, stones in the common bile duct, reoperative biliary tract operation, acute cholecystitis, and age greater than 70 years also are indications for prophylaxis in biliary tract operations.

OTHER HOSPITAL-ACQUIRED INFECTIONS

Urinary Tract Infection Urinary tract infection (UTI) accounts for 40 percent of hospital-acquired infections. Two-thirds of patients with hospital-acquired UTI have had an operation on the lower urinary tract, instrumentation of the bladder, or catheterization. Catheter-associated UTIs cause bacteremia in 2–4 percent of patients and are associated with a case-fatality rate three times as high as that of nonbacteremic patients. Bacteriuria occurs in 1–5 percent of patients after a single short-term catheterization. The risk of infection is higher in pregnant patients, in elderly or debilitated patients, and in patients with urologic abnormalities. The risk of bacteriuria in patients with long-term indwelling catheters is ap-

proximately 5–10 percent for each day the catheter is in place. Urinary catheters should be placed only when necessary and should be removed as soon as possible. If prolonged urinary tract catheterization is required, suprapubic or condom catheters can be used to reduce the risk of infection.

Lower Respiratory Tract Infection Anesthesia, operations on the head and neck, and postoperative endotracheal intubation interfere with the normal protective cough reflex and may permit aspiration of contaminated material. Pain associated with thoracic or upper abdominal operations and trauma interferes with coughing and deep breathing and promotes the collection of material in the tracheobronchial tree and atelectasis, which in turn predispose to infection. Pulmonary edema or adult respiratory distress syndrome resulting from cardiac failure, trauma, sepsis, renal failure, or inhalation of hot gases by burn patients also predisposes to pulmonary infection.

Hospitalized patients may have gram-negative bacteria as part of their oral flora. These bacteria may be aspirated into the lungs during the postoperative period. Tracheostomies and respiratory care devices also predispose to the entry of bacteria into the lower respiratory tract. Lower respiratory tract infections are common in intubated patients in intensive care units, occurring in as many as 20–25 percent of patients.

The most common causative organisms of lower respiratory tract infection in hospitalized patients are *Staph. aureus*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Escherichia coli*, and *Enterobacter* species. These bacteria, especially in the intensive care unit setting, may be resistant to commonly used antibiotics. Specially protected specimen swabs can be introduced into the lungs through a flexible bronchoscope, with sensitivity rates for diagnosing the pneumonia between 70 and 90 percent. Bronchoalveolar lavage has increased the accuracy of bronchoscopic diagnosis.

Vascular Catheter–Related Infection Central venous catheters have a higher infection rate than peripheral venous catheters, and polyethylene catheters have a higher infection rate than Silastic catheters. The most common source of catheter sepsis is believed to be microorganisms at the skin exit site that follow the catheter into the vein rather than microorganisms originating from a distant site that colonize the catheter via the bloodstream. *Staph. aureus* and *Staph. epidermidis* usually originate from the skin and cause most catheter-related infections. Most yeast vascular-access infections result from hematogenous dissemination from another site.

Gram-negative enteric bacteria also may infect catheters hematogenously.

The duration of catheterization, the number of catheter manipulations, inexperience of the inserter, violations of aseptic technique, and use of multilumen catheters are all associated with an increased risk of infection. There are no data proving that practices such as changing catheters at intervals, changing infusion tubing every 24–48 h, and using in-line filters reduce the risk of infection.

Any evidence of phlebitis or cellulitis or any suspicion of septic complications caused by intravenous cannulas should lead to prompt removal of the cannulas. Because many central venous catheters are used in compromised hosts who are prone to fever, these catheters generally should not be removed because of fever alone until other potential sources of fever have been eliminated. When an infected catheter is removed and another central venous catheter is immediately inserted at the same site, infection of the new catheter usually does not occur.

Catheter infections caused by *Staph. epidermidis* occasionally can be treated with antibiotics alone or by removal of the catheter. If antibiotics are used, a short course (3–7 days) is recommended. Vascular-access infections caused by *Staph. aureus* always require antibiotic therapy for a 2–3-week course. Vascular catheter infection caused by yeasts should always be treated by catheter removal and administration of an antifungal agent if cultures remain positive after removal or if there is infection elsewhere.

SURGICAL MICROBIOLOGY

Bacteria

Bacteria can be classified according to staining characteristics with Gram stain (positive or negative), shape (cocci, rods, spirals), and ability to grow without oxygen (aerobic, facultative, anaerobic) or according to a combination of these characteristics. Gram-positive cocci, gram-negative aerobic and facultative rods, and anaerobic bacteria are three groups into which most bacteria-causing surgical infections can be placed.

GRAM-POSITIVE COCCI

Staphylococcus and *Streptococcus* species are the gram-positive cocci that cause primary surgical infections and postoperative infections. The genus *Staphylococcus* is composed of facultatively anaerobic gram-positive cocci that are found on moist areas of the body, the anterior nares, and mucous membranes. In addition, these bacteria can be found on the body surfaces of many species of

mammals and birds, in the air and dust of occupied buildings, and in milk, food, and sewage.

Staph. aureus is the most common pathogen isolated from wound infections. An enterotoxin is responsible for food poisoning. Epidermolytic toxin can cause a variety of skin lesions; the most characteristic are the diffuse exfoliative bullae seen in children with the scalded-skin syndrome. Another exotoxin, TSS toxin-1, is responsible for toxic shock syndrome. Other extracellular products make *Staph. aureus* resistant to H_2O_2-mediated intracellular killing (catalase) and cause cell death (leukocidin, alpha toxin, beta toxin).

Staph. epidermidis, a member of the flora of the skin and mucous membranes, causes infection in the presence of foreign bodies such as plastic catheters, ventricular shunts, and prosthetic joints and heart valves. Surgically important members of the genus *Streptococcus* include *Strep. pyogenes, Strep. pneumoniae,* and the viridans group, which includes *Strep. mutans, Strep. mitior, Strep. salivarius, Strep. sanguis,* and *Strep. milleri.*

Group A streptococci have cell surface components and extracellular products that inhibit host defenses or promote spread of the bacterium. Streptococci can cause postoperative infections, including cellulitis, wound infection, endocarditis, UTI, and bacteremia. These bacteria also can cause primary necrotizing soft tissue infections and abscesses. *Strep. pyogenes* is an uncommon cause of necrotizing soft tissue infections.

Enterococcus faecalis, E. faecium, and *E. durans* formerly were classified as members of the genus *Streptococcus,* but a separate genus is now recognized. They are part of the normal flora of the GI tract and vagina. They are found commonly in patients with peritoneal and pelvic infections as part of the mixed flora typical of these infections. Enterococcal bacteremia has a poor prognosis when associated with intraabdominal or pelvic infection and is found most often in patients who have been hospitalized for a long time.

AEROBIC AND FACULTATIVELY ANAEROBIC GRAM-NEGATIVE BACILLI

There are numerous gram-negative rods that can cause human disease, but relatively few are of surgical significance. Their cell walls have common chemical constituents, most prominent of which is lipopolysaccharide or endotoxin, which is responsible for most of the biologic effects of these bacteria. Most are members of the family Enterobacteriaceae that are inhabitants of the GI tract. The genera *Escherichia, Klebsiella, Proteus, Enterobacter, Serratia,* and *Providencia* frequently can be cultured from patients with intraabdominal and pelvic peritonitis and abscess, postoperative wound infection, pneumonia, and UTI.

The family Pseudomonadaceae is composed of obligate aerobes that lack the ability to ferment sugars, unlike members of the Enterobacteriaceae. *Pseudomonas aeruginosa* is the species in this family responsible for most surgical infections. They cause infections similar to those of gram-negative enteric bacteria in association with GI disease, pneumonia, UTI, and burns. They are found frequently in immunologically compromised patients, especially if they have been hospitalized for some time. They cause necrotizing infections, especially pneumonia and vasculitis.

ANAEROBIC BACTERIA

Anaerobic bacteria require reduced oxygen tension for growth. They are found predominantly in the mouth, vagina, and GI tract, where they greatly outnumber the aerobic bacteria. Anaerobic bacteria, which are pathogenic, can tolerate an initial exposure of up to 3% oxygen. Vascular disease, cold, shock, edema, trauma, devitalized tissue, operation, foreign bodies, and malignant disease can lower the oxidation-reduction potential and predispose to infection with these organisms.

In most infections with anaerobic bacteria, facultative or aerobic bacteria are also present. Aerobic or facultative bacteria make conditions favorable for anaerobic bacteria by lowering the oxidation-reduction potential. The aerobic bacteria also may supply a growth factor necessary for another organism or may interfere with local or systemic host resistance.

Anaerobes such as the *Bacteroides fragilis* group have an endotoxin, but it differs chemically from the endotoxin of the enteric facultative or aerobic gram-negative bacilli, and it exhibits poor biologic activity. The cell wall of anaerobic bacteria is important in abscess formation.

The genus *Clostridium* is the most virulent of all anaerobes. *Clostridium,* which can be found in soil and stool, can cause necrotizing soft tissue infection. The exotoxins produced by these bacteria are believed to be responsible for most of the local and systemic manifestations. *C. perfringens, C. septicum,* and *C. novyi,* which can cause necrotizing infections, produce toxins that can destroy cell membranes and lyse red blood cells, collagenase, hyaluronidase, and other enzyme toxins that enhance the spread of the infection through the tissues.

C. perfringens and *C. difficile* both produce an enterotoxin. *C. difficile* causes pseudomembranous colitis and occurs in patients treated with antibiotics. It produces a cytotoxin that is cytopathic for almost all tissue culture cell lines. *C. tetani* and *C. botulinum* produce neurotoxins that cause muscle spasms and paralysis, respectively.

In the colon the ratio of anaerobic bacteria to aerobic bacteria is between 300:1 and 1000:1. The most common pathogens in the colon are members of the genera *Bacteroides, Fusobacterium,* and *Peptostreptococcus.* Of these, *Bacteroides* is the most commonly cultured genus in patients with intraabdominal infections. The *B. fragilis* group, composed of *B. fragilis, B. thetaiotaomicron, B. distasonis, B. ovatus,* and *B. vulgatus,* accounts for most infections with this genus. Colonic anaerobes almost never cause infections by themselves but only as part of a mixed flora, often with facultative enteric gram-negative bacilli.

Fungi

Fungi can be grouped as primary pathogens, which can cause disease in individuals with intact host defenses, and opportunists, which cause disease in patients with compromised host defenses. Among the primary pathogens are *Histoplasma, Coccidioides,* and *Blastomyces. Candida, Cryptococcus, Aspergillus,* and the phycomycetes (*Mucor, Absidia,* and *Rhizopus*) cause most of the opportunistic infections.

In surgical patients, opportunists cause most infections. *Candida albicans* and other *Candida* species are by far the most common. They cause infections in patients being treated with broad-spectrum antibiotics and in those receiving steroids and other immunosuppressive agents, in malnourished patients, in patients with malignant neoplasms, and in other compromised hosts. In these patients they can cause vascular catheter–related infections, bacteremia, intraabdominal infections, pneumonia, and UTIs. These infections can be treated by stopping antibiotic administration, correcting host defenses, and therapy with amphotericin B or one of the azole antifungal agents.

Viruses

Members of the herpesvirus family, especially cytomegalovirus (CMV), herpes simplex virus, varicella-zoster virus, and Epstein-Barr virus, can cause infections in immunosuppressed patients such as organ transplant recipients. CMV causes most viral infections in organ transplant recipients. In these patients, CMV can cause ulcerative lesions of the GI tract leading to bleeding or perforation for which operations might be required. Epstein-Barr virus is implicated as the cause of a polyclonal B-cell lymphoma in transplant recipients. Hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV) are of importance to surgeons because of the possibility that they can become infected from patient exposure

and that patients can potentially be infected by physicians who harbor these viruses. Hepatitis B prophylaxis is available should a health care worker sustain a percutaneous or permucosal exposure (Table 5-2).

HUMAN IMMUNODEFICIENCY VIRUS

CD4+ cells infected with the retrovirus HIV are not able to carry out their normal immune functions, which leads to opportunist infections and the development of Kaposi's sarcoma. The development of opportunist infections and tumors (Kaposi's sarcoma and lymphomas) is accompanied by a decrease in the number of T cells to less than 200/mm^3. The most recent definition of AIDS includes all patients infected with HIV who have a CD4+ count of less than 200 cells/mm^3.

Epidemiology The Centers for Disease Prevention and Control (CDC) estimates that for every person with AIDS there are approximately eight persons with HIV infection who have not yet developed clinical AIDS. There are approximately 5 million people infected with HIV in the United States. Approximately 30.6 million people are infected with HIV worldwide.

HIV has been isolated from blood, semen, saliva, tears, vaginal secretions, alveolar fluid, cerebrospinal fluid, breast milk, synovial fluid, and amniotic fluid. Only blood and blood products, semen, vaginal secretions, and breast milk have been linked to transmission. The groups at highest risk for HIV infection are (1) homosexual and bisexual men, (2) intravenous drug abusers, (3) persons with hemophilia and other coagulation disorders, (4) heterosexual contacts of the individuals in the three previous categories, and (5) children born to HIV-positive mothers. Recipients of transfusions of blood and blood products from HIV-positive donors have approximately a 95 percent chance of developing HIV infection. The CDC has estimated that the number of cases of transfusion-acquired AIDS could eventually reach 12,000. Since testing blood donors for evidence of HIV became mandatory in 1985, transfusion-acquired HIV infection has been virtually eliminated. The current risk of transmission of HIV by screened blood in the United States is estimated to be between 1 in 450,000 and 1 in 660,000.

Serologic Events Patients infected with HIV develop viremia accompanied by a generalized lymphadenopathy, fever, and malaise. Approximately 6–12 weeks after infection, antibody to HIV develops. During this time, the viral titer in blood decreases markedly from 10^4/mL to 10–100/mL. A low virus titer persists until the patient develops AIDS approximately 7–9 years after infection. When

AIDS develops, the virus titer rapidly increases to a level of 10^4/mL. Serologic testing examines antibody to HIV, and seroconversion usually occurs within 12 weeks of infection but has been known to take as long as 6 months. During this period (the "window"), it is possible for patients to have circulating virus and to be potentially infectious to those around them and yet test negative for HIV.

Surgery in HIV-Infected Patients Patients with HIV infection and AIDS generally do not require any extra preoperative preparation. Malnutrition associated with HIV infection may require correction if time permits. Perioperative antimicrobial therapy is given for the same indications as for patients without HIV infection. These patients generally do not have difficulty with wound healing and do not have a higher rate of wound infections or other postoperative hospital-acquired infections. Drains and open wounds require precaution to avoid contamination with HIV-infected blood and other body fluids.

HIV and AIDS in Health Care Workers As of June 30, 1997, 166 health care workers (HCWs) had developed HIV infection as a result of occupational exposure, most as a result of exposure to blood from HIV-infected patients. Most of the infected HCWs are nurses or technicians, and 6 are surgeons.

Risk of HIV Seroconversion in Health Care Workers Of 1948 HCWs in 12 reports who sustained a total of 1051 mucous membrane exposures to blood or blood-containing body fluids from HIV-infected patients, 6 (0.29 percent per exposure) seroconverted. Risk of HIV infection is associated with deep injury, visible blood on the device, a procedure involving a needle placed directly in a vein or artery, terminal illness in the source patient, and no postexposure use of zidovudine (AZT). Most exposures are to the skin, and their numbers can be minimized by wearing two pairs of gloves and face shields.

Prevention of Blood-Borne Infections in Health Care Workers The CDC issued guidelines designed to minimize the risk of transmission of HIV in the health care setting (Table 5-3). Although universal precautions were issued to reduce the transmission of HIV in health care settings, they also are appropriate for reducing the transmission of other blood-borne viruses, including hepatitis B virus (HBV), hepatitis C virus (HCV), and the recently described hepatitis G virus (HGV).

Compliance in a large inner-city hospital emergency room was found to be only 18 percent, and it fell to 5 percent if the patient

TABLE 5-2
RECOMMENDATIONS FOR HEPATITIS B PROPHYLAXIS AFTER PERCUTANEOUS OR PERMUCOSAL EXPOSURE

HB Vaccination Status of Exposed Person	HB_sAg Status of Source of Exposure		
	HB_sAg-Positive	HB_sAg-Negative	Untested or Unknown
Unvaccinated	Give single doses of HBIG Initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated Known responder	Test exposed person for anti-HB_s. If anti-HB_s level is adequate,[a] no treatment is needed; if it is inadequate, give an HB vaccine booster dose	No treatment is needed	No treatment is needed
Known nonresponder	Give two doses of HBIG or one dose of HBIG plus one dose of HB vaccine	No treatment is needed	If source is at high risk for HB infection, consider proceeding as if it had been demonstrated to be HB_sAg-positive

Response unknown	Test exposed person for anti-HB_s. If anti-HB_s level is adequate,[a] no treatment is needed; if it is inadequate, give one dose of HBIG plus an HB vaccine booster dose	No treatment is needed	Test exposed person for anti-HB_s. If Anti-HB_s level is adequate,[a] no treatment is needed; if it is inadequate, give an HB vaccine booster dose

[a]An adequate anti-HB_s level is $\geq$ 10 mU/mL, which is approximately equivalent to 10 sample ratio units (SRU) on radioimmunoassay or positive result on enzyme immunoassay.

HBIG = hepatitis B immune globulin; HB = hepatitis B

SOURCE: From Centers for Disease Control: Recommendations for protection against viral hepatitis. *MMWR* 34:313, 1985.

TABLE 5-3
GUIDELINES TO PREVENT TRANSMISSION OF HIV

Universal Precautions

1. All health care workers should use appropriate barrier precautions routinely to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. Gloves should be worn for touching blood and body fluids, mucous membranes, or nonintact skin of all patients; for handling items or surfaces soiled with blood or body fluids; and for performing venipuncture and other vascular-access procedures. Gloves should be changed after contact with each patient. During procedures that are likely to generate aerosolized droplets of blood or other body fluids, masks and protective eyewear or face shields should be worn to prevent exposure of mucous membranes of the mouth, nose, and eyes. Gowns or aprons should be worn during procedures that are likely to generate splashes of blood or other body fluids.
2. Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids. Hands should be washed immediately after gloves are removed.
3. All health care workers should take precautions to prevent injuries caused by needles, scalpels, and other sharp instruments or devices during procedures; when cleaning used instruments; during disposal of used needles; and when handling sharp instruments after procedures. To prevent needlestick injuries, needles should not be recapped, purposely bent or broken by hand. After they are used, disposable syringes and needles, scalpel blades, and many other sharp items should be placed in puncture-resistant containers for disposal; the puncture-resistant containers should be located as close as practical to the area of use. Large-bore reusable needles should be placed in a puncture-resistant container for transport to the reprocessing area.
4. Although saliva has not been implicated in HIV transmission, to minimize the need for emergency mouth-to-mouth resucitation, mouth-pieces, resucitation bags, or other ventilation devices should

be available for use in areas in which the need for resuscitation is predictable.

5. Health care workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care equipment until condition resolves.
6. Pregnant health care workers are not known to be at greater risk for contacting HIV infection than health care workers who are not pregnant; however, if a health care worker acquires HIV infection during pregnancy, the infant is at risk for infection resulting from perinatal transmission. Because of this risk, pregnant health care workers should be especially familiar with and strictly adhere to precautions to minimize the risk of HIV transmission.

Additional Precautions for Invasive Procedures

1. All health care workers who participate in invasive proedures must use appropriate barrier precautions routinely to prevent skin and mucous membrane contact with blood and other body fluids of all patients. Gloves and surgical masks must be worn for all invasive procedures. Protective eyewear or face shields should be worn for procedures that commonly result in the generation of aerosolized droplets, splashing of blood or other body fluids, or the generation of bone chips. Gowns or aprons made of materials that provide an effective barrier should be worn during invasive procedures that are likely to result in the splashing of blood or other body fluids. All health care workers who perform or assist in vaginal or cesarean deliveries should wear gloves and gowns when handling the placenta or the infant until blood and amniotic fluid have been removed from the infant's skin and should wear gloves during postdelivery care of the umbilical cord.
2. If a glove is torn or a needlestick or other injury occurs, the glove should be removed and a new glove used as promptly as patient safety permits; the needle or instrument involved in the incident should also be removed from the sterile field.

SOURCE: Centers for Disease Control: Recommendations for prevention of HIV transmission in health-care settings. *MMWR* 36(2S):1S, 1987.

was bleeding from an external injury. The rates of noncompliance with universal precautions are reported to be 74 percent in the surgical intensive care unit and 34 percent on the surgical wards.

Testing Patients for Blood-Borne Pathogens The CDC does not recommend routine HIV testing of all patients. HIV testing of patients is recommended for management of HCWs who sustain parenteral or mucous membrane exposure to blood or other body fluids from a patient, for patient diagnosis and management, and for counseling associated with efforts to prevent and control HIV transmission in the community.

Management of HCWs Exposed to Patients' Blood and Other Body Fluids The Department of Labor and the CDC have published detailed employer responsibilities in protecting workers from acquisition of blood-borne diseases in the workplace. Now that a serologic test is available for HCV, the patient also should be tested for that virus (and probably also for HGV when testing becomes available).

HIV Postexposure Management If an HCW is exposed percutaneously or by a splash to the eye or mucous membrane from a patient who has HIV infection or AIDS or who refuses to be tested, the worker should be counseled regarding the risk of infection and be evaluated clinically and serologically for evidence of HIV infection as soon as possible after the exposure. The worker should be advised to report and seek medical evaluation for any acute febrile illness that occurs within 12 weeks after exposure. After the initial test at the time of exposure, seronegative workers should be retested 6 weeks, 12 weeks, and 6 months after exposure to determine whether transmission has occurred. During this period, the worker should refrain from blood or semen donation and should use appropriate protection during sexual intercourse. If the source individual is found to be seronegative, baseline testing of the exposed worker with follow-up 12 weeks later may be performed if desired or recommended by the health care provider.

AZT is used to treat patients with HIV infection and has been proposed as chemoprophylaxis to prevent occupational infection in HCWs. Postexposure AZT use by HCWs is associated with a lower risk of HIV transmission. The CDC now recommends that HCWs exposed to blood from HIV-infected individuals be treated with AZT and lamivudine (3TC). If the exposure is high risk (a large volume of blood containing a high titer of HIV), the protease inhibitor indinavir also should be given. Prophylaxis should be given within 1–2 h of exposure. If the HIV status of the source patient is

unknown, the use of postexposure prophylaxis should be decided on a case-by-case basis. A dilemma arises when the source individual refuses to be tested; some states permit testing blood specimens obtained for another purpose if an HCW has been exposed to a patient's blood or other body fluid and the patient refuses testing. AZT prophylaxis protocols generally advise administering 200 mg AZT every 4 h for 28–42 days. Some protocols skip the 4:00 A.M. dose.

Transmission of Blood-Borne Pathogens from HCWs to Patients HIV, HBV, and HCV can be transmitted potentially to a patient during invasive procedures when a surgeon sustains a percutaneous injury with a needle or sharp instrument that then recontacts the patient. Only HBV and HCV have been demonstrated to be transmitted from physicians to patients. One dentist has transmitted HIV to six patients; the mechanism of transmission is unclear, however. More than 9000 patients cared for by more than 75 HCWs with AIDS have been followed, and no cases of transmission by HCW to patient have been reported.

Management of the HIV-, HBV-, or HCV-Infected HCW The report of a dentist's having passed HIV to his patients sparked considerable discussion in the scientific and popular press about the HIV-positive HCW, especially surgeons and dentists, since they are most likely to participate in invasive procedures. The CDC first issued guidelines for the management of HIV-infected personnel in 1985. It subsequently issued guidelines for management of HIV-infected HCWs who participate in invasive procedures. The CDC recommended that HCWs who are otherwise fit for duty and who do not participate in invasive procedures be allowed to perform their regular duties. The CDC recommended that HIV-infected personnel who do participate in invasive procedures be evaluated on a case-by-case basis.

ANTIMICROBIAL THERAPY

Antimicrobial therapy is only an adjunct in treating surgical infection; operative treatment (or percutaneous radiologically guided drainage of infected material) is more important. The goal of antimicrobial therapy is to prevent or treat infection by reducing or eliminating organisms until the host's own defenses can get rid of the last pathogens.

Efficacy is the most important consideration in choosing an antimicrobial agent. Effective antimicrobial agents must be active

against the pathogens causing the infection and must be able to reach the site of infection in adequate concentrations. All antibiotics have potential toxicity. Toxic effects may be idiosyncratic, such as allergy or the rare instances of bone marrow aplasia caused by chloramphenicol. They also can cause damage to tissues and organs, such as in the renal toxicity or ototoxicity seen with the aminoglycosides or amphotericin B. Antimicrobial agents also exert selective pressures on the microbial ecology of the hospital that lead to resistant microbes, a problem that is especially important in intensive care units. Cost is the final consideration in the selection of antimicrobial agents. Determining the costs of antimicrobial therapy includes more than just the cost of the drug. Drug administration charges, nursing time, intravenous fluid and lines, and monitoring costs also must be considered. Additionally, any increased hospital time that occurs when an inexpensive agent that is less effective or that causes more toxicity is used ultimately makes that agent a more expensive antimicrobial.

Distribution of Antimicrobial Agents

Successful treatment of localized infections with systemic antimicrobial agents requires that an adequate concentration of drug be delivered to the site of infection. Ideally, the tissue concentration of antibiotics should exceed the minimum inhibitory concentration. Tissue penetration depends in part on protein binding of antibiotics. Only the unbound form of antibiotics will pass through the capillary wall or act to inhibit bacterial growth. Therapeutic outcome, on the other hand, does not appear to be correlated with protein affinity, presumably because protein binding is easily reversible. Lipid solubility of antibiotics is also an important factor in tissue penetration. It determines the ability of antibiotics to pass through membranes by non-ionic diffusion or into wounds, bone, cerebrospinal fluid, the eye, endolymph of the ear, vegetations of bacterial endocarditis, and abscesses.

Blood Rapidity of excretion and protein binding are two main determinants of blood concentration of antimicrobial agents. Protein binding affects the rapidity of excretion. Antibiotics that are highly protein bound are not excreted as rapidly as those with a low binding affinity and thus have longer half-lives. Therefore, highly protein-bound antibiotics generally do not have to be given as frequently as those with low protein binding. The efficacy of penicillins, cephalosporins, and other antibiotics that affect bacterial cell wall synthesis depends on the amount of time during which serum levels are above the minimum inhibitory concentrations rather than their peak serum concentration. The efficacy of amino-

glycosides, on the other hand, is related to achieving peak serum concentrations that are four to eight times the minimum inhibitory concentration. Monitoring of serum aminoglycoside concentrations usually is necessary to ensure that these concentrations have been achieved. Some antimicrobial agents such as nitrofurantoin and norfloxacin are excreted so rapidly in the urine that they never achieve blood (or tissue) levels sufficient to reach effective antibacterial concentrations. They do, however, reach high urinary concentrations and are effective agents for treating UTIs.

Urine Most commonly used antibiotics (sulfonamides, penicillins, cephalosporins, aminoglycosides, tetracyclines, quinolones, and azoles) are excreted principally in the urine and achieve high urinary concentrations—up to 50–200 times their serum concentrations. Notable exceptions are erythromycin and chloramphenicol. Because concentrating ability is severely compromised in patients with renal disease, infections of the urinary tract are more difficult to treat in these patients. The pH of urine can be changed to facilitate antibiotic activity. For instance, aminoglycosides are more active in an alkaline medium, whereas other urinary antibacterial agents (tetracyclines, nitrofurantoin, methenamine mandelate) are more active in an acidic environment. The antimicrobials most commonly used to treat UTIs have antimicrobial activity across a broad pH range.

Bile Besides urine, only bile regularly has antibiotic concentrations higher than serum levels. The biliary concentrations of many of the penicillins (especially nafcillin, piperacillin, mezlocillin, and azlocillin), cephalosporins (especially cefazolin, cefamandole, ceforanide, cefoxitin, cefoperazone, and cefadroxil), tetracyclines, and clindamycin frequently are several times their serum concentrations. Nafcillin and rifampin achieve biliary concentrations 20–100 times those of serum. Aminoglycoside antibiotics enter bile less well, especially in the presence of liver disease, and their biliary concentrations usually are lower than serum levels.

Interstitial Fluid and Tissue High, prolonged serum concentration and low protein binding favor diffusion of antibiotics from serum into extravascular tissue. Absolute tissue levels may not accurately reflect the therapeutic potential of the antibiotic, however, because the agent may be tightly bound to tissue and thus be unavailable for binding to bacteria.

Abscesses The generalization that no antibiotics penetrate abscesses is not true. While the penicillins, cephalosporins, and some other antibiotics penetrate mature abscesses poorly, others such as

metronidazole, chloramphenicol, and clindamycin can achieve inhibitory concentrations in abscesses.

A separate problem is whether, after penetration, an antibiotic can retain its antimicrobial efficacy under the conditions that exist in an abscess. The acidic pH, the low oxidation-reduction potential, and the large numbers of microbial and tissue products that can bind antibiotics all serve to reduce antimicrobial efficacy. Multiple types of bacteria within an abscess make it more likely that one type will inactivate an agent effective against it or another bacterium. The lack of efficacy of penicillins and cephalosporins in treating most abscesses may be a result of the high concentrations of beta-lactamases that accumulate there. Metronidazole and clindamycin can enter abscesses and retain antibacterial activity, but they are not effective against the aerobic gram-negative bacteria that usually are present together with the anaerobic bacteria against which they are effective.

An additional reason that antibiotics alone are seldom effective in treating abscesses is that antibiotics are most effective against actively metabolizing, rapidly dividing bacteria. Conditions in abscesses usually are unfavorable for bacterial growth, so the antibiotic is not able to enter and be active against the bacteria. For all these reasons antibiotics alone should not be relied on for the treatment of most abscesses. Drainage is the mainstay of treating abscess.

Use of Antibiotics in Surgery

Prophylactic Antibiotics Antibiotics frequently are administered prophylactically to patients undergoing operation to prevent wound infection when the likelihood of infection is high (e.g., when the tissues have been exposed to bacteria such as occurs during colon surgery) or when the consequences of infection are great even though the risk of infection is low (e.g., when a prosthetic device is implanted). Antibiotic prophylaxis should be administered to patients with previously placed prosthetic devices such as cardiac valves or artificial joints who are having any operation or dental procedure.

Therapeutic Use of Antibiotics Many infections can be treated successfully with oral antibiotics on an outpatient basis. Severe surgical infections should be treated with intravenous antibiotics. Initial antibiotic therapy usually is empiric, because it should not be postponed until microbiotic studies are complete. Antibiotic therapy generally should be initiated before cultures are obtained in patients with peritonitis, abscesses, and necrotizing soft tissue infections.

Empiric Therapy Rational empiric antibiotic therapy requires familiarity with the microbes most likely to cause infection at the involved site and antibiotic susceptibility patterns in the hospital or intensive care unit. Intraabdominal surgical infections are nearly always caused by mixed gram-negative and gram-positive aerobic and anaerobic bacteria.

Most necrotizing soft tissue infections, especially those originating after an intraabdominal operation or occurring below the waist, also are a result of a mixed bacterial flora, and broad-spectrum empiric therapy should be initiated. Because clostridia or streptococci also can cause these infections, penicillin G generally should be included. Once Gram stain and culture results are available, antibiotic therapy can be modified.

Prosthetic device infections usually progress much more slowly than intraabdominal or necrotizing soft tissue infections. Gram-positive cocci, especially *Staph. aureus* and *Staph. epidermidis*, play a prominent role in these infections, but they also can be caused by gram-negative bacteria.

Numerous single and combination antimicrobials are available for initial and empiric therapy. The Surgical Infection Society (SIS) recommends against using drugs such as cefazolin and other first-generation cephalosporins, penicillin, cloxacillin and other anti-staphylococcal penicillins, ampicillin, erythromycin, and vancomycin because these drugs do not provide adequate coverage for both aerobic and anaerobic organisms.

Metronidazole and clindamycin should not be used as single agents for mixed infection because they lack activity against aerobic enteric organisms. Other antibiotics, such as aminoglycosides, aztreonam, cefuroxime, cefonicid, cefamandole, ceforanide, cefotetan, cefotaxime, ceftizoxime, cefoperazone, ceftriaxone, ceftazidime, and polymyxin, should not be used alone because of the inadequate coverage of anaerobic gram-negative bacilli. Because of inadequate clinical data documenting efficacy and concerns about resistance, the SIS also recommends against using as single agents for empiric therapy antibiotics such as piperacillin, mezlocillin, azlocillin, ticarcillin, and carbenicillin despite their relative safety and broad in vitro antibacterial activity. Chloramphenicol has an appropriate in vitro spectrum of activity but is not acceptable because it can produce serious side effects.

Acceptable agents for community-acquired intraabdominal infections include cefoxitin, cefotetan, cefmetazole, and ticarcillin/clavulanic acid. These antibiotics should not be used for patients whose abdominal infection develops in the hospital after previous antibiotic therapy. For these infections and serious intraabdominal infections, antibiotics such as imipenem-cilastatin (Primaxin)

should be used. Combination therapy such as metronidazole or clindamycin plus an aminoglycoside or an antianaerobic antibacterial agent plus a third-generation cephalosporin or clindamycin plus a monobactam is acceptable. The combination of an antianaerobic antibiotic plus an aminoglycoside plus penicillin or ampicillin is recommended only if enterococcal infection is suspected on the basis of a Gram stain or thought to be clinically relevant (e.g., associated with *Enterococcus* bacteremia). Community-acquired intraabdominal infections are seldom associated with serious *Enterococcus* infection.

Definitive Therapy Antimicrobial therapy may have to be altered when the results of Gram stain, culture, and sensitivity data are available. Sensitivity data may determine that one of the antibiotics currently being used is not active against one of the bacteria isolated. In addition, change to a less toxic or less costly antimicrobial agent may be possible once laboratory results are available.

Infections originating in the intensive care unit are frequently caused by antibiotic-resistant bacteria. This especially is true for hospital-acquired *Staph. aureus*, which often is resistant to methicillin. For hospital-acquired staphylococcal infections, vancomycin generally should be initiated if methicillin-resistant *Staph. aureus* is a problem in the hospital until definitive sensitivity data are available. If the *Staph. aureus* is sensitive to penicillin G or methicillin, these agents should be used because they are more effective and less costly than vancomycin. Two drugs generally are used to treat *P. aeruginosa* infections, an antipseudomonal beta-lactam drug such as mezlocillin or ceftazidime in combination with an aminoglycoside, in an attempt to prevent development of resistance and to take advantage of possible synergism.

Drug Administration

Route For seriously ill surgical patients, the antimicrobial agent should be administered intravenously to ensure adequate serum levels. Absorption by other routes is inconsistent in seriously ill patients whose GI tract is not functioning properly and who have problems maintaining blood pressure. If patients need prolonged antimicrobial therapy, other routes can be used once they have begun to recover, or long-term IV antimicrobial therapy can be given on an outpatient basis.

Recommendations provided by the manufacturer should be used as guidelines for appropriate doses of antimicrobial agents. In

general, there is a wide margin between therapeutic and toxic concentrations with drugs such as the penicillins and cephalosporins. Other agents, such as the aminoglycosides, have a much narrower margin between therapeutic and toxic levels. For these antibiotics, the calculated dose in adults is based on lean body weight.

Duration Most surgical infections can be treated effectively in 5–7 days of antibiotic therapy. It generally is safe to stop antibiotics as long as the patient is making clinical progress and has a normal temperature and white blood cell count, and GI function has returned in patients with peritonitis. If clinical improvement is not evident within 4–5 days after operation and fever or leukocytosis persists after more than 5 days of therapy, a reason for the apparent treatment failure should be sought.

Treatment Failure Although failure of a bacterial infection to respond to a particular antibiotic is commonly regarded as evidence that the wrong antibiotic was selected, usually other factors are responsible. Patients with intraabdominal infections who remain febrile or have persistent leukocytosis usually have recurrent (tertiary) peritonitis or an intraabdominal abscess that requires drainage. Patients with necrotizing soft tissue infections may have persistent infections. Other causes of fever such as pneumonia, UTI, vascular catheter–related infection, drug fever, and thrombophlebitis should be investigated. The antibiotic may be the wrong antibiotic, or it may have been given in an inadequate dose or by an inappropriate route. The bacteria may not be susceptible to the antibiotic at the concentration achievable at the site of infection, or the site may have become superinfected by another bacterium not sensitive to the antibiotic.

Drug Toxicity Normally antibiotics are excreted primarily by the kidneys and accumulate in the serum of patients with impaired renal function. Therefore, with many antibiotics it is necessary to reduce the dose or to increase the interval between doses in patients with renal failure. Toxic drugs such as the aminoglycosides should either not be used in patients with renal failure or impaired renal function or, if used, their serum or plasma concentrations must be obtained frequently to verify that toxic levels are not being reached. The general approach to antibiotic usage in patients with renal failure is to give a first dose of 80–100 percent of the usual amount and then to estimate the timing and the amount of the second dose according to various schedules based on the normal half-life of the antibiotic.

Immunotherapy and Biologic Therapy of Infection

Antibodies to bacterial products and to mediators of sepsis are new (and extremely costly) therapeutic modalities that are currently being evaluated. Results thus far have been disappointing. There are no currently approved immunotherapeutic agents for treating infections. A previously approved antiendotoxin antibody (HA-1A) has been taken off the market. Other molecules or antagonists of molecules of the inflammatory or septic response are being investigated in the laboratory or undergoing clinical trials.

For a more detailed discussion, see Howard RJ: Surgical Infections, chap. 5 in *Principles of Surgery,* 7th ed.

CHAPTER

6

TRAUMA

INITIAL EVALUATION AND RESUSCITATION OF THE INJURED PATIENT

Primary Survey of the Trauma Patient

Airway Management Ensuring an adequate airway is the first priority in the primary survey. Efforts to restore cardiovascular integrity will be futile if the oxygen content of the blood is inadequate.

Patients who are conscious and have a normal voice do not require further evaluation or early attention to their airway. Exceptions to this principle include patients with penetrating injuries to the neck and an expanding hematoma; patients with evidence of chemical or thermal injury to the mouth, nares, or hypopharynx; and patients with extensive subcutaneous air in the neck, complex maxillofacial trauma, or airway bleeding. These patients initially may have a satisfactory airway, but it may become obstructed if soft tissue swelling or edema progresses.

Patients who have an abnormal voice or altered mental status require further airway evaluation. Direct laryngoscopic inspection often reveals blood, vomit, the tongue, foreign objects, or soft tissue swelling as sources of airway obstruction. Suctioning can offer immediate relief in many patients. Altered mental status is the most common indication for intubation because of the patient's inability to protect the airway. Options for airway access include nasotracheal intubation, orotracheal intubation, or operative intervention.

Orotracheal intubation can be performed in patients with potential cervical spine injuries provided that manual in-line cervical immobilization is maintained. The advantages of orotracheal intubation are direct visualization of the vocal cords, the ability to use larger-diameter endotracheal tubes, and applicability to apneic patients. The disadvantage of orotracheal intubation is that conscious patients usually require neuromuscular blockade or deep sedation.

Patients in whom attempts at intubation have failed or are precluded because of extensive facial injuries require a surgical

airway. Cricothyroidotomy and percutaneous transtracheal ventilation are preferred over tracheostomy because of their simplicity and safety. One disadvantage of cricothyroidotomy is the inability to place a tube greater than 6 mm in diameter because of the limited aperture of the cricothyroid space. Cricothyroidotomy also is contraindicated in patients under the age of 12 because of the risk of damage to the cricoid cartilage and the subsequent risk of subglottic stenosis.

Percutaneous transtracheal ventilation is accomplished by inserting a large-bore intravenous catheter through the cricothyroid membrane into the trachea and attaching it with tubing to an oxygen source capable of delivering 50 lb/in^2 or more. A hole cut in the tubing allows for intermittent ventilation by occluding and releasing the hole. Adequate oxygenation can be maintained for more than 30 min. Because exhalation occurs passively, ventilation is limited, and carbon dioxide retention can occur.

Breathing Once a secure airway is obtained, adequate oxygenation and ventilation must be ensured. All injured patients should receive supplemental oxygen therapy and be monitored by pulse oximetry. Immediate threats to life because of inadequate ventilation are (1) tension pneumothorax, (2) open pneumothorax, and (3) flail chest/pulmonary contusion. The diagnosis of tension pneumothorax is implied by the finding of respiratory distress in combination with any of the following physical signs: tracheal deviation away from the affected side, lack of or decreased breath sounds on the affected side, distended neck veins or systemic hypotension, or subcutaneous emphysema on the affected side. Immediate tube thoracostomy is indicated without awaiting chest x-ray confirmation.

An open pneumothorax or sucking chest wound occurs with full-thickness loss of the chest wall, permitting a free communication between the pleural space and the atmosphere. In addition to collapse of the lung on the injured side, if the diameter of the injury is greater than the narrowest portion of the upper airway, air preferentially moves through the injury site rather than the trachea and impairs ventilation on the contralateral side. Occlusion of the injury may result in converting an open pneumothorax into a tension pneumothorax. Definitive treatment requires wound closure and tube thoracostomy.

Flail chest occurs when four or more ribs are fractured in at least two locations. Paradoxical movement of this free-floating segment of chest wall may be sufficient to compromise ventilation. It is of greater physiologic importance that patients with flail chest frequently have an underlying pulmonary contusion. Respiratory

failure in these patients may not be immediate, and frequent reevaluation is warranted.

Circulation With a secure airway and adequate ventilation established, circulatory status is determined. A rough first approximation of the patient's cardiovascular status is obtained by palpating peripheral pulses. External control of hemorrhage should be obtained before restoring circulating volume. Manual compression and splints frequently control extremity hemorrhage as effectively as tourniquets. Blind clamping should be avoided because of the risk to adjacent structures. Digital control of hemorrhage for penetrating injuries of the head, neck, thoracic outlet, groin, and extremities is important. Scalp lacerations through the galea aponeurotica tend to bleed profusely; these can be controlled temporarily with Rainey clips or a full-thickness large nylon continuous stitch.

Intravenous access for fluid resuscitation is begun with two peripheral catheters, 16-gauge or larger in an adult. Blood is drawn simultaneously and sent for typing and hematocrit measurement. For patients requiring vigorous fluid resuscitation, saphenous vein cutdowns at the ankle or percutaneous femoral vein catheter introducers are preferred. The saphenous vein is reliably found 1 cm anterior and 1 cm superior to the medial malleolus.Venous access in the lower extremities provides effective volume resuscitation in cases of abdominal venous injury, including the inferior vena cava.

In hypovolemic pediatric patients less than 6 years of age, percutaneous femoral vein cannulation is contraindicated because of the risk of venous thrombosis. If two attempts at percutaneous peripheral access are unsuccessful, interosseous cannulation should be performed in the proximal tibia or in the distal femur if the tibia is fractured.

Initial Fluid Resuscitation Initial fluid resuscitation is a 1-L intravenous bolus of isotonic crystalloid in an adult or 20 mL/kg of body weight lactated Ringer's solution in a child. This is repeated once in an adult and twice in a child before administering red blood cells. The goal of fluid resuscitation is to reestablish tissue perfusion. Classic signs and symptoms of shock are tachycardia, hypotension, tachypnea, mental status changes, diaphoresis, and pallor. None of these signs or symptoms taken alone can predict the patient's organ perfusion status.

Hypotension is not a reliable early sign of hypovolemia. In healthy patients, blood volume must decrease by 30–40 percent before hypotension occurs (Table 6-1). Younger patients with good sympathetic tone can maintain systemic blood pressure with severe intravascular deficits until they are on the verge of cardiac arrest.

TABLE 6-1
SIGNS AND SYMPTOMS FOR DIFFERENT CLASSES OF SHOCK

	Class I	Class II	Class III	Class IV
Blood loss	Up to 750 mL	750–1500 mL	1500–2000 mL	>2000 mL
Blood loss (% BV)	Up to 15%	15–30%	30–40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Urine output	>30 mL/h	20–30 mL/h	5–15 mL/h	Negligible
CNS/Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic

Acute changes in mental status can be caused by hypoxia, hypercarbia, or hypovolemia, or they may be an early sign of increasing intracranial pressure (ICP). Urine output is a quantitative and relatively reliable indicator of organ perfusion. Adequate urine output is 0.5 mL/kg/h in an adult, 1 mL/kg/h in a child, and 2 mL/kg/h in an infant less than 1 year of age.

Central venous pressure (CVP) determines right ventricular preload; in otherwise healthy trauma patients, its measurement yields objective information regarding the patient's overall volume status. A hypotensive patient with flat neck veins and a CVP of less than 5 cmH_2O is hypovolemic and is likely to have ongoing hemorrhage. In trauma patients, the differential diagnosis of cardiogenic shock is indicated by (1) tension pneumothorax, (2) pericardial tamponade, (3) myocardial contusion or infarction, and (4) air embolism. Tension pneumothorax is the most frequent cause of cardiac failure. Traumatic pericardial tamponade most often is associated with penetrating injury to the heart. As blood leaks out of the injured heart, it accumulates in the pericardial sac. Because the pericardium is not acutely distendible, the pressure in the pericardial sac rises to match that of the injured chamber. This pressure usually is greater than that of the right atrium; right atrial filling is impaired, and right ventricular preload is reduced. This leads to decreased right ventricular output and increased CVP. This cycle may progress insidiously with injury of the venae cavae or atria or precipitously with injury of either ventricle. The classic findings of Beck's triad (hypotension, distended neck veins, and muffled heart sounds) and pulsus paradoxus are not reliable indicators of acute tamponade. Ultrasound imaging in the emergency room using a subxiphoid or parasternal view is helpful if the findings are clearly positive, but equivocal findings are common. Early in the course of tamponade, blood pressure and cardiac output transiently improve with fluid administration.

Once the diagnosis of cardiac tamponade is established, pericardiocentesis should be performed. Evacuation of as little as 15–25 mL of blood can dramatically improve the patient's hemodynamic profile. While pericardiocentesis is being performed, preparation should be made for emergent transport to the operating room. Emergent pericardiocentesis is successful in decompressing the tamponade in approximately 80 percent of patients; most failures are a result of clotted blood within the pericardium. If pericardiocentesis is unsuccessful and the patient remains severely hypotensive (systolic blood pressure < 70 mmHg) or shows other signs of hemodynamic instability, emergency room thoracotomy should be performed.

Myocardial contusion from direct myocardial impact occurs in approximately one-third of patients sustaining significant blunt

chest trauma. The diagnostic criteria for myocardial contusion include specific electrocardiogram (ECG) abnormalities, i.e., ventricular dysrhythmias, atrial fibrillation, sinus bradycardia, and bundle branch block. Transient sinus tachycardia is not indicative of contusion. Serial cardiac enzyme determinations (CPK-MB fraction) lack sensitivity. Arrhythmias are treated by pharmacologic suppression. The management of cardiogenic shock from cardiac pump failure includes an urgent ECG to rule out septal or free wall rupture, valvular disruption, or pericardial tamponade.

Air embolism is a frequently overlooked lethal complication of pulmonary injury. It occurs when air from an injured bronchus enters an adjacent injured pulmonary vein and returns to the left side of the heart. Air accumulation in the left ventricle impedes diastolic filling, and during systole, it is pumped into the coronary arteries, disrupting coronary perfusion. The typical scenario is a patient with a penetrating chest injury who appears hemodynamically stable but suddenly goes into cardiac arrest after being intubated and placed on positive-pressure ventilation. The patient should be placed in the Trendelenburg position to trap the air in the apex of the left ventricle. Emergency thoracotomy is followed by cross-clamping the pulmonary hilum on the side of the injury to prevent further introduction of air. Air is aspirated from the apex of the left ventricle with an 18-gauge needle and 50-mL syringe. Vigorous open cardiac massage is used to force the air bubbles through the coronary arteries. The highest point of the aortic root also is aspirated to prevent air from entering the coronary arteries or embolizing to the brain. The patient should be kept in the Trendelenburg position and the hilum clamped until the pulmonary venous injury is controlled.

Secondary Survey

When the conditions that constitute an immediate threat to life have been attended to or excluded, the patient is examined in a systematic fashion to identify occult injuries. Patients should undergo digital rectal examination to evaluate sphincter tone and to look for blood, perforation, or a high-riding prostate. A Foley catheter should be inserted to decompress the bladder, obtain a urine specimen, and monitor urine output. Stable patients at risk for urethral injury should undergo urethrography before catheterization. A nasogastric tube should be inserted to decrease the risk of gastric aspiration and allow inspection of the contents for blood suggestive of occult gastroduodenal injury.

Selective radiographs are obtained early in the emergency room. For patients with severe blunt trauma, anteroposterior chest and pelvic radiographs should be obtained as soon as possible. For pa-

tients with truncal gunshot wounds, posteroanterior and lateral radiographs of the chest and abdomen are warranted.

Regional Assessment of Injury and Special Diagnostic Tests

Head A score based on the Glasgow Coma Scale (GCS) should be determined for all injured patients (Table 6-2). Examination of the head should focus on potentially treatable neurologic injuries. The presence of lateralizing findings is important; e.g., a unilateral dilated pupil unreactive to light, asymmetric movement of the extremities either spontaneously or in response to noxious stimuli, or a unilateral Babinski's reflex suggests a treatable intracranial mass lesion or major structural damage. Stroke syndromes should prompt a search for carotid dissection or thrombosis using duplex scanning or angiography. Otorrhea, rhinorrhea, "raccoon eyes," and Battle's sign (ecchymosis behind the ear) can be seen with basilar skull fractures.

Cerebral pathologic lesions from blunt trauma include hematomas, contusions, hemorrhage into ventricular and subarachnoid spaces, and diffuse axonal injury (DAI). Epidural hematomas occur when blood accumulates between the skull and the dura and are caused by disruption of the middle meningeal artery or other small arteries in that potential space from a skull fracture. Subdural hematomas occur between the dura and the cerebral cortex and are caused by venous disruption or laceration of the parenchyma of the brain. Because of the underlying brain injury, the prognosis is worse with subdural hematomas. Intraparenchymal hematomas and contusions can occur anywhere within the brain. Hemorrhage may occur into the ventricles, and though usually not massive, this blood may cause postinjury hydrocephalus. Diffuse hemorrhage into the subarachnoid space may cause vasospasm and reduce cerebral blood flow. DAI results from high-speed deceleration injury and represents direct axonal damage. Early evidence of DAI on computed tomographic (CT) scan is associated with a poor outcome.

Neck In evaluating the neck of a blunt trauma victim, attention should be focused on signs and symptoms of an occult cervical spine injury. Because of the devastating consequences of quadriplegia, all patients should be assumed to have cervical spine injuries until proved otherwise. The presence of posterior midline pain or tenderness should provoke a thorough radiologic evaluation. A cervical spine series including lateral view with visualization of C7–T1, anteroposterior view, and transoral odontoid view are sufficient to detect most significant fractures and subluxations.

TABLE 6-2
GLASGOW COMA SCALE*

		Adults	Infants/Children
Eye opening	4	Spontaneous	Spontaneous
	3	To voice	To voice
	2	To pain	To pain
	1	None	None
Verbal	5	Oriented	Alert, normal vocalization
	4	Confused	Cries, but consolable
	3	Inappropriate words	Persistently irritable
	2	Incomprehensible words	Restless, agitated, moaning
	1	None	None
Motor response	6	Obeys commands	Spontaneous, purposeful
	5	Localizes pain	Localizes pain
	4	Withdraws	Withdraws
	3	Abnormal flexion	Abnormal flexion
	2	Abnormal extension	Abnormal extension
	1	None	None

*Score is calculated by adding the scores of the best motor response, best verbal response, and eye opening. Scores range from 3 (the lowest) to 15 (normal).

If pain or tenderness persists despite normal appearance on plain x-ray films, a CT scan should be done. CT identifies most fractures but can miss some subluxations. A combination of plain film and CT imaging can identify virtually all injuries; an exception is a purely ligamentous injury. These rare and dangerous injuries may not be visible with standard imaging techniques. Flexion and extension views can be performed and may reveal opening of the intervertebral space. This should only be done in the presence of an experienced surgeon; patients with injuries have become permanently quadriplegic when flexed and extended by inexperienced individuals.

There are several partial or incomplete spinal cord injury syndromes. Central cord syndrome usually occurs in older persons who suffer hyperextension injuries. Motor function, pain, and temperature sensation are preserved in the lower extremities but diminished in the upper extremities. Some functional recovery usually occurs, but it is seldom a return to normal. Anterior cord syndrome is characterized by diminished motor function and pain and temperature sensation below the level of the injury. Position, vibratory, and crude touch sensation is maintained. Prognosis for recovery is poor. Brown-Séquard's syndrome usually is the result of a penetrating injury in which the right or left half of the spinal cord is transected. This rare lesion is characterized by ipsilateral loss of motor function, proprioception, and vibratory sensation; pain and temperature sensation is lost on the contralateral side.

Penetrating injuries of the anterior neck that violate the platysma are considered significant because of the density of critical structures in this region. Selective management is based on the neck's division into three zones (Fig. 6-1). Zone I is between the clavicles and the cricoid cartilage and is also referred to as the *thoracic outlet.* Zone II is between the cricoid cartilage and the angle of the mandible, and Zone III is above the angle of mandible. Because the operative incision to be made may depend on the injured structures, a precise preoperative diagnosis is desirable. Patients with Zone I injuries should undergo angiography of the great vessels, soluble-contrast esophagram followed by barium esophagram, esophagoscopy, and bronchoscopy. Hemodynamically unstable patients should not undergo this extensive evaluation but should be taken directly to the operating room.

Patients with Zone II injuries are the easiest to evaluate. Unstable patients or those with evidence of airway compromise, an expanding hematoma, or significant external hemorrhage (including hemorrhage into the mouth) should be explored promptly. Stable patients without these findings can be evaluated selectively. Penetrating neck wounds in stable patients should be explored

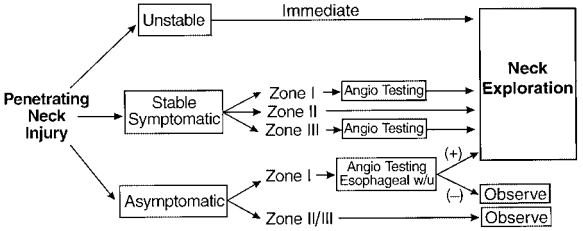


FIGURE 6-1 Algorithm for the selective management of penetrating neck injuries.

locally to determine the depth of penetration. Patients with right-to-left transcervical gunshot wounds may require diagnostic studies. Carotid and vertebral angiography, direct laryngoscopy, tracheoscopy, esophagoscopy, and esophagram might be necessary, depending on the bullet's trajectory.

Patients with Zone III penetrating injuries require carotid and vertebral angiography if there is evidence of arterial bleeding. This is important for three reasons: (1) exposure of the distal internal carotid and vertebral arteries is difficult, (2) the internal carotid artery may have to be ligated, a maneuver associated with a high risk of stroke, and (3) active hemorrhage from the external carotid and vertebral arteries can be controlled by selective embolization.

Chest The most threatening occult injury in trauma surgery is a tear of the descending thoracic aorta. Widening of the mediastinum on anteroposterior chest x-ray strongly suggests this injury. The widening is caused by the formation of a hematoma around the injured aorta that is temporarily contained by the mediastinal pleura. Posterior rib fractures and laceration of small vessels also can produce similar hematomas. Other findings suggestive of an aortic tear are noted in Table 6-3. This injury may be present with an entirely normal chest x-ray, although the incidence is approximately 2 percent. Because of the dire consequences of missing the diagnosis, CT and angiography are frequently performed after certain types of injury. In 2–5 percent of patients the tear occurs in the ascending aorta, in the transverse arch, or at the diaphragm. Dynamic, spiral CT is an excellent screening test. A clearly widened mediastinum on chest x-ray or abnormalities on CT are an absolute indication for emergent aortography.

TABLE 6-3
FINDINGS ON CHEST X-RAY SUGGESTIVE OF AN AORTIC TEAR*

1. Widened mediastinum
2. Abnormal aortic contour
3. Tracheal shift
4. Nasogastric tube shift
5. Left apical cap
6. Left or right paraspinal stripe thickening
7. Depression of the left main bronchus
8. Obliteration of the aorticopulmonary window
9. Left pulmonary hilar hematoma

*Findings are listed in the order of decreasing sensitivity.

Penetrating thoracic trauma is considerably easier to evaluate. Depending on the estimated trajectory of the missile or blade, bronchoscopy should be performed to evaluate the trachea. Esophagoscopy can be performed to evaluate the esophagus, but injuries have been missed with the use of this technique alone. Patients at risk also should undergo a soluble-contrast esophagram. Stable patients should be evaluated carefully for tracheal and esophageal injuries. Angiography occasionally is indicated.

Abdomen For the majority of patients suffering blunt abdominal trauma, it is not clear whether exploration is needed. Serial examinations by the same surgeon can detect early peritoneal inflammation and the need for laparotomy before serious infections and hemorrhagic complications occur. In contrast to gunshot wounds, stab wounds that penetrate the peritoneal cavity are less likely to injure intraabdominal organs. Superficial anterior and lateral stab wounds to the trunk may be explored under local anesthesia in the emergency room to determine whether the peritoneum has been violated. Stab wounds to the flank and back are more difficult to evaluate. Some authorities have recommended a triple-contrast CT scan to detect occult retroperitoneal injuries of the colon, duodenum, and urinary tract. Diagnostic peritoneal lavage (DPL) is the most sensitive test available for determining the presence of intraabdominal injury.

Blunt abdominal trauma is evaluated by ultrasound imaging in most major trauma centers and, in selected patients, with CT

scanning to refine the diagnosis. Ultrasound performed by a surgeon or an emergency physician in the emergency room has largely replaced DPL. Ultrasound is used in specific anatomic regions (e.g., Morison's pouch, the left upper quadrant, the pelvis) to identify free intraperitoneal fluid. Despite these limitations, CT is an important diagnostic tool because of its specificity for hepatic, splenic, and renal injuries. CT is indicated primarily for hemodynamically stable patients who are candidates for nonoperative therapy. CT also is indicated for hemodynamically stable patients who have unreliable physical examinations or other conditions (i.e., intracranial injury) requiring CT evaluation.

Pelvis Blunt injury to the pelvis frequently produces complex fractures. Plain x-rays reveal gross abnormalities, but CT scanning may be necessary to assess the pelvis for stability. Urethral injuries are suspected by the findings of blood at the meatus, scrotal or perineal hematomas, and a high-riding prostate on rectal examination. Urethrograms should be done in stable patients before placing the Foley catheter to avoid false passage and subsequent stricture.

Life-threatening hemorrhage can be associated with pelvic fractures. The source may be the lower lumbar arteries and veins or branches of the internal iliac arteries and veins. These injuries are frequently not amenable to surgical repair and usually occur with disruption of the posterior elements of the pelvis.

Extremities Injury of the extremities from any cause requires plain x-ray films to evaluate fractures. Physical examination serves to identify and localize arterial injuries in many instances. Physical findings are classified as hard signs or soft signs (Table 6-4). Hard signs constitute indications for operative exploration, whereas

TABLE 6-4
SIGNS AND SYMPTOMS OF ARTERIAL INJURY

Hard Signs (Operation mandatory)	Soft Signs (Further evaluation desirable)
Pulsatile hemorrhage	Proximity
Significant hemorrhage	Minor hemorrhage
Thrill or bruit	Small hematoma
Acute ischemia	Associated nerve injury

soft signs are indications for observation or additional testing. Arteriography may be helpful in localizing the injury in some patients with penetrating injuries and hard signs.

The controversy in vascular trauma is in the management of patients with soft signs of injury, particularly injuries that are in proximity to major vessels. Some of these patients will have arterial injuries that require repair. One approach is to measure systolic blood pressures using Doppler ultrasound and compare the injured side with the uninjured side. If the pressures are within 10 percent of each other, a significant injury is excluded, and no further evaluation is performed.

TREATMENT

TRANSFUSION

Most trauma patients receive between 1 and 5 units of packed red blood cells (pRBCs) and no other components, but major trauma centers have the capability of transfusing tremendous quantities of blood components. It is not unusual for 100 component units to be transfused during one procedure. Red cell transfusion rates of 20–40 units of pRBCs per hour are common in severely injured patients.

Transfusion practices in trauma require the surgeon to identify the insidious signs of coagulopathy, such as excessive bleeding from the cut edges of skin, fascia, and peritoneum that were previously controlled. The usual measurements of coagulation capability, i.e., prothrombin time (PT), partial thromboplastin time (PTT), and platelet count, have a turnaround time of more than 30 min in most institutions. Under such conditions, transfusion must be empiric and based on the surgeon's observations. At the first sign of coagulopathic hemorrhage, the previously lost plasma proteins and platelets must be restored with fresh frozen plasma (FFP) and platelet packs.

Platelet dysfunction is a well-documented complication of massive transfusion that is aggravated by associated hypothermia.[3] Consequently, the recommended target of more than 100,000/mm^3 for platelet transfusion in other high-risk patients should be extended to the severely injured.

Blood typing and, to a lesser extent, crossmatching are essential to avoid life-threatening intravascular hemolytic transfusion reactions. A complete type and crossmatch requires 20–45 min to complete and reduces the risk of an intravascular hemolysis to approximately 0.004 percent. Trauma patients requiring emergency transfusions are given type O, type-specific, or biologically

compatible red blood cells. As a cross-check for ABO compatibility, a saline crossmatch often is performed.

The administrative and laboratory time required is approximately 5 min, and the risk of intravascular hemolysis is about 0.05 percent. The risk increases to 1.0 percent with a history of previous transfusions or pregnancy and up to 3.0 percent with both. If blood is subsequently needed urgently, low-titer, type-specific red cells can be administered with the same risk of intravascular hemolysis as with fully typed and crossmatched blood, provided the screen for irregular antibodies is negative. Unstable patients should receive O-negative, O-positive, or type-specific red cells, depending on the patient's age and sex and the availability of blood cell types. Other components should be type specific or biologically compatible.

PROPHYLACTIC MEASURES

All injured patients undergoing an operation should receive preemptive antibiotic therapy. Recommended are second-generation cephalosporins for laparotomies and first-generation cephalosporins for all other operations. Tetanus prophylaxis is administered to all patients according to the American College of Surgeons guidelines. Deep venous thrombosis and other venous complications occur more often in injured patients than generally is believed. This is particularly true for patients with major fractures of the pelvis and lower extremities, those with spinal cord injury or in a coma, and those with injury of the large veins in the abdomen and lower extremities.

Another prophylactic measure is thermal protection. Hemorrhagic shock impairs perfusion and metabolic activity throughout the body. With declining metabolism, heat production and body temperature decrease. The injured patient receives a second thermal insult with the removal of insulating clothing. As a result, trauma patients can become seriously hypothermic, with temperatures as low as 34°C by the time they reach the operating room. Hypothermia impairs coagulation and myocardial contractility and increases myocardial irritability. Intentional hypothermia has protective features for patients with massive head injuries, but most physicians agree that the deleterious effects outweigh the potential benefits. Injured patients whose intraoperative core temperature drops below 32°C are at risk for fatal arrhythmias and defective coagulation.

VASCULAR REPAIR

The initial control of vascular injuries should be accomplished digitally by applying enough pressure directly on the bleeding site to

stop the hemorrhage. The exposed intima and media at the site of the injury are highly thrombogenic, and small clots often form. These clots should be removed carefully to prevent thrombosis or embolism when the clamps are removed. Because of the frequency that embolism occurs, routine balloon catheter exploration of the distal vessel has been recommended. Ragged edges of the injury site should be judiciously debrided using sharp dissection.

Injuries of the large veins such as the venae cavae or the innominate and iliac veins pose a special problem for hemostasis. Numerous large tributaries make adequate hemostasis difficult to achieve, and their thin walls render them susceptible to additional iatrogenic injury. If hemostasis is not adequate to expose the vessel proximal and distal to the injury, sponge sticks can be placed strategically on either side of the injury and carefully adjusted to improve hemostasis.

Some arteries and most veins can be ligated without significant sequelae. Arteries for which repair should always be attempted include the aorta and the carotid, innominate, brachial, superior mesenteric, proper hepatic, renal, iliac, femoral, and popliteal arteries. In the forearm and lower leg, at least one of the two palpable vessels should be salvaged. The list of veins for which repair should be attempted is the superior vena cava, the inferior vena cava proximal to the renal veins, and the portal vein. There are notable vessels for which repair is not necessary, e.g., the subclavian artery and the superior mesenteric vein. The portal vein can be ligated successfully provided adequate fluid is administered to compensate for the dramatic but transient edema that occurs in the bowel. Some arterial injuries have been treated by observation without subsequent complications. These include small pseudoaneurysms, intimal dissections, small intimal flaps and arteriovenous fistulas in the extremities, and occlusions of small (<2 mm) arteries. Lateral suture is appropriate for small arterial injuries with little or no loss of tissue. End-to-end anastomosis is used if the vessel is transected or nearly so. The severed ends of the vessel are mobilized, and small branches are ligated and divided as necessary to obtain the desired length. Arterial defects of 1–2 cm usually can be bridged.

Interpositional grafts are used when end-to-end anastomosis cannot be accomplished without tension despite mobilization. For vessels less than 6 mm in diameter, autogenous saphenous vein from the groin should be used because polytetrafluoroethylene (PTFE) grafts less than 6 mm in diameter have a prohibitive rate of thrombosis. Injuries of the brachial, popliteal, and internal carotid arteries require the saphenous vein for interpositional grafting. Larger arteries must be bridged by artificial grafts.

Arterial injuries are often grossly contaminated from enteric or external sources, in which case many surgeons are reluctant to place artificial grafts in situ. This situation arises most often in injuries to the aortic or iliac artery when the colon also is injured. For the aorta, there are few options. Even in the presence of fecal contamination, it is common practice to use PTFE or Dacron in situ for aortic injuries. A similar approach can be used for injuries to the iliac artery, but in most cases this can be avoided by the innovative use of transposition procedures.

Venous injuries are more difficult to repair successfully because of their propensity to thrombose. Small injuries without loss of tissue can be treated with lateral suture. More complex repairs often fail. Thrombosis does not occur acutely but rather gradually over 1–2 weeks. Adequate collateral circulation, sufficient to avoid acute venous hypertensive complications, usually develops within several days. It is reasonable to use PTFE for venous interpositional grafting and accept a gradual but eventual thrombosis while waiting for collateral circulation to develop.

STAGED OPERATIONS

Staged operations are indicated when a coagulopathy develops and core temperature drops below 34°C. A refractory acidosis is almost always present. Several unorthodox techniques can be used to expedite wound closure. Bleeding raw surfaces, often of the liver, are packed with laparotomy pads. Small enteric injuries are closed with staples, and large ones are stapled on both sides with the GIA stapler and the damaged segment removed. Clamps may be left on unrepaired vascular injuries, or the vessels may be ligated. Injuries of the pancreas and kidneys are not treated if they are not bleeding. No drains are placed, and the abdomen is closed with sharp towel clips placed 2 cm apart, which include only the skin. The goal is to complete the procedure as soon as possible. If the patient's condition improves, as evidenced by normalization of coagulation studies, the correction of acid-base imbalance, and a core temperature of at least 36°C, the patient should be returned to the operating room for removal of packs and definitive treatment of injuries.

A second complication is referred to as the *abdominal or thoracic compartment syndrome*, and it is caused by an acute increase in intracavitary pressure. In the abdomen, the compliance of the abdominal wall and the diaphragm permits the accumulation of many liters of fluid before intraabdominal pressure (IAP) increases. The resulting edema may be dramatic. As fluid continues to accumulate, the compliant limit of the abdominal cavity is eventually exceeded, and IAP increases. When IAP exceeds 15 mmHg, serious physiologic changes begin to occur. As IAP exceeds 25–30 mmHg, life-threatening hypoxia and anuric renal failure occur. Cardiac out-

put is further reduced but can be returned toward normal with volume expansion and inotropic support. The only method for treating hypoxia and renal failure is to decompress the abdominal cavity by opening the incision. This results in an immediate diuresis and a resolution of hypoxia. Failure to decompress the abdominal cavity eventually causes lethal hypoxia or organ failure.

NONOPERATIVE MANAGEMENT

Nonoperative treatment for blunt injuries of the liver, spleen, and kidneys is the rule rather than the exception. Up to 90 percent of children and 50 percent of adults are treated in this manner. The primary requirement for this therapy is hemodynamic stability. The extent of the patient's injuries should be delineated by CT scanning. Recurrent hemorrhage from the liver and kidneys has been infrequent, but delayed hemorrhage or rupture of the spleen is an important consideration in the decision to pursue nonoperative management. The patient should be monitored in the intensive care unit for the first 24 h.

Head

Attention is focused on maintaining or enhancing cerebral perfusion rather than merely lowering intracranial pressure (ICP). Hyperventilation to a PCO_2 below 30 mmHg to induce cerebral vasoconstriction exacerbates cerebral ischemia despite decreasing ICP. Secondary iatrogenic cerebral injuries cause more harm than previously appreciated. Other treatments or conditions that must be avoided include decreased cardiac output because of the excessive use of osmotic diuretics, sedatives, or barbiturates, and hypoxia. The tube also permits the withdrawal of cerebrospinal fluid, which is the safest method for lowering ICP. Although an ICP of 10 mmHg is believed to be the upper limit of normal, therapy usually is not initiated until the ICP reaches 20 mmHg. Cerebral perfusion pressure (CPP), which is equal to the mean arterial pressure (MAP) minus the ICP, is an important measurement that is used to monitor therapy. The lowest acceptable CPP is 60 mmHg.

Indications for operative intervention for space-occupying hematomas are based on the amount of midline shift, the location of the clot, and the patient's ICP. A shift of more than 5 mm usually is considered an indication for evacuation.

Neck

Cervical Spine Treatment of injuries to the cervical spine is based on the level of injury, the stability of the spine, the presence of subluxation, the extent of angulation, and the extent of

neurologic deficit. Surgical fusion usually is reserved for those with neurologic deficit, those who demonstrate angulation greater than 11 degrees on flexion and extension x-rays, or those who are unstable after external fixation.

Spinal Cord Injuries of the spinal cord, particularly complete injuries, are essentially untreatable. Approximately 3 percent of patients who present with flaccid quadriplegia have concussive injuries, and these patients represent the very few who seem to have miraculous recoveries. Methylprednisolone improves the outcome (usually one or two spinal levels) for those who receive the corticosteroid within 8 h of injury.

Larynx The larynx may be fractured by a direct blow, which can result in airway compromise. A hoarse voice in a trauma patient is highly suggestive of laryngeal fracture. In patients with severe fracture, a cricothyroidotomy or tracheostomy should be performed to protect the airway. The larynx is repaired with fine wires and sutures. If direct repair of internal laryngeal structures is necessary, the thyroid cartilage is split longitudinally in the midline and opened like a book. This is referred to as a *laryngeal fissure.*

Carotid and Vertebral Arteries Blunt injury to the carotid or vertebral artery may cause dissection, thrombosis, or pseudoaneurysm. More than half the patients with such injuries have a delayed diagnosis. Facial contact resulting in hyperextension and rotation appears to be the mechanism of injury. To reduce delayed recognition, CT angiography is performed in patients at risk to identify these injuries before neurologic symptoms develop. The injuries frequently occur at or extend into the base of the skull and usually are not surgically accessible. Accepted treatment for thrombosis and dissection is anticoagulation therapy with heparin followed by warfarin sodium (Coumadin) for 3 months. Pseudoaneurysms also occur near the base of the skull. If they are small, they can be followed with repeat angiography. If enlargement occurs, consideration should be given to the placement of a stent across the aneurysm by an interventional radiologist. Another method is to approach the intracranial portion of the carotid artery by removing the overlying bone and performing a direct repair.

Venous Injuries Thrombosis of the internal jugular veins caused by blunt trauma can occur unilaterally or bilaterally. These injuries usually are discovered incidentally and generally are asymptomatic. Bilateral thrombosis can aggravate cerebral edema in patients with serious head injuries. Stent placement should be con-

sidered in such patients if their ICP remains elevated. Laryngeal edema resulting in airway compromise also can occur.

PENETRATING INJURIES

Penetrating injuries in Zone II or Zone III that require operative intervention are explored using an incision along the anterior border of the sternocleidomastoid muscle. If bilateral exploration is necessary, the inferior end of the incision can be extended to the opposite side. Midline wounds or significant bilateral injuries can be exposed via a large collar incision at the appropriate level. Alternatively, bilateral anterior sternocleidomastoid incisions can be used.

Carotid and Vertebral Arteries Exposure of the distal internal carotid artery in Zone III is difficult. The first step is to divide the ansa cervicalis and mobilize the hypoglossal nerve. Next, the portion of the posterior belly of the digastric muscle that overlies the internal carotid artery is resected. The glossopharyngeal and vagus nerves are mobilized and retracted. If accessible, the styloid process and attached muscles are removed. At this point, anterior displacement of the mandible may be helpful, and various methods for accomplishing this have been devised. Some authorities have advocated division and elevation of the vertical ramus, but two remaining structures prevent exposure of the internal carotid to the base of the skull, the parotid gland and the facial nerve. Unless the surgeon is willing to resect the parotid and divide the facial nerve, division of the ramus seldom is helpful. Penetrating carotid artery injuries, regardless of the patient's neurologic status, usually require repair, except in comatose patients. Otherwise, the artery will need to be thrombosed or ligated. If ligation is necessary, the patient should be given anticoagulation therapy with heparin followed by warfarin sodium (Coumadin) for 3 months.

Vertebral artery injuries usually result from penetrating trauma, although thrombosis and pseudoaneurysms can occur from blunt injury. The diagnosis is made by angiography or when significant hemorrhage is noted posterior to the carotid sheath during neck exploration. Exposure of the vertebral artery above the C6 vertebra where it enters its bony canal is complicated by the overlying anterior elements of the canal and the tough fascia covering the artery between the elements. The artery is approached through an anterior neck incision by retracting the contents of the carotid sheath laterally. The muscular attachments to the anterior elements are removed. Care must be taken to avoid injury to the cervical spinal nerves that are located directly behind and lateral to the bony canal. Some authorities have recommended using a high-speed burr to

remove the anterior aspect of the canal, thereby avoiding the venous plexus between the elements. We have not found this to be a problem and often have excised the fascia between the elements and lifted the artery out of its canal with a tissue forceps. The treatment for vertebral artery injuries is ligation proximal and distal to the injury.

Trachea and Esophagus Injuries of the trachea are repaired with a running 3-0 absorbable monofilament suture. Tracheostomy is not required in most patients. Esophageal injuries are repaired in a similar fashion. If an esophageal wound is large, or if tissue is missing, a sternocleidomastoid muscle pedicle flap is warranted, and a closed-suction drain is a reasonable precaution. The drain should be near but not in contact with the esophageal or any other suture line. It can be removed in 7–10 days if the suture line remains secure.

Thoracic Outlet

Great Vessels Most injuries of the great vessels of the thoracic outlet (Zone I) are caused by penetrating trauma. Angiography is desirable for planning the incision. If this is not possible because of hemodynamic instability, a reasonable approach can be inferred from the chest x-ray and the location of the wounds. A median sternotomy is used for exposure of the innominate, proximal right carotid and subclavian, and proximal left carotid arteries.

The proximal left subclavian artery presents a unique challenge. Because it arises from the aortic arch far posteriorly, it is not readily approached via a median sternotomy. A posterolateral thoracotomy provides excellent exposure but severely limits access to other structures and is not recommended. The best option is to create a full-thickness flap of the upper chest wall. This is accomplished with a third or fourth interspace anterolateral thoracotomy for proximal control, a supraclavicular incision with a resection of the medial third of the clavicle, and a median sternotomy, which links the two horizontal incisions. The ribs can be cut laterally for additional exposure, which allows the flap to be folded laterally with little effort. The subclavian vein is mobilized, and the artery is directly underneath. The anterior scalene muscle is divided for injuries just proximal to the thyrocervical trunk; the relatively small phrenic nerve should be identified on its anterior aspect and spared. Iatrogenic injury to cords of the brachial plexus can occur.

Trachea and Esophagus The trachea and esophagus are difficult to approach at the thoracic outlet. The combination of a neck inci-

sion and a high anterolateral thoracotomy may be used. Alternatively, these structures can be approached via a median sternotomy, provided the left innominate vein and artery are divided. Temporary division of the innominate artery is tolerated well in otherwise healthy people, but the vessel should be repaired after treatment of the tracheal or esophageal injury. The vein does not need to be repaired. As in the neck, adjacent suture lines should be separated by viable tissue. A portion of the sternocleidomastoid can be rotated down for this purpose.

Chest

The most common life-threatening complications from blunt and penetrating thoracic injury are hemothorax, pneumothorax, or a combination of the two. Approximately 85 percent of these patients can be treated definitively with a chest tube. Common sources of blood loss include intercostal vessels, internal thoracic artery, pulmonary parenchyma, and the heart. Less common sources are the great vessels, aortic arch, azygos vein, superior vena cava, and inferior vena cava. Blood also may enter the chest from an abdominal injury through a perforation or tear in the diaphragm. The indications for thoracotomy in blunt trauma are based on specific preoperative diagnoses. These include pericardial tamponade, tear of the descending thoracic aorta, rupture of a main bronchus, and rupture of the esophagus.

Thoracic Incisions The selection of incision is important and depends on the organs being treated. For exploratory thoracotomy for hemorrhage, the patient is supine, and an anterolateral thoracotomy is performed. Depending on findings, the incision can be extended across the sternum or even farther for a bilateral anterolateral thoracotomy. The fifth interspace usually is preferred unless the surgeon has a precise knowledge of which organs are injured and knows that exposure would be enhanced by selecting a different interspace. The heart, lungs, aortic arch, great vessels, and esophagus are accessible with these incisions. Care should be taken to ligate the internal thoracic artery and veins if they are transected. This step often is overlooked, resulting in continuous blood loss that obscures the field and endangers the patient.

The heart also can be approached via a median sternotomy. Because little else can be done in the chest through this incision, it usually is reserved for stab wounds of the anterior chest in patients who present with pericardial tamponade. Posterolateral thoracotomies rarely are used because ventilation is impaired in the dependent lung, and the incision cannot be extended. There are two

specific exceptions. Injuries of the posterior aspect of the trachea or main bronchi near the carina tracheae are inaccessible from the left or from the front. The only possible approach is through the right chest using a posterolateral thoracotomy. A tear of the descending thoracic aorta can be repaired only through a left posterolateral thoracotomy. Because we use left heart bypass for these procedures, the patient's hips and legs are rotated toward the supine position to gain access to the left groin for femoral artery cannulation. It is also helpful for optimal exposure to resect the fourth rib and enter the chest through its bed.

Heart Most cardiac injuries are the result of penetrating trauma, and any part of the heart is susceptible. Control of hemorrhage while the heart is being repaired is crucial, and several techniques can be used. The atria can be clamped with a Satinsky vascular clamp. If the hole is small, a "peanut" sponge clamped in the tip of a hemostat can be placed into the wound, or the blood loss may be accepted while sutures are being placed. For larger holes, a 16F Foley catheter with a 30-mL balloon can be inflated with 10 mL of saline solution.

Immediate repair of valvular damage or acute septal defects rarely is necessary and requires total cardiopulmonary bypass, which has a high mortality in this situation. Most patients who survive to make it to the hospital do well with only external repair. The right coronary artery can be ligated anywhere, but the resulting arrhythmias may be extremely resistant to treatment. The left anterior descending and circumflex arteries cannot be ligated proximally without causing a large infarct.

Lungs Pulmonary injuries requiring operative intervention usually result from penetrating injury. Formerly the entrance and exit wounds were oversewn to control hemorrhage. This allowed for air embolism, which occasionally caused sudden death in the operating room or in the immediate postoperative period. Pulmonary tractotomy has been used to reduce this problem as well as the need for pulmonary resection. Linear stapling devices are inserted directly into the injury tract and positioned to cause the least degree of devascularization Lobectomy or pneumonectomy rarely is necessary. Lobectomy is indicated only for a completely devascularized or destroyed lobe. Parenchymal injuries severe enough to require pneumonectomy rarely are survivable, and major pulmonary hilar injuries necessitating pneumonectomy usually are lethal in the field.

Trachea and Esophagus Injuries of the trachea and esophagus are managed in the same fashion as described earlier for lung in-

juries. Because exposure can be difficult, provisions should be made to deflate the lung on the operative side by using a double-lumen endotracheal tube. Repair of injuries of the main bronchi and the trachea near the carina tracheae can result in a complete loss of ventilation when the overlying pleura is opened. Gases from the ventilator preferentially escape from the injury, and neither lung will be ventilated.

Descending Thoracic Aorta The occurrence of paraplegia from ischemic injury of the spinal cord has been a concern in injuries to the descending thoracic aorta. Conceptually, two techniques have been advocated. The simpler technique, often referred to as "clamp and sew," is accomplished with the application of vascular clamps proximal and distal to the injury and repair or replacement of the damaged portion of the aorta. This method results in transient hypoperfusion of the spinal cord distal to the clamps as well as all abdominal organs. If the clamping time is short, less than 30 min, paraplegia is uncommon. An alternative approach is to provide some method for maintaining a reasonable degree of perfusion for organs distal to the clamps. Two techniques have been used to accomplish this goal. The first is with the use of a shunt, a temporary extraanatomic route around the clamps. A heparin-impregnated tube, the Gott shunt, has been designed specifically for this purpose, but the volume of blood flow to the distal aorta is marginal. The second method is to use left heart bypass. With this method, a volume of oxygenated blood is siphoned from the left side of the heart and pumped into the distal aorta. The left superior pulmonary vein, rather than the left atrium, is cannulated to remove blood from the heart because the vein is tougher and less prone to tearing. The left femoral artery is cannulated to return the blood to the distal aorta.

Injuries of the transverse aortic arch do occur from blunt trauma. The proximal clamp usually can be placed between the innominate and left carotid arteries without cerebral infarction. The proximal clamp, however, cannot be placed proximal to the innominate artery. A possible approach to injuries in which the clamps completely exclude the cerebral circulation is to use profound hypothermia and circulatory arrest.

Abdomen

All abdominal explorations in adults are performed using a long midline incision because of its versatility. For children under the age of 6 years, a transverse incision may be advantageous. If the patient has been in shock or is currently unstable, no attempt should

be made to control bleeding from the abdominal wall until major sources of hemorrhage have been identified and controlled.

If exsanguinating hemorrhage is encountered on opening the abdomen, it usually is caused by injury to the liver, aorta, inferior vena cava, or iliac vessels. If the liver is the source, the hepatic pedicle should be immediately clamped (a Pringle maneuver) and the liver compressed posteriorly by tightly packing several laparotomy pads between the hepatic injury and the underside of the right anterior chest wall. This combination of maneuvers temporarily controls the hemorrhage from most survivable hepatic injuries.

If exsanguinating hemorrhage originates near the midline in the retroperitoneum, direct manual pressure is applied with a laparotomy pad, and the aorta is exposed at the diaphragmatic hiatus and clamped. The same approach is used in the pelvis except that the infrarenal aorta can be clamped, which is easier and safer because splanchnic and renal ischemia is avoided. Injuries of the iliac vessels pose a particular problem for emergency vascular control. Because there are so many large vessels in proximity, multiple vascular injuries are common. Venous injuries are not controlled with aortic clamping. A helpful maneuver in these instances is pelvic vascular isolation. For stable patients with large midline hematomas, clamping the aorta proximal to the hematoma also is a wise precaution.

Vascular Injuries Injury to the major arteries and veins in the abdomen is a technical challenge to the surgeon and often is fatal. All vessels are susceptible to injury in penetrating trauma. Vascular injuries in blunt trauma are far less common and usually involve the renal arteries and veins, although all other vessels, including the aorta, can be injured. Several vessels are difficult to expose: the retrohepatic vena cava, the suprarenal aorta, the celiac axis, the proximal superior mesenteric artery, the junction of the superior mesenteric, splenic, and portal veins, and the bifurcation of the vena cava. The suprarenal aorta, the celiac axis, and the proximal superior mesenteric and left renal arteries can be exposed by left medial visceral rotation. This is accomplished by incising the left lateral peritoneal reflection beginning at the distal descending colon and extending the incision past the splenic flexure, around the posterior aspect of the spleen, behind the gastric fundus, and ending at the esophagus. This incision permits the left colon, spleen, pancreas, and stomach to be rotated toward the midline. Division of the left crus of the diaphragm permits access to the aorta well above the celiac axis. In contrast, mobilization of the right colon and a Kocher maneuver expose the entire inferior vena cava except the retrohepatic portion, and they are technically simple. These are re-

ferred to as a *right medial visceral rotation*. The kidney can be left in situ or mobilized with the remaining viscera with right and left medial rotations.

The junction of the superior mesenteric, splenic, and portal veins can be exposed in elective surgery by dissecting the vessels from the pancreas, as required when performing a distal splenorenal shunt. In the presence of massive bleeding from a venous injury, this may be impossible. Therefore, the neck of the pancreas is divided without hesitation. This provides excellent exposure of this difficult area.

The bifurcation of the vena cava is obscured by the right common iliac artery. This vessel should be divided to expose extensive vena caval injuries of this area. The artery must be repaired after the venous injury is treated. Amputation occurs in approximately 50 percent of patients in whom the vessels are not repaired.

Liver The lower costal margins impair visualization and a direct approach to the liver. Exposure of the right lobe can be improved by elevating the right costal margin with a large Richardson retractor. The right lobe can be mobilized by dividing the right triangular and coronary ligaments. After division of the right triangular ligament, the dissection is continued medially, dividing the superior and inferior coronary ligaments. The right lobe then can be rotated medially into the surgical field. Mobilization of the left lobe is accomplished in the same fashion. Care must be taken when dividing any of the coronary ligaments because of their proximity to the hepatic veins and the retrohepatic vena cava. It may be necessary to extend the midline abdominal incision into the chest. This is best accomplished with a median sternotomy. The pericardium and diaphragm can be divided toward the center of the inferior vena cava. The combination of incisions provides outstanding exposure of the hepatic veins and retrohepatic vena cava while avoiding injury to the phrenic nerves.

The Pringle maneuver is one of the most useful techniques for evaluating the extent of hepatic injuries. In patients with extensive hepatic injuries, the Pringle maneuver differentiates between hemorrhage from the hepatic artery and portal vein, which ceases when the clamp is applied, and hemorrhage from the hepatic veins and retrohepatic vena cava, which does not. The prefered method is to manually tear the lesser omentum and place the clamp from the left side while guiding the posterior blade of the clamp through the foramen of Winslow with the aid of the left index finger. This approach has the advantage of avoiding injury to the structures within the hepatic pedicle, ensuring that the clamp will be placed properly the first time, and including any anomalous or accessory left

hepatic arteries between blades of the clamp. The temporizing hemostatic techniques that have proved most useful are hepatic compression, the Pringle maneuver, and perihepatic packing. Manual compression is best suited for immediate attempts to prevent exsanguination and for periodic control during a complex procedure. Perihepatic packing also is capable of controlling hemorrhage from most hepatic injuries, and it has the advantage of freeing the surgeon's hands. The laparotomy pads, two or three stacked together, should remain folded. The right costal margin is elevated, and the pads are strategically placed over and around the bleeding site. Additional pads should be placed between the liver, diaphragm, and anterior chest wall until the bleeding has been controlled. Ten to fifteen pads may be required to control the hemorrhage from an extensive right lobar injury. Hemorrhage from the left lobe usually can be controlled by mobilizing the lobe and compressing it between the surgeon's hands. Tight packing can compress the inferior vena cava and reduce cardiac filling, and the right diaphragm will be forced cephalad, increasing airway pressure and decreasing tidal volume and functional residual capacity.

Another option for temporary control of hepatic hemorrhage is to use a tourniquet. After mobilization of the bleeding lobe, a 1-in Penrose drain is wrapped around the liver near the anatomic division between the left and right lobes. The drain is cinched until hemorrhage ceases; tension is maintained by placing a clamp on the drain. Tourniquets are difficult to use, however, because they often slip off or even tear through the parenchyma. Special techniques have been developed for controlling hemorrhage from juxtahepatic venous injuries. These formidable procedures include hepatic vascular isolation with clamps, the atriocaval shunt, and the Moore-Pilcher balloon. Hepatic vascular isolation with clamps is accomplished by the application of a Pringle maneuver, clamping the aorta at the diaphragm, and clamping of the suprarenal and suprahepatic vena cava. Although this technique has success in elective procedures, its use in trauma patients has had mixed results because patients in profound hemorrhagic shock do not tolerate the precipitous loss of venous return to the heart.

The atriocaval shunt was designed to achieve hepatic vascular isolation while permitting venous blood to enter the heart from below the diaphragm. Enthusiasm for the shunt has declined because mortality rates with its use range from 50–80 percent.

Numerous methods for the definitive control of hepatic hemorrhage have been developed. Minor lacerations may be controlled with manual compression applied directly to the injury site. For similar injuries that do not respond to compression, topical hemostatic techniques have been successful. Small bleeding vessels may

be controlled with electrocautery, although the power output of the machine may have to be increased. Bleeding surfaces immune to electrocautery may respond to the argon beam coagulator. Microcrystalline collagen can be used.

Suturing of the hepatic parenchyma is an effective hemostatic technique. This treatment has been maligned as a cause of hepatic necrosis, but hepatic sutures often are used for persistently bleeding lacerations less than 3 cm in depth. It also is an appropriate alternative for deeper lacerations if the patient will not tolerate further hemorrhage. The preferred suture is 2-0 or 0 chromic attached to a large, curved, blunt needle. The large diameter of the suture helps to prevent it from pulling through Glisson's capsule. A simple running technique is used to approximate the edges of shallow lacerations. Deeper lacerations can be managed with interrupted horizontal mattress sutures placed parallel to the edge of the laceration. When tying the suture, adequate tension exists when visible hemorrhage ceases or the liver blanches around the suture.

Hepatic arterial ligation may be appropriate for patients with recalcitrant arterial hemorrhage from deep within the liver. Its utility is limited because hemorrhage from the portal and hepatic venous systems continues. Its primary role is in transhepatic injuries when application of the Pringle maneuver results in the cessation of arterial hemorrhage.

An uncommon, perplexing hepatic injury is the subcapsular hematoma. This lesion occurs when the parenchyma of the liver is disrupted by blunt trauma, but Glisson's capsule remains intact. Subcapsular hematomas discovered during an exploratory laparotomy that involve less than 50 percent of the surface of the liver and are not expanding or ruptured should be left alone or packed. Hematomas that are expanding during an operation may require exploration. An alternative strategy is to pack the liver to control venous hemorrhage, close the abdomen, and transport the patient to the angiographic suite for hepatic arteriography and embolization of the bleeding vessel. Ruptured hematomas require exploration and selective ligation, with or without packing. Omentum has been used to fill large defects in the liver, with the rationale that it provides an excellent source for macrophages and that it fills a potential dead space with viable tissue.

The complications after significant hepatic trauma include hemorrhage, infection, and various fistulas. Postoperative hemorrhage can be expected in a considerable percentage of patients treated with perihepatic packing. Arteriography with embolization can be considered in selected patients. Infections within and around the liver occur in about 3 percent of injured patients. Perihepatic infections develop more often in victims of penetrating trauma than

blunt trauma, presumably because of the greater frequency of enteric contamination of the former.

Gallbladder and Extrahepatic Bile Ducts Injuries of the gallbladder are treated by lateral suture or cholecystectomy, whichever is easier. Injuries of the extrahepatic bile ducts are a challenge. Because of the proximity of the portal vein, hepatic artery, and vena cava, associated vascular injuries are common, and the patient's physiologic status often is poor. These injuries can be treated by the insertion of a T tube through the wound or by lateral suture using 4-0 to 6-0 monofilament absorbable suture. Most transections and any injury associated with significant tissue loss require a Roux-en-Y choledochojejunostomy.

Injuries of the hepatic ducts are almost impossible to repair satisfactorily under emergency circumstances. One approach is to intubate the duct for external drainage and attempt a repair when the patient recovers. Alternatively, the duct can be ligated if the opposite lobe is normal and uninjured. For patients who are critically ill, the common duct also can be treated by intubation with external drainage.

Spleen Splenic injuries are treated by splenic repair (splenorrhaphy), partial splenectomy, resection, or nonoperatively, depending on the extent of the injury and the condition of the patient. Enthusiasm for splenic salvage has been driven by the evolving trend toward nonoperative management of solid organ injuries and the rare but often fatal complication of overwhelming postsplenectomy infection (OPSI).

Partial splenectomy can be used in patients in whom only a portion of the spleen has been destroyed, usually the superior or inferior half. After removal of the damaged portion, the same methods used to control hemorrhage from hepatic parenchyma can be used for the spleen. When placing horizontal mattress sutures across a raw edge, gentle compression of the parenchyma by an assistant facilitates hemostasis. After ligation of the sutures and release of compression, the spleen expands slightly and further tightens the sutures. If splenectomy is performed, vaccines against the encapsulated bacteria are administered. The pneumococcal vaccine is given routinely, and those effective against *Haemophilus influenzae* and *Neisseria meningitidis* should be used.

Diaphragm In blunt trauma the diaphragm is injured on the left in 75 percent of cases, presumably because the liver diffuses some of the energy on the right side. For blunt and penetrating trauma, the diagnosis is suggested by an abnormality of the diaphragmatic shadow on chest x-ray. Many of these are subtle, particularly with

penetrating injuries, and additional diagnostic evaluation may be warranted. The typical diaphragmatic injury from blunt trauma is a tear in the central tendon that may be large.

Duodenum Duodenal hematomas are caused by a direct blow to the abdomen, and they occur more often in children. Blood accumulates between the seromuscular and submucosal layers, eventually causing obstruction. Most duodenal hematomas in children can be managed nonoperatively with nasogastric suction and parenteral nutrition. If surgical intervention is necessary, evacuation of the hematoma is associated with equal success and fewer complications than bypass procedures.

Duodenal perforations can be caused by blunt and penetrating trauma. Mortality can exceed 30 percent if the lesion is not identified and treated within 24 h. The perforations are not reliably identified by initial oral contrast CT examinations. Most perforations of the duodenum can be treated by primary repair. The wound should be closed in a direction that results in the largest residual lumen.

Challenges arise when there is a substantial loss of duodenal tissue. Extensive injuries of the first portion of the duodenum can be repaired by debridement and anastomosis because of the mobility and rich blood supply of the distal gastric antrum and pylorus. In contrast, the second portion is tethered to the head of the pancreas by its blood supply and the pancreatic and accessory pancreatic ducts (ducts of Wirsung and Santorini) so that the length of duodenum that can be mobilized from the pancreas is limited to approximately 1 cm. As a result, suture repair of the second portion when tissue is lost often results in an unacceptably narrow lumen, and an end-to-end anastomosis is almost impossible, requiring more sophisticated repairs. For extensive injuries proximal to the accessory papilla, debridement and end-to-end anastomosis are appropriate. For lesions between the accessory papilla and the papilla of Vater, a vascularized jejunal graft, either a patch or a tubular interposition graft, may be required. Experience with these procedures is limited. Duodenal injuries with tissue loss distal to the papilla of Vater and proximal to the superior mesenteric vessels are best treated by Roux-en-Y duodenojejunostomy.

Injuries to the third and fourth portions of the duodenum with tissue loss pose other problems. Because of the short mesentery of the third and fourth portions of the duodenum, the risk of ischemia limits mobilization. While end-to-end duodenojejunal anastomoses are possible in these regions, the technique used must resemble that of a hand-sewn low anterior rectal anastomosis. Resection of the third and fourth portions and a duodenojejunostomy on the right side of the superior mesenteric vessels are recommended.

An important adjunct for high-risk or complex duodenal repairs is the pyloric exclusion technique. By occluding the pylorus and performing a gastrojejunostomy, the GI stream can be diverted away from the duodenal repair. If a fistula does develop, it is functionally an end fistula, which is easier to manage and more likely to close than a lateral fistula, and the patient can take food by mouth to maintain nutritional status. A linear staple line across the outside of the pylorus provides the most enduring pyloric closure.

Pancreas Blunt pancreatic transection at the neck of the pancreas can occur with a direct blow to the abdomen. As an isolated injury, it is more difficult to detect than blunt duodenal rupture, but a missed pancreatic injury is more benign. CT will not identify a significant number of transections if performed within 6 h of injury.

Optimal management of pancreatic trauma is determined by the location of the injury and whether or not the main pancreatic duct is injured. Pancreatic injuries in which the pancreatic duct is not injured may be treated by drainage or left alone. In contrast, pancreatic injuries associated with a ductal injury always require treatment to prevent pancreatic ascites or a major external fistula.

No ideal method exists for identifying pancreatic ductal injuries that cannot be ruled out by direct exploration. This dilemma tends to encourage aggressive local exploration, which may create a ductal injury where none existed. For injuries involving the neck, body, or tail of the pancreas, this is of minor consequence because a simple resection distal to the injury cures the lesion. This is not the case for injuries to the head of the pancreas, which cannot be treated with a simple resection. Rather than accepting the risks of pancreatography or aggressive local exploration, an option for identifying ductal injuries in the head of the pancreas is to do nothing other than drain the pancreas. If a pancreatic fistula or pseudocyst develops, the diagnosis is confirmed. The majority of pancreatic fistulas close spontaneously with only supportive care. This is the preferred approach to operative pancreatography when the diagnosis of ductal injury in the head of the pancreas is not apparent and endoscopic retrograde pancreatography (ERP) is not promptly available.

Several options are available for treating injuries of the neck, body, and tail of the pancreas when the main duct is transected. Distal pancreatectomy with splenectomy has been the preferred approach, but increasing interest in splenic preservation has stimulated the use of the splenic-preserving distal pancreatectomy.

For injuries to the head of the pancreas that involve the main pancreatic duct but not the intrapancreatic bile duct, there are few options. A more limited resection from the site of the injury to the neck of the pancreas, with preservation of the pancreaticoduodenal

vessels and common duct, allows closure of the injured proximal pancreatic duct. Pancreatic function can then be preserved by a Roux-en-Y pancreatojejunostomy with the distal pancreas.

In contrast to injuries of the pancreatic duct, diagnosis of injuries to the intrapancreatic common bile duct is simple. The first method is to squeeze the gallbladder and observe the pancreatic wound. Small tangential perforations of the intrapancreatic bile duct may heal with simple drainage, but it is seldom recommended. Most authorities advocate division of the common bile duct superior to the first portion of the duodenum, ligation of the distal common duct, and reconstruction with a Roux-en-Y choledochojejunostomy.

Pancreaticoduodenal Injuries Because the pancreas and duodenum are in physical contact, combined pancreaticoduodenal injuries are not uncommon, particularly in penetrating trauma. These lesions are dangerous because of the risk of duodenal suture line dehiscence and the development of a lateral duodenal fistula. The simplest treatment is to repair the duodenal injury and drain the pancreatic injury. This method is appropriate for combined injuries without major duodenal tissue loss and without pancreatic or biliary ductal injuries. With more extensive injuries, consideration should be given to providing additional protection for the duodenal suture line. Pyloric exclusion is preferred to other alternatives.

While most pancreatic and duodenal injuries can be treated with relatively simple procedures, a few require extensive operations, such as pancreatoduodenectomy. Examples of such injuries include transection of the intrapancreatic bile duct and the main pancreatic duct in the head of the pancreas, avulsion of the papilla of Vater from the duodenum, and destruction of the entire second portion of the duodenum. Most injuries of that nature are caused by higher-energy gunshot wounds. In patients with a pancreaticoduodenal injury who also have an intrapancreatic bile duct injury, it is possible to use the combination of a pyloric exclusion and Roux-en-Y choledochojejunostomy to avoid a pancreatoduodenectomy.

Colon There are three conceptually different methods for treating colonic injuries: primary repair, colostomy, and exteriorized repair. Primary repairs include lateral suture of perforations and resection of the damaged colon with reconstruction by ileocolostomy or colocolostomy. The advantage of primary repairs is that definitive treatment is performed at the initial operation.

The advantage of colostomy is that it avoids an unprotected suture line in the abdomen. The disadvantage is that a second operation is required to close the colostomy. Often overlooked

disadvantages are the complications associated with the creation of a colostomy, some of which may be fatal. Numerous large, retrospective and several prospective studies have demonstrated that primary repair is safe and effective in most patients with penetrating injuries. One approach is to repair all injuries regardless of the extent and location (including colocolostomy) and reserve colostomy for patients with protracted shock and extensive contamination. Systemic factors are more important than local factors in determining whether a suture line heals.

Complications related to the colonic injury and its treatment may include intraabdominal abscess, fecal fistula, wound infection, and stomal complications. Intraabdominal abscess occurs in approximately 10 percent of patients, and most are managed with percutaneous drainage. Fistulas occur in 1–3 percent of patients. Stomal complications include necrosis, stenosis, obstruction, and prolapse. Taken together, they occur in approximately 5 percent of patients, and most require reoperation. Necrosis is a serious complication that must be recognized and treated promptly. Failure to do so can result in life-threatening septic complications, including necrotizing fasciitis.

Rectum Rectal injuries are similar to colonic injuries with respect to the ecology of the luminal contents, the structures and blood supply of the wall, and the nature and frequency of complications. They differ in two important ways: mechanisms of injury and accessibility.

The diagnosis is suggested by the course of projectiles, the presence of blood on digital examination of the rectum, and history. Patients in whom a rectal injury is suspected should undergo proctoscopy. Hematomas, contusions, lacerations, and gross blood may be seen. If the diagnosis is in question, x-ray examinations with soluble contrast medium enemas are indicated.

Injuries of the intraperitoneal portion (including its posterior aspect) are treated as previously outlined in the section on colonic injuries. Access to extraperitoneal injuries is so restricted, especially in the narrow male pelvis, that indirect treatment usually is required. While colostomies proximal to a suture line are avoided in patients with colonic injuries, there is often no option in patients with extraperitoneal injuries; sigmoid colostomies are appropriate for most patients. Properly constructed loop colostomies are preferred because they are quick and easy to fashion. If a perforation is inadvertently uncovered during dissection, it should be repaired as described previously. Otherwise, it is not necessary to explore the extraperitoneal rectum to repair perforation. It may be extremely difficult or impossible to accomplish exploration.

Extraperitoneal injuries of the rectum should be drained via a retroanal incision. There have been reports of treating small extraperitoneal rectal injuries by suture or drainage alone. The outcomes have been acceptable, and colostomies have been avoided. There is insufficient experience to recommend this approach because pelvic sepsis associated with rectal injury is highly lethal.

Stomach and Small Intestine Injuries of the stomach and small bowel pose no special problems. Gastric injuries can be missed occasionally if a wound is located within the mesentery of the lesser curvature or high in the posterior fundus. A running two-layer suture line is preferred for the stomach because of its rich blood supply and because postoperative hemorrhage has occurred when the single-layer technique has been used in the stomach.

Wounds of the mesenteric border can be missed if the exploration is not comprehensive. Most injuries are treated with a lateral single-layer running suture. Multiple penetrating injuries often occur close together. Rather than performing many lateral repairs, judicious resections with end-to-end anastomoses can save considerable time.

Kidneys Three imaging techniques—CT, intravenous pyelography (IVP), and arteriography—can be used to evaluate accurately the extent of renal injury. Almost 95 percent of all blunt renal injuries are treated nonoperatively. The diagnosis is suspected by the finding of microscopic or gross hematuria and confirmed by CT or IVP. Most cases of urinary extravasation and hematuria resolve in a few days with bed rest. Persistent gross hematuria can be treated by embolization. Persistent urinomas can be drained percutaneously. If a perinephric hematoma is encountered during laparotomy from blunt trauma, exploration is indicated if it is expanding or pulsatile.

Hemostatic and reconstructive techniques used to treat blunt renal injuries are similar to those used to treat the liver and spleen. The collecting system should be closed separately and the renal capsule preserved to close over the repair of the collecting system. Permanent sutures should be avoided because of the risk of calculus formation. We prefer absorbable monofilament sutures because of their lack of abrasiveness.

The renal arteries and veins are uniquely susceptible to traction injury caused by blunt trauma. As the artery is stretched, the inelastic intima and media may rupture. This causes thrombus formation, resulting in high-grade stenosis or thrombosis. The injury can be detected by CT, IVP, or duplex scanning. If the patient does not have more urgent injuries and treatment and repair can be accomplished within 3 h of admission, it should be attempted.

Ureters Injuries of the ureters from external trauma are rare. They occur in a few patients with pelvic fractures and are uncommon in penetrating trauma because the silhouette they present is small. The diagnosis in blunt trauma may be made by CT, IVP, or retrograde ureterography. If an injury is suspected but not identified, methylene blue or indigo carmine is administered intravenously. Staining of the tissue adjacent to the injury can facilitate identification of the injury site. Most injuries can be repaired primarily using the same technique as that described earlier for small arteries, using 5-0 absorbable monofilament suture. When the ureter is mobilized, the dissection should be at least 1 cm lateral and medial to the ureter to avoid injury to its delicate vascular plexus.

Bladder Bladder injuries are diagnosed by cystography, CT, or during laparotomy. A postvoid view enhances the accuracy of cystography. Blunt ruptures of the intraperitoneal portion are closed with a running single-layer closure using 3-0 absorbable monofilament suture. Blunt extraperitoneal rupture is treated with a Foley catheter; direct operative repair is not necessary. Penetrating bladder injuries are treated in the same fashion, although injuries near the trigone should be repaired through an incision in the dome so that iatrogenic injury to the intravesicular ureter is avoided by direct visualization.

Urethra Blunt disruption of the posterior urethra is managed by bridging the defect with a Foley catheter. This usually requires passing catheters through the urethral meatus and through an incision in the bladder. Once the catheter bridges the defect, healing occurs as the intervening hematoma resorbs. Strictures are not uncommon but can be managed electively. Penetrating injuries are treated by direct repair.

Gynecologic Injuries Occasionally, the vagina is lacerated by a sharp bone fragment from a pelvic fracture. The usual hemostatic techniques are used to control bleeding, and suture repair is used to close defects that communicate with a lumen. Transection at the injury site with proximal ligation and distal salpingectomy is a more prudent approach.

Trauma in pregnancy also is rare. Blunt trauma can cause uterine rupture, which almost always results in fetal demise. The outcome of penetrating uterine injuries is more variable and depends on penetration of the uterine cavity, damage to the placenta, and fetal injury.

Pelvis

Pelvic fractures can cause exsanguinating retroperitoneal hemorrhage without associated major vascular injury; branches of the internal iliac vessels and the lower lumbar arteries often are responsible. Hemorrhage also comes from small veins and from the cancellous portion of the fractured bones. A direct surgical approach rarely is effective because many of the sources of hemorrhage are outside the surgical field.

Several methods have been used to control hemorrhage associated with pelvic fractures. These include immediate external fixation, medical antishock trousers (MAST), angiography with embolization, and pelvic packing. No single technique is effective for treating all fractures, and there is little agreement among specialists as to which should be used. Anterior external fixation is not intended to provide definitive fracture stabilization in most instances. It is intended to decrease pelvic volume, to tamponade bleeding, and to prevent secondary hemorrhage that may occur if the fractured bones shift. Antishock trousers can provide some stability for the fracture and probably tamponade venous hemorrhage. Disadvantages are the loss of access to the abdomen and the risk of lower extremity compartment syndrome. Angiography with embolization is effective for controlling arterial hemorrhage.

Another challenge is the open pelvic fracture. In many instances the wounds are located in the perineum, and the risk of pelvic sepsis and osteomyelitis is high. To reduce the risk of infection, a sigmoid colostomy is recommended. The pelvic wound is manually debrided and irrigated daily with a high-pressure pulsatile irrigation system until granulation tissue covers the wound. The wound is then left to heal by secondary intention. This approach has been highly successful (Fig. 6-2).

Extremities

Vascular Injuries with Fractures Vascular injuries associated with fractures are rare and also are more severe than isolated vascular injuries or fractures, and amputation rates of more than 50 percent have been noted. These injuries can be caused by blunt and penetrating trauma. Particular fractures and dislocations are more likely to be associated with vascular injury than others. In the upper extremity, a fracture of the clavicle or the first rib may lacerate the distal subclavian artery. The axillary artery may be injured in patients with dislocations of the shoulder or proximal humeral fractures. Supracondylar fractures of the distal humerus and

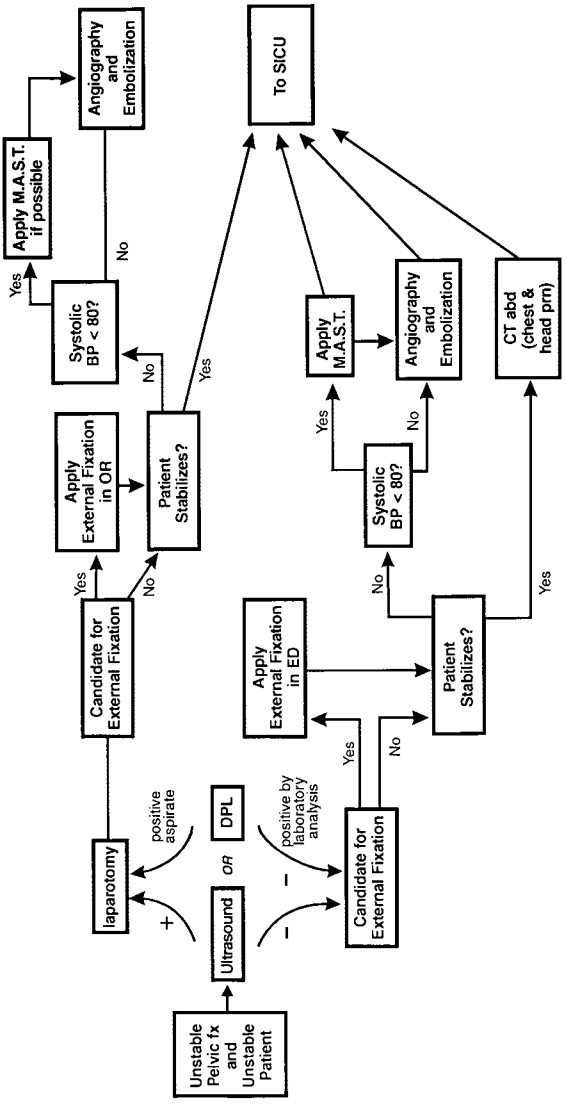


FIGURE 6-2 Algorithm for the management of mechanically unstable pelvic fractures in hemodynamically unstable patients.

dislocations of the elbow are known for their association with brachial artery injuries. In all these fractures and dislocations, vascular injuries are uncommon and occur in only a small fraction of patients.

In the lower extremity, the orthopaedic injury most commonly associated with vascular injury is dislocation of the knee, in which the popliteal artery or vein may be injured in as many as 30 percent of patients. The popliteal vessels also may be injured in patients with supracondylar fractures of the femur or tibial plateau fractures. Vascular injury can occur in patients with combined fractures of the tibia and fibula.

Compartment Syndrome A compartment syndrome can occur anywhere in the extremities, including the thighs, buttocks, arms, and hands. The pathophysiology is an acute increase in pressure in a closed space that impairs blood flow to the structures within. The causes of extremity compartment syndrome include arterial hemorrhage into a compartment, venous ligation or thrombosis, crush injuries, infections, crotalid envenomation, and ischemia/reperfusion. In conscious patients, pain is the prominent symptom.

Treatment consists of measures to reduce compartment pressure, including elevation of the extremity, evacuation of hematomas, and fasciotomy. The evacuation of hematomas as a consequence of arterial injury almost always results in a fasciotomy because the compartment must be opened to treat the vascular injury. Note that the soleus muscle must be detached from the tibia to decompress the deep flexor compartment.

Prognosis is related to the severity, duration, and cause of the compartment syndrome. The best results are obtained in patients with arterial hemorrhage and venous ligation or thrombosis who undergo early fasciotomy. Those who develop compartment syndrome from crush injuries, crotalid envenomation, and particularly ischemia/reperfusion have a poor prognosis because of the preexisting muscle and nerve damage caused by the original insult. Fasciotomy should be attempted, although infection and amputation are a frequent outcome.

BITES AND STINGS OF ANIMALS AND INSECTS

Rabies

Circumstances surrounding the attack frequently furnish vital information as to whether or not vaccination is indicated. Most domestic animal bites are provoked attacks; if this history is obtained,

rabies vaccine usually can be withheld if the animal appears healthy. Bites during attempts to feed or handle an apparently healthy animal are generally regarded as provoked. Postexposure prophylaxis combining local wound treatment, passive immunization, and vaccination is over 90 percent effective when applied appropriately.

Clinical signs of rabies in wild animals cannot be interpreted reliably; therefore, any wild animal that bites or scratches a person should be killed at once (without unnecessary damage to the head) and the brain examined for evidence of rabies. It is accepted that the incubation period for rabies in human beings ranges from 10 days to 1 year, with most cases occurring within 20–90 days of exposure. In cases of exposure of the head, neck, or upper extremities, the incubation period is potentially less than 30 days.

Postexposure prophylaxis in addition to local wound treatment consists of human rabies immune globulin (HRIG) (Imogam Rabies) and vaccine (Table 6-5). There are two rabies vaccines available in the United States: human diploid cell rabies vaccine (HDCV) or rabies vaccine adsorbed (RVA) (Imovax). Either is administered in conjunction with HRIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV or RVA is given intramuscularly.

HRIG is administered only once to provide immediate antibodies until the patient responds to the vaccine by actively producing antibodies. If HRIG was not given when vaccination was begun, it can be given through the seventh day after administration of the first dose of vaccine.

Snakes

In North America, all the poisonous snakes of medical importance are pit vipers, of the family Crotalidae, and the coral snake, of the family Elapidae. The pit vipers include the rattlesnake, the cottonmouth moccasin, and the copperhead. Over 98 percent of bites occur on the extremities. Rattlesnakes are responsible for approximately 70 percent of deaths from snakebites, whereas death from the bite of a copperhead is extremely rare.

The venoms of poisonous snakes consist of enzymatic complex proteins that affect all soft tissues. Venoms have been shown to have neurotoxic, hemorrhagic, thrombogenic, hemolytic, cytotoxic, antifibrinolytic, and anticoagulant effects. Most venoms contain hyaluronidase, which enhances the rapid spread of venom by way of the superficial lymphatics.

Pain from the bite of a pit viper is excruciating, and probably the symptom that most easily differentiates poisonous from nonpoisonous snakebites. Pit vipers characteristically produce one or

two fang marks. Hypotension, weakness, sweating and chills, dizziness, nausea, and vomiting are other systemic symptoms. Symptoms can include swelling, tenderness, pain, and ecchymosis and may appear within minutes at the site of venom injection. If no edema or pain is present within 30 min after injury, the snake probably did not inject any venom. Swelling may continue to increase for 24 h.

The venom from rattlesnakes produces deleterious changes in the blood cells, defects in blood coagulation, injuries to the intimal linings of vessels, damage to the heart muscle, alterations in respiration, and to a lesser extent, changes in neuromuscular conduction. Pulmonary edema is common in severe poisoning, and hemorrhage into the lungs, kidneys, heart, and peritoneum can occur.

Blood should be drawn immediately for typing and crossmatching because hemolysis may later make this difficult. Because hemolysis and injury to kidneys and liver may occur, it is important to follow alterations in clotting mechanism, renal and liver function, and electrolyte status.

Management of Snake Bites Application of a tourniquet, incision, and suction are appropriate if used within 1 h of the time of the bite. The snake injects venom into the subcutaneous tissue, which is absorbed by capillaries and lymphatics. The tourniquet should be applied loosely to obstruct only venous and lymphatic flow. The tourniquet is not released once applied and may be left in place during the 30 min that suction is applied. The tourniquet may be removed after definitive treatment has been instituted and the patient is not in shock.

Incision and suction for 30 min may be beneficial if accomplished within 30 min after snakebite. The incision should be longitudinal and not cruciate. When two fang marks are seen, the depth of the venom injection is generally considered to be one-third of the distance between the fang marks.

The average snakebite does not require surgical excision. This procedure is reserved for the most severe envenomations. The most important treatment for a snakebite is antivenin, although many patients do not require it. Copperhead envenomation rarely necessitates antivenin. Most snakebite fatalities in the United States during the past 20 years have involved either delay in obtaining treatment, no antivenin treatment, or inadequate dosage. Because antivenin contains horse serum, before its administration, skin testing is required. Epinephrine 1:1000 in a syringe should be available before antivenin is given. Physicians confronted with this situation may obtain advice from the local poison center or the Antivenin Index Center of the Oklahoma Poison Information Center, Oklahoma City, Oklahoma (405–271–5454).

TABLE 6-5
RABIES POSTEXPOSURE PROPHYLAXIS SCHEDULE, UNITED STATES, 1991

Vaccination Status	Treatment	Regimen[a]
Not previously vaccinated	Local wound cleaning	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water.
	HRIG	20 IU/kg body weight. If anatomically feasible, up to one-half the dose should be infiltrated around the wound(s) and the rest should be administered IM in the gluteal area. HRIG should not be administered in the same syringe or into the same anatomic site as vaccine. Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV or RVA, 1.0 mL, IM (deltoid area[b]) one each on days 0, 3, 7, 14, and 28.

Previously vaccinated[c]	Local wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water.
	HRIG	HRIG should not be administered.
	Vaccine	HDCV or RVA, 1.0 mL, IM (deltoid area[b]), one each on days 0 and 3.

[a] These regimens are applicable for all ages groups, including children.

[b] The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

[c] Any person with a history of preexposure vaccination with HDCV or RVA, prior postexposure prophylaxis with HDCV or RVA, or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

SOURCE: Rabies Prevention—United States 1991: Recommendation of the Immunization Practices Advisory Committee (ACIP). *MMWR*, 40(RR-3):1–19, 1991.

Antivenin should be withheld until a physician can determine whether it is indicated. Approximately 30 percent of all poisonous snakebites in the United States result in no envenomation. The indication for antivenin is governed by the degree of envenomation. With frequent observations using the classification presented in Table 6-6, the severity of the bite is often found to increase with time, and therefore, a change in grade is observed. Most bites will have reached a final staging within 12 h.

Stinging Insects and Animals

HYMENOPTERA

The most important insects that produce serious and possibly fatal anaphylactic reactions are arthropods of the order Hymenoptera. This group includes the honeybee, bumblebee, wasp, yellow and black hornet, and the fire ant. The venom of these stinging insects is just as potent as that of snakes and causes more deaths in the United States yearly than are caused by snakebites.

Symptoms are one or more of the following: localized pain, swelling, generalized erythema, a feeling of intense heat throughout the body, headache, blurred vision, injected conjunctivae, swollen and tender joints, itching, apprehension, urticaria, petechial hemorrhages of the skin and mucous membranes, dizziness, weakness, sweating, severe nausea, abdominal cramps, dyspnea, constriction of the chest, asthma, angioneurotic edema, vascular collapse, and possible death from anaphylaxis. Fatal cases may manifest glottal and laryngeal edema, pulmonary and cerebral edema, visceral congestion, meningeal hyperemia, and intraventricular hemorrhage. Death results from a combination of shock, respiratory failure, and central nervous system changes. Most deaths from insect stings occur within 15–30 min.

STINGRAYS

Approximately 750 persons each year are stung by stingrays. As the spine, which is curved and has serrated edges, enters the flesh, the sheath surrounding the spine ruptures, and venom is released. As the spine is withdrawn, fragments of the sheath may remain in the wound. The wound edges are often jagged and bleed freely. Pain usually is immediate and severe, increasing to maximum intensity in 1–2 h and lasting for 12–48 h. Treatment consists of copious irrigation with water to wash out any toxin and fragments of the spine's integumentary sheath. Venom is inactivated when exposed to heat. The area of the bite should be placed in water as hot as the patient can stand without injury for 30 min to 1 h. After soaking, the wound may be further debrided and treated appropriately.

TABLE 6-6
GRADING OF CROTALID ENVENOMATION

Grade	Signs and Symptoms
0—No envenomation	One or more fang marks; minimal pain, less than 1 in of surrounding edema and erythema at 12 h, no systemic involvement.
I—Minimal envenomation	Fang marks, moderate to severe pain, 1 to 5 in of surrounding edema and erythema in the first 12 h after bite, systemic involvement usually not present.
II—Moderate envenomation	Fang marks; severe pain; 6 to 12 in of surrounding edema and erythema in first 12 h after bite; possible systemic involvement including nausea, vomiting, giddiness, shock, or neurotoxic symptoms
III—Severe envenomation	Fang marks; severe pain; more than 12 in of surrounding edema and erythema usually present and may include generalized petechiae and ecchymosis.
IV—Very severe envenomation	Systemic involvement is always present, and symptoms may include renal failure, blood-tinged secretions, coma, and death; local edema may extend beyond the involved extremity to the ipsilateral trunk.

PORTUGUESE MAN-OF-WAR

After a severe sting by a Portuguese man-of-war, there may be almost immediate severe nausea, gastric cramping, and constriction and tightness of throat and chest with severe muscle spasm. There is intense, burning pain with weakness and perhaps respiratory distress. The most important emergency treatment is to inactivate the nematocysts immediately to prevent their continuous firing of toxins. This is accomplished by applications of a substance of high alcohol content, such as rubbing alcohol, followed by application of a drying agent, such as flour, baking soda, talc, or shaving cream. The tentacles may then be removed by shaving. An alkaline agent such as baking soda is then applied in order to neutralize the toxins, which are acidic. Demerol and Benadryl may dramatically relieve the pain and symptoms. Aerosol corticosteroid-analgesic balm is helpful.

SPIDERS

Black Widow Spider The most common biting spider in the United States is the black widow (*Latrodectus mactans*). The female spider has a reddish orange hourglass-shaped marking on its ventral surface. *L. mactans* venom is primarily neurotoxic in action and centers on the spinal cord. After a bite by the black widow spider, the majority of patients experience pain within 30 min, and a small wheal with an area of erythema appears. Nausea and vomiting occur in approximately one-third of patients, headache in one-fourth, and dyspnea may develop. The time of onset of symptoms after the bite is 30 min to 6 h. The severe symptoms last from 24–48 h. Generalized muscle spasm is the most prominent physical finding. Cramping muscle spasms occur in the thighs, lumbar region, abdomen, or thorax. Priapism and ejaculation have been reported. Most patients recover within 24 h. Treatment consists of narcotics for the relief of pain and a muscle relaxant for relief of spasm. Methocarbamol (Robaxin) or 10 mL of a 10% solution of calcium gluconate relieves the symptoms. It is believed that calcium acts by depressing the threshold for depolarization at the neuromuscular junctions. Calcium gluconate may give instant relief of muscular pain, and methocarbamol can be administered intravenously 10 mL over a 5-min period, with a second ampule started in a saline solution drip. Although *L. mactans* antivenin is available, it rarely is required.

Brown Recluse Spider The distinguishing mark of the *Loxosceles reclusa* is the darker violin-shaped band over the dorsal cephalothorax. The spider is native to the south central United

States. The body ranges from 7–12 mm; including the legs, the spider's size ranges from 2–3 cm.

The initial bite may go unnoticed or be accompanied by a mild stinging sensation. Pain may recur 6–8 h afterward. A mild envenomation is associated with local urticaria and erythema that usually resolve spontaneously. More severe bites result in progression to necrosis and sloughing of skin with residual ulcer formation. A generalized macular and erythematous rash may appear in 12–24 h. Erythema develops, with bleb or blister formation surrounded by an irregular area of ischemia. A zone of hemorrhage and induration and a surrounding halo of erythema may develop peripherally. The central ischemia turns dark, and eschar forms by day 7; by day 14, the area sloughs, leaving an open ulcer. Approximately 3 weeks is required for the lesion to heal. The pain may be out of proportion with the size of the area involved. The progression from blue to black gives the bite a necrotic appearance, and the more severe bites develop within a few hours to 2 days.

Treatment is conservative because of the difficulty in predicting the severity of the bite. Various treatments have been advocated in addition to early excision, including treatment with corticosteroids, heparin, phentolamine, dextran, and infusion, but clinical studies have failed to identify the benefit of these agents. A leukocyte inhibitor, dapsone (used in leprosy), is effective in reducing inflammation at the site of the brown recluse venom injection. Treatment with dapsone is 100 mg daily for 14 days before surgical excision, if required.

SCORPIONS

Of the numerous species of scorpions in the United States, only one, *Centruroides exilicauda,* or the bark scorpion, is medically significant. It is found primarily in the desert Southwest. Ranging in length from 1–7 cm, it usually is yellowish brown in color and may have vertical bands on its dorsum. A tubercle at the base of the stinger distinguishes the bark scorpion from other species. The venom is neurotoxic and causes the release of neurotransmitters from the autonomic nervous system and the adrenal glands. The sting causes intense pain with few other local symptoms. Hyperesthesia persists at the site so that a light tap will reproduce the intense pain. The tap test reinforces the diagnosis. In addition to pain, other symptoms reflect the neurotoxic nature of the venom, including anxiety, blurred vision or temporary blindness, wandering eye movements, dyspnea, wheezing, dysphagia, involuntary urination and defecation, and opisthotonos. Somatic muscular contractions resembling seizures, hypertension, supraventricular tachyarrhythmias, and fever also are seen. These stings have been of

little significance in adults and are satisfactorily treated with cold compresses. Conversely, infants and small children have died from scorpion envenomation, although not since 1968. Small children with signs of envenomation should be admitted to the hospital and monitored.

For a more detailed discussion, see Burch JM, Franciose RJ, and Moore EE: Trauma, chap. 6 in *Principles of Surgery*, 7th ed.

CHAPTER

7

BURNS

Thermal burns and related injuries are a major cause of death and disability in the United States. The introduction of burn centers in 1945 heralded a rapid improvement in survival and reduction in morbidity of burn patients and provided the basis for regional specialty treatment centers in other disciplines. The initial acute care of a burn is only a small part of the total treatment. Burn patients often require years of supervised rehabilitation, reconstruction, and psychosocial support.

EPIDEMIOLOGY

In the United States, approximately 2 million individuals annually are burned seriously enough to seek health care. About 70,000 of these require hospitalization, and 5000 die. Burns are usually caused by carelessness or ignorance and are completely preventable; nearly half are smoking- or alcohol-related. More than 90 percent of all burns are preventable by taking ordinary precautions.

Advances in the care of burned patients during the past 20 years are among the most dramatic in medicine. The number of burn deaths in the United States has decreased from 15,000 in 1970 to 5000 in 1996. Over the same period, the size of burn associated with a 50 percent survival rate has increased from 30 percent of the total body surface area (TBSA) to over 80 percent TBSA in otherwise healthy young adults. Hospital stay has been cut in half. Ninety-six percent of patients admitted to burn centers survive, and 80 percent of them return to their preburn physical and social situation within a year of the injury.

The quality of burn care is not only measured by survival but also by long-term function and appearance. Although small burns are not usually life-threatening, they need the same attention as larger burns to achieve the best possible functional and cosmetic outcome. The interactive multidisciplinary burn team has proved to be the most efficient and least expensive method of treating serious burn injury. The goal for any burn is well-healed, durable skin with normal function and near-normal appearance. Scarring can be

minimized by appropriate early surgical intervention and long-term scar management. These goals require individualized patient care plans based on burn characteristics and host factors. Omission of any step in the treatment regimen can result in less than optimal outcome.

PATHOLOGY AND NATURAL HISTORY

Cutaneous burns are caused primarily by the application of heat to the skin resulting in coagulative necrosis of some or all of the epidermis and dermis. Cold, electricity, radiation, and caustic chemicals will result in similar pathologic damage. The thickness of skin varies with the age and sex of the individual and the area of the body. The thickness of the living epidermis is relatively constant, but keratinized (dead and cornified) epidermal cells may reach a height of 0.5 cm on the palms of hands and the soles of feet. The thickness of the dermis varies from less than 1 mm on eyelids and genitalia to more than 5 mm on the posterior trunk. The proportional thickness of skin in each body area in children is similar to that in adults, but infant skin thickness in each specific area may be less than half that of adult skin. The skin reaches adult thickness after puberty. In patients over 50 years of age, dermal atrophy begins, and the skin becomes thinner with age.

The depth of burn depends on the heat of the burn source, the thickness of the skin, the duration of contact, and the heat-dissipating capability of the skin (blood flow). A scald in an infant or elderly patient will be deeper than an identical scald in a young adult. Burns are classified according to increasing depth as first degree, second degree (superficial dermal and deep dermal), third degree (full thickness), and fourth degree. Because most deep burns are removed surgically and grafted, such a precise characterization is usually not necessary. A more pertinent classification might be *shallow burns* and *deep burns.*

Shallow Burns *First-Degree Burns* First-degree burns involve only the epidermis. They do not blister, but they are painful and become erythematous because of dermal vasodilation. In 2–3 days the erythema and the pain subside. By about day 4, the injured epithelium desquamates in the phenomenon of *peeling,* which is well known after sunburn.

Superficial Dermal Burns (Second Degree) Superficial dermal burns include the upper layers of dermis and characteristically form blisters at the interface of the epidermis and dermis. Blistering may

not occur immediately, and burns originally appearing to be first degree may be diagnosed as superficial dermal burns after 12–24 h. When blisters are removed, the wound is pink and wet, and currents of air passing over it cause pain. The wound is hypersensitive, and the burns blanch with pressure. If infection is prevented, superficial dermal burns heal spontaneously in less than 3 weeks and do so with no functional impairment. They rarely cause hypertrophic scarring, but the healed burn may never completely match the color of the surrounding normal skin.

Deep Burns *Deep Dermal Burns (Second Degree)* Deep dermal burns extend into the reticular layers of the dermis. Deep dermal burns also blister, but the wound surface is usually a mottled pink and white color immediately after the injury because of the varying blood supply to the dermis. The patient complains of discomfort rather than pain. When pressure is applied to the burn, capillary refill occurs slowly or may be absent. The wound is often less sensitive to pinprick than the surrounding normal skin. By the second day, the wound may be white and is usually fairly dry. If infection is prevented, these burns will heal in 3–9 weeks but do so with considerable scar formation. Unless active physical therapy is continued throughout the healing process, joint function can be impaired, and hypertrophic scarring is common.

Full-Thickness Burns (Third Degree) Full-thickness burns involve all layers of the dermis and can heal only by wound contracture, by epithelialization from the wound margin, or by skin grafting. Full-thickness burns appear white, cherry red, or black and may or may not have deep blisters. Full-thickness burns are leathery and firm and may be depressed when compared with adjoining normal skin. They are also insensitive to light touch or pinprick. The difference in depth between a deep dermal burn and a full-thickness burn may be less than a millimeter. The clinical appearance of full-thickness burns can resemble that of deep dermal burns. They may be mottled, they rarely blanch on pressure, and they may have a dry, white appearance. In some cases the burn is translucent, with clotted vessels visible in the depths. Some full-thickness burns, particularly immersion scalds, have a red appearance and may be confused with superficial dermal burns. However, they do not blanch with pressure. Full-thickness burns develop a classic burn eschar. If not debrided, the eschar separates from the underlying viable tissue over days or weeks.

Fourth-Degree Burns Fourth-degree burns involve not only all layers of the skin but also subcutaneous fat and deeper structures.

These burns almost always have a charred appearance, and frequently only the cause of the burn gives a clue to the amount of underlying tissue destruction. Electrical burns, contact burns, some immersion burns, and burns sustained by patients who are unconscious at the time of burning are commonly fourth degree.

ETIOLOGY

Scald Burns In civilian practice, scalds are the most common cause of burns, and the usual agent is water. Deliberate scalds are the most common form of reported child abuse and are responsible for about 5 percent of pediatric admissions to burn centers. At 140°F (60°C) ("medium" setting on a water heater), water results in a deep dermal or full-thickness burn in 3 s. At 156°F (69°C) ("high"), the same burn occurs in 1 s. Freshly brewed coffee from an automatic percolator generally is about 180°F (82°C). Hot cooking oil and grease may be in the range of 400°F, and scalds from these are usually deep dermal or full thickness. Factors that extend the duration of exposure also affect the depth of the burn. These include the viscosity of the hot liquid, clothing (which can retain heat), immersion, and the thickness of the skin burned.

Flame Burns Flame burns are the next most common and typically result in deep burns. Although the incidence of injuries caused by house fires has decreased with the use of smoke detectors, smoking-related fires, improper use of flammable liquids, automobile accidents, and ignition of clothing from stoves or space heaters still exact their toll. Patients whose bedding or clothes have been on fire rarely escape without some full-thickness burns.

Flash Burns Explosions of natural gas, propane, gasoline, and other flammable liquids cause intense heat for a very brief time. Unless it ignites, clothing is protective against flash burns. Flash burns generally have a distribution over all exposed skin, with the deepest areas facing the source of ignition. Flash burns are mostly dermal, but their depth depends on the amount and kind of fuel that explodes. These burns may cover a large skin area and be associated with significant thermal damage to the upper airway.

Contact Burns These burns result from contact with hot metals, plastic, glass, or hot coals. The area burned is usually limited in extent, but the injury is invariably very deep. Many industrial accidents involve contact with presses or other hot, heavy objects, resulting in associated crush injuries as well. Automobile accidents

may leave victims in contact with hot engine parts. The exhaust pipes of motorcycles cause a characteristic burn of the medial leg that is small but usually requires excision and grafting. Contact burns are often fourth-degree burns, especially those in unconscious or postictal patients and those caused by molten materials.

Electrical and Chemical Burns Electricity and chemicals, most commonly acids and alkalis, also cause coagulative necrosis of tissue. These are discussed more fully later.

HOSPITAL ADMISSION AND BURN CENTER REFERRAL

The need for hospital admission and specialized care for burns and/or smoke inhalation is dictated by the severity of symptoms, the magnitude of associated burns, and the presence of associated injuries or medical problems. Otherwise healthy patients with no burns and only mild symptoms from smoke inhalation [only a few expiratory wheezes, minimal sputum production, carboxyhemoglobin (COHb) level $<$ 10 percent, and normal blood gases] who have a place to go and someone to stay with them can be observed for an hour or two and then discharged. Any patient who is symptomatic with smoke inhalation and has more than trivial burns or preexisting cardiovascular or pulmonary disease should be admitted for observation. If the burns cover more than 15 percent TBSA, or if there are severe respiratory symptoms [air hunger, severe wheezing, copious (usually carbonaceous) sputum, COHb level $>$ 10 percent], the patient should be referred immediately to a burn unit.

Burn Severity and Classification The severity of injury caused by burns is directly related to the size of the total burn, the depth of the burn, the age of the patient, and associated medical problems or injuries. Burns are classified as minor, moderate, and severe. *Minor* burns are superficial and involve less than 15 percent TBSA. Approximately 95 percent of all burns treated in the United States are minor, and they rarely require hospitalization, except for concomitant disease or high risk, pain control, or social reasons. The physician should have a low threshold for admission of elderly patients and infants. Any patient (child or adult) with suspicion of abuse must be admitted.

Moderate burns may be superficial and involve 15–25 percent TBSA in adults or 10–20 percent TBSA in children, or they may be full-thickness injuries involving less than 10 percent TBSA. These patients usually do require hospitalization at least briefly for

stabilization and pain control. Newer techniques of wound care and closure have made burn care more complex, and an increasing number of patients with minor and moderate burns are being referred to specialized burn care facilities. Even if the total burn size is small, burns of the eyes, ears, face, hands, feet, or perineum require specialized care because of the cosmetic and functional risks associated with these injuries.

Burn Center Referral Criteria Patients with *major* burns should be referred to a specialized burn care facility or burn center. The currently accepted criteria defining major burns and identifying those patients who require triage to a burn center or referral after initial assessment and stabilization were promulgated by the American Burn Association (Table 7-1).

Transport and Transfer Protocols Definitive care should begin at the initial hospital and continue without interruption during transport and at the burn center. Once a patent airway is ensured and resuscitation begun, burned patients are eminently suitable for transport. Resuscitation can continue en route because the patient usually will remain stable for some period of time. Transfer should be from physician to physician, and contact should be established as soon as the patient arrives in the emergency room of the initial hospital.

Before transport, special attention should be paid to airway and oxygenation. Supplemental oxygen can be given during transport, but if the patient's oxygenation is marginal or there is any question of upper airway edema, it may be best to intubate and ventilate the patient. Intubation is difficult en route, especially under urgent circumstances. Two large-bore intravenous lines are mandatory. Patients transported by air should have a nasogastric tube inserted and placed on dependent drainage. If there is danger of compromised circulation due to circumferential full-thickness burns, escharotomies (see below) should be considered at the referring hospital, especially if the total hospital-to-hospital time will be more than 2 h. Burned patients have difficulty maintaining body temperature, and they should be warmly wrapped prior to transport. Bulky dressings, a blanket, and a Mylar sheet (usually available from the flight team) can help maintain body temperature.

EMERGENCY CARE

Care at the Scene

Airway Once flames are extinguished, initial attention must be directed to the airway. Immediate cardiopulmonary resuscitation is rarely necessary. Any patient rescued from a burning building or

TABLE 7-1
BURN CENTER REFERRAL CRITERIA

1. Second- and third-degree burns > 10 percent TBSA in patients under 20 or over 50 years of age
2. Second- and three-degree burns > 20 percent TBSA in any age group
3. Second- and three-degree burns involving the face, hands, feet, genitalia, perineum, and major joints
4. Third-degree burns > 5 percent TBSA in any age group
5. Electrical burns, including lightning injury
6. Chemical burns
7. Inhalation injury
8. Burns of any size in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
9. Burns with concomitant mechanical trauma (e.g., fractures) where the burn injury poses the greatest risk of morbidity or mortality (If the trauma poses the greater immediate risk, the patient should be treated initially and stabilized in a trauma center and then transferred to a burn center, in accord with established regional triage protocols.)
10. Burns in children if there are no qualified personnel or equipment for pediatric care at the initial hospital
11. Burns in patients requiring special social, emotional, and/or long-term rehabilitative support, including cases of suspected child abuse, substance abuse, etc.

exposed to a smoky fire should be placed on 100% oxygen by tight-fitting mask because of the possibility of smoke inhalation. If the patient is unconscious, an endotracheal tube should be placed and attached to a source of 100% oxygen.

Other Injuries and Transport Once an airway is secured, the patient is assessed for other injuries and then transported to the nearest appropriate hospital per EMS protocol. If a burn center is within a 30-min drive and the burn is severe, the patient should be taken directly to that facility. If appropriately trained, the emergency medical technicians should place an intravenous line and begin fluid administration of crystalloid solution at a rate of approximately 1 L/h. For transport, the patient should be wrapped in a

clean sheet and blanket. Sterility is not required. Before or during transport, constricting clothing and jewelry should be removed from burned parts because local swelling begins almost immediately and constricting objects will exacerbate the edema formation and possibly compromise distal circulation.

Cold Application Smaller burns, particularly scalds, are treated with immediate application of cool water. After several minutes have elapsed, further cooling does not alter the pathologic process. Iced water should never be used even on the smallest of burns. If ice is used on larger burns, systemic hypothermia may follow, and the associated cutaneous vasoconstriction can extend the thermal damage.

Emergency Room Care

Initial Assessment Although a burn is a dramatic injury, following the ABCs of resuscitation—airway, breathing, circulation—and searching for other life-threatening injuries are the first priorities. Only after making an overall assessment of the patient's condition should attention be directed to the burns. The following sections address emergency department care of problems specifically encountered in the burn patient.

Assessment of Inhalation Injury The history is important. Inhalation injury should be suspected in anyone with a flame burn, especially if burned in an enclosed space. The rescuers are the most important historians and should be questioned before they leave the emergency facility. Hoarseness and expiratory wheezes are signs of potentially serious airway edema or smoke poisoning. The mouth and pharynx should be inspected for swelling, blisters, soot, or other signs of direct burn injury. Copious mucus production and carbonaceous sputum are sure signs of the inhalation of smoke and other products of combustion, but their absence does not rule out airway injury.

Arterial blood should be analyzed for blood gasses and carboxyhemoglobin (COHb) levels. A COHb level of greater than 10 percent or any symptoms of carbon monoxide poisoning are presumptive evidence of associated smoke inhalation. A decreased ratio of arterial PO_2 to fraction of inspired oxygen (FIO_2) is another early indicator of smoke inhalation. A ratio of less than 250 (e.g., PaO_2 of 100 mmHg and an FIO_2 of 0.4) is an indication for aggressive pulmonary support rather than for increasing the inspired oxygen concentration. Fiberoptic bronchoscopy is inexpensive, quickly performed in experienced hands, and useful for assessing and documenting edema of the hypopharynx, trachea, and major

bronchi. It does not, however, materially influence the treatment of pulmonary injury.

Fluid Resuscitation Patients with burns of 20 percent or more TBSA typically develop burn shock. This is due in part to hypovolemia secondary to extravasation of fluid and protein. Thus fluid resuscitation should be instituted as soon as possible with lactated Ringer's solution at a rate of 1000 mL/h in adults and 20 mL/kg in children. Burn patients requiring intravenous resuscitation (those with burns over 20 percent TBSA) also should have a Foley catheter placed and urine output monitored hourly.

Patients with burns of less than 50 percent TBSA usually can be resuscitated with a single large-bore peripheral intravenous line. Because of the high incidence of septic thrombophlebitis, lower extremities should not be used as portals for intravenous lines. Upper extremities are preferable, even if the intravenous line must pass through burned skin. Patients with burns over 50 percent TBSA, those with associated medical problems, the very young or very old, or those who have concomitant smoke inhalation should be transferred as quickly as possible to an intensive care setting for cardiopulmonary monitoring and support.

Tetanus Burns are tetanus-prone wounds. The need for tetanus prophylaxis is determined by the patient's current immunization status. Previous immunization within 5 years requires no treatment, immunization within 10 years requires a tetanus toxoid booster, and unknown immunization status requires hyperimmune serum (Hyper-Tet).

Gastric Decompression Many burn centers begin tube feeding on admission. This protects the stomach from stress ulceration and may prevent the development of paralytic ileus, as well as providing nutrition. If the patient is to be transported, however, the safest course is usually to decompress the stomach with a nasogastric tube.

Pain Control During the shock phase of burn care, medications should be given intravenously. Subcutaneous and intramuscular injections are absorbed variably depending on perfusion and should be avoided. Pain control is best managed with small intravenous doses of morphine, usually 2–5 mg, given until pain control is adequate, without affecting blood pressure.

Psychosocial Care Psychosocial care should begin immediately. The patient and family must be comforted and given a realistic

assessment regarding the prognosis of the burns. If the circumstances of a burn in a child are suspicious, physicians in all states are required by law to report the incident to local authorities as raising a concern about child abuse.

Care of the Burn Wound After all other assessments are complete, attention should be directed to the burn. If the patient is to be transferred during the first postburn day, which is almost always the case, the burn wounds do not require special dressings and can be left alone. However, the size of the burn should be calculated to establish the proper level of fluid resuscitation, and pulses distal to circumferential full-thickness burns should be monitored. The patient should be wrapped in a clean, dry sheet and kept warm until arriving at the definitive care center.

Escharotomy and Fasciotomy

Coagulated, necrotic skin is called *eschar.* Unlike uninjured skin, it is rigid and unyielding. As fluid and protein extravasate into underlying tissues, the eschar cannot expand. Large, circumferential burns of the chest or extremities, therefore, can result in increased tissue pressure sufficient to interfere with breathing or limb perfusion. Incision of the eschar, *escharotomy,* may need to be performed early in a patient's course to restore normal function. Unless transport times are expected to be prolonged (>2 h), this procedure usually may be deferred until admission to the burn center.

Chest Escharotomy Early respiratory distress may be due to compromise of ventilatory function caused by a cuirass effect from a deep circumferential burn wound of the chest. Rapid, shallow breathing will develop, and if the patient is mechanically ventilated, peak inspiratory pressure and arterial PCO_2 will rise. Inhalation injury, pneumothorax, or other causes also may result in respiratory distress.

When escharotomy is required in a patient with a circumferential chest wall burn, it is performed in the anterior axillary line bilaterally. If there is significant extension of the burn onto the adjacent abdominal wall, the escharotomy incisions should be extended to this area and should be connected by a transverse incision along the costal margin (Fig. 7-1).

Escharotomy of Extremities Edema formation in the tissues under the tight, unyielding eschar of a circumferential burn of an extremity may produce significant vascular compromise that, if unrecognized and untreated, will lead to permanent, serious neurologic and vascular deficits. Skin color, sensation, capillary refill, and peripheral pulses must be assessed hourly in any extremity with a cir-

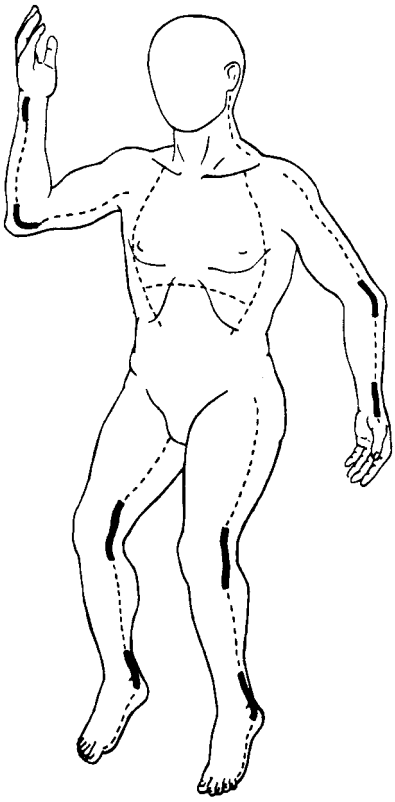


FIGURE 7-1 Locations for escharotomy incisions. These incisions are placed along the midmedial and midlateral lines of the extremities. The skin is especially tight along major joints, and decompression at these sites must be complete. Chest and neck escharotomies are rarely necessary.

cumferential burn. The occurrence of any of the following signs or symptoms may indicate poor perfusion of the distal extremity: cyanosis, deep tissue pain, progressive paresthesia (loss of sensation), progressive decrease in or absence of pulse, or sensation of cold extremities. An ultrasonic flowmeter (Doppler) is a reliable means for assessing arterial blood flow. If the signal diminishes, this may

indicate the need for escharotomy. Direct monitoring of intramuscular compartment pressure provides objective evidence for adequacy of deep circulation. While elevation and manipulation of the extremity may relieve minor deviations of pressure, escharotomy and, if ineffective, fasciotomy are necessary to decompress the tissues when pressures reach 30 mmHg or higher.

Both escharotomies and fasciotomies may be done as bedside procedures with a sterile field and scalpel. Local anesthesia is unnecessary because third-degree eschar is insensate. The incision should be placed along the midmedial or midlateral aspect of the extremity and should extend through the eschar down to the subcutaneous fat. The incision should be carried through the length of the constricting third-degree burn and across involved joints (see Fig. 7-1). When a single escharotomy incision in an extremity does not result in adequate distal perfusion, a second escharotomy incision on the contralateral aspect of the extremity should be performed. A finger escharotomy is seldom required.

Escharotomy and/or fasciotomy is rarely required within the first 6 h postburn. Because burn patients are at risk for developing a compartment syndrome up to 72 h postburn, any involved extremity should be reassessed continually for signs of dangerous elevation in compartment pressures that can occur even after initial decompression.

BURN SEVERITY

The severity of any burn injury is related to the size and depth of the burn and to the part of the body that has been burned. Burns are the only quantifiable form of trauma. Initial fluid resuscitation requirements, metabolic responses, nutritional requirements, need for specialized care, likelihood of complications, and mortality are all related to the size of the burn.

Burn Size A general idea of burn size can be made by using the *Rule of Nines*. Each upper extremity accounts for 9 percent of TBSA, each lower extremity accounts for 18 percent, the anterior and posterior trunk each account for 18 percent, the head and neck account for 9 percent, and the perineum accounts for 1 percent. Although the Rule of Nines is reasonably accurate for adults, a number of more precise charts have been developed. Most emergency rooms have a chart available comparable with the one shown in Figure 7-2. A diagram of the burn can be drawn on the chart, and a more precise estimation of burn size can be made.

Even when using precise diagrams, individual observer variation may differ by as much as 20 percent. An observer's experience with burned patients rather than educational level appears to be the

best predictor of accuracy of estimation. For small burns, an accurate assessment of burn size can be made by using the patient's hand. The palmar surface, including the fingers, accounts for 1 percent of the TBSA (see Fig. 7-2).

Burn Depth Along with burn extent and patient age, the depth of the burn is a determinant of mortality. It is also the primary determinant of the patient's long-term appearance and function. Burns not extending all the way through the dermis leave behind epithelium-lined skin appendages: sweat glands and hair follicles with

Burn Estimate and Diagram
Age vs Area

Initial Evaluation

Cause of burn_____

Date of Burn_____

Time of Burn_____

Age_____

Sex_____

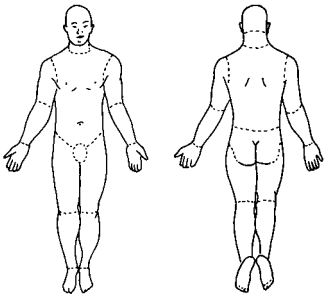
Weight_____

Date of Admission_____

Signature_____

Date_____

Burn Diagram



Area	Birth 1 yr.	1-4 yrs.	5-9 yrs.	10-14 yrs.	15 yrs.	Adult	2°	3°	Total	Donor Areas
Head	19	17	13	11	9	7				
Neck	2	2	2	2	2	2				
Ant. Trunk	13	13	13	13	13	13				
Post. Trunk	13	13	13	13	13	13				
R. Buttock	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
L. Buttock	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
Genitalia	1	1	1	1	1	1				
R.U. Arm	4	4	4	4	4	4				
L.U. Arm	4	4	4	4	4	4				
R.L. Arm	3	3	3	3	3	3				
L.L. Arm	3	3	3	3	3	3				
R. Hand	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
L. Hand	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
R. Thigh	5 1/2	6 1/2	8	8 1/2	9	9 1/2				
L. Thigh	5 1/2	6 1/2	8	8 1/2	9	9 1/2				
R. Leg	5	5	5 1/2	6	6 1/2	7				
L. Leg	5	5	5 1/2	6	6 1/2	7				
R. Foot	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2				
L. Foot	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2	3 1/2				
						Total				

FIGURE 7-2 Burn diagram for documenting extent and depth of burn. The most important concept for use of these diagrams is their provision for changing proportions of body surface area with increasing age. Clinical data for the burn diagrams are most accurately obtained immediately after initial burn debridement.

attached sebaceous glands. When dead dermal tissue is removed, epithelial cells swarm from the surface of each appendage to meet swarming cells from neighboring appendages, forming a new, fragile epidermis on top of a thinned and scarred dermal bed. Skin appendages vary in depth, and the deeper the burn, the fewer the appendages that contribute to healing and the longer the burn takes to heal. The longer the burn takes to heal, the less dermis remains, the greater the inflammatory response, and the more severe the scarring.

Burns that heal within 3 weeks usually do so without hypertrophic scarring or functional impairment, although long-term pigmentary changes are common. Burns that take longer than 3 weeks to heal often produce unsightly hypertrophic scars, frequently lead to functional impairment, and provide only a thin, fragile epithelial cover for many weeks or months. Contemporary burn care, at least in patients with small to moderate-sized burns, involves early excision and grafting of all burns that will not heal within 3 weeks. Distinguishing between deep burns that are best treated by early excision and grafting and shallow burns that heal spontaneously is not always straightforward, however, and many burns have a mixture of clinical characteristics, making precise classification difficult.

Assessment of Burn Depth The standard technique for determining burn depth has been clinical observation of the wound. The difference in depth between a burn that heals in 3 weeks, a deep dermal burn that heals only after many weeks, and a full-thickness burn that will not heal at all may be only a matter of a few tenths of a millimeter. A burn appearing shallow on day 1 may appear considerably deeper by day 3. The kind of topical wound care used may dramatically change the appearance of the burn. Evaluation by an experienced surgeon as to whether an intermediate-depth dermal burn will heal in 3 weeks is about 50 percent accurate. Although there is considerable interest in technology that might be able to make an early, accurate assessment and prognosis of the wound, no technique to date has proven consistently superior to clinical assessment. In experienced hands, furthermore, early excision and grafting provide better results than nonoperative care for such indeterminate burns.

PHYSIOLOGIC RESPONSE TO BURN INJURY

Burn Shock

Burn shock is a complex process of circulatory and microcirculatory dysfunction not easily or fully repaired solely by fluid resuscitation. Hypovolemic shock and tissue trauma result in the forma-

tion and release of local and systemic mediators that produce an increase in vascular permeability and microvascular hydrostatic pressure. Most mediators act to increase permeability by altering venular membrane integrity. The early phase of burn edema, lasting from minutes to an hour, is attributed to mediators such as histamine, bradykinin, and vasoactive amines, products of platelet activation, the complement cascade, hormones, prostaglandins, and leukotrienes. Vasoactive amines also may act directly by increasing microvascular blood flow or vascular pressures, accentuating the burn edema.

The activation of the proteolytic cascades, including those of coagulation, fibrinolysis, the kinins, and the complement system, occurs immediately after burn injury. Kinins, specifically the bradykinins, increase vascular permeability. In addition to the loss of capillary integrity, thermal injury also causes changes at the cellular level. Baxter demonstrated a generalized decrease in cellular transmembrane potential involving uninjured and thermally injured cells. Platelet-activating factor is also released after burn injury and increases capillary permeability.

The reduction in cardiac output after burn injury is a result of hypovolemia; increased systemic vascular resistance due to sympathetic stimulation and the release of catecholamines, vasopressin, angiotensin II, and neuropeptide Y; and increasing viscosity. Decreased flow to the skin may result in ischemia of partially injured tissue, thus leading to additional coagulative necrosis and increasing the depth of burn. Decreased cardiac output may lead to cardiac depression with eventual cardiac failure in healthy patients or to myocardial infarction in patients with preexisting coronary artery disease. Reduced central nervous system (CNS) flow may manifest as restlessness followed by lethargy and finally by coma. If resuscitation is inadequate, burns of 30 percent or more TBSA frequently lead to acute renal failure, which almost invariably results in a fatal outcome. With successful resuscitation, however, cardiac output normalizes after 18–24 h and then increases to supernormal levels during the wound-healing phase of burn management.

Metabolic Response to Burn Injury

Hypermetabolism Resting energy expenditure (REE) increases after burn injury, usually in relation to burn size. It may be as much as 50–100 percent above predictions based on standard tables for body size, age, and sex. Increased heat loss from the burn wound and increased beta-adrenergic stimulation are important factors. Radiant heat loss is increased from the burn wound secondary to high blood flow and loss of skin integrity.

Protein is broken down at an accelerated rate. The increased efflux of amino acids from muscle supports, in part, increased gluconeogenesis. In this process the amino acids lose their amino nitrogen as urea, making them unavailable for reincorporation into protein. Thus there is a progressive erosion of muscle mass, leading to weakness and debility. Plasma insulin levels that are usually normal are elevated in burn patients. Despite this, the basal rate of glucose production is elevated, reflecting hepatic insulin resistance. Fatty acids are released at a rate in excess of requirements of fatty acids and energy substrates. In burn patients, over 70 percent of released fatty acids are not oxidized but rather are reesterified into triglyceride, resulting in fat accumulation in the liver. This is unfortunate because use of fat for energy decreases dependence on proteolysis.

Major trauma, burns, and sepsis have in common a rapid net catabolism of body protein, as well as a redistribution of the nitrogen pool within the body. Muscle protein breakdown is accelerated while "acute phase" proteins are produced at an increased rate in the liver. Wound repair requires amino acid protein synthesis and increased immunologic activity and may require accelerated protein synthesis. Protein intake over 1 g/kg/day has been recommended for thermally injured patients. If renal function is normal, the recommended protein intake is as much as 2 g/kg/day.

Neuroendocrine-Mediator Response Catecholamines appear to be the major endocrine mediators of the hypermetabolic response in thermally injured patients. Pharmacologic blockade of beta receptors diminishes the intensity of postburn hypermetabolism. Thyroid hormone serum concentrations are not elevated in patients with large burns. Total thyronine (T_3) and thyroxine (T_4) concentrations are reduced, and reverse T_3 concentrations are elevated, while cellular concentrations are likely normal. Concentrations of free T_3 and T_4 fall markedly in the presence of sepsis in burned patients. Burn injury abolishes the normal diurnal variation in glucocorticoid concentrations. These hormones have a permissive role in catecholamine stimulation, and they are responsible for insulin resistance and, in part, for increased proteolysis. Glucagon concentrations are related directly to metabolic rate and cortisol concentrations and may modulate resting metabolism through anti-insulin effects.

Immune Response to Burn Injury

The immune status of the burn patient has a profound impact on outcome in terms of survival, death, and major morbidity. The greatest difficulty in attempting to decipher the body's response to

injury is the complex interaction of the cytokine cascade, the arachidonic acid cascade, and the neuroendocrine axis.

Cytokine Cascade Cytokines were considered originally to be regulatory chemicals secreted by cells of the immune system. Growth factors were seen as originating from inflammatory and reparative tissue. The distinction between growth factors and peptides, hormones, and cytokines, however, is no longer so distinct. The role of individual cytokines and other mediatory in the response to injury is discussed in Chapter 1.

Cell-Mediated Immunity Cell-mediated immunity is impaired after burn injury, including documented delays in allograft rejection, impairment in mitogenic and antigenic responsiveness of lymphocytes, burn-size-related suppression of graft-versus-host activity, suppression of delayed cutaneous sensitivity tests, and diminution of peripheral lymphocyte and thoracic duct lymphocyte concentrations. There is agreement that the functional capacity of thymus-dependent lymphocytes (T cells) to perform their normal physiologic response is impaired. Whether this failure is the result of "overuse" or indirectly the result of downregulation by cytokine cascades and other products of the inflammatory reaction is unclear.

Macrophages Macrophage function is impaired after thermal injury. Macrophage products suppress mitogenic responsiveness in normal lymphocytes. Proinflammatory cytokines are produced by macrophages in short bursts, probably inhibited by a feedback loop with decreased receptor expression. Activation includes pulmonary macrophages and may provide the background for the development of the adult respiratory distress syndrome seen in burn patients.

Neutrophils Neutrophil dysfunction after thermal injury is manifested by a decreased Fc receptor expression, depressed intracellular killing capacity, and decreased leukocyte chemotaxis that is accompanied by a brief increase in neutrophil respiratory burst. In addition, expression of CD16 (FcR, Fc, IgG receptors) and CD11 (adhesion molecules) on neutrophils is impaired, and this reduction seems to be related directly to the appearance of bacteremia and pneumonia. Baseline granulocyte oxidative activity in burn neutrophils is increased. Induction of neutrophil activation probably requires several different stimulants.

Humoral Immunity After thermal injury, there is a marked diminution in total serum immunoglobulin G (IgG) concentration

and all subclasses. These levels return to normal between 10 and 14 days postburn. Extremely low levels of IgG on admission are predictive of a poor prognosis. These changes have been ascribed to a combination of leakage through the burn wound, protein catabolism, and a relative diminution in synthesis of IgG. IgM and IgA levels appear to be relatively unaffected.

The classical and alternative complement pathways are depleted, but the alternative pathway is more profoundly altered. Complement inactivation by heat appears to ameliorate cell-mediated immunosuppression, suggesting that some of the impairment of the cell-mediated immunosuppression postburn may be due to a complement-associated mechanism. The production of granulocyte colony-stimulating factor (GCSF) and of granulocyte-macrophage colony-stimulating factor (GM-CSF) is also impaired.

FLUID MANAGEMENT

Proper fluid management is critical to survival in major thermal injury. In the 1940s, hypovolemic shock or shock-induced renal failure was the leading cause of death after burn injury. A vigorous approach to fluid therapy has led to reduced mortality rates in the first 48 h postburn, but 50 percent of the deaths occur within the first 10 days after burn injury from a multitude of causes. One of the most significant causes is inadequate fluid resuscitation therapy. Fluid management after burn shock resuscitation is also important.

Pathophysiology of Burn Shock Burn shock is hypovolemic and cellular in nature and is characterized by specific hemodynamic changes including decreased cardiac output, extracellular fluid, and plasma volume and oliguria. As with other forms of shock, the primary goal is to restore and preserve tissue perfusion. In burn shock, resuscitation is complicated by obligatory burn edema, and the voluminous transvascular fluid shifts that result from a major burn are unique to thermal trauma.

Maximal edema formation occurs between 8 and 12 h postinjury in smaller burns and between 12 and 24 h postinjury in major thermal injuries. The rate of progression of tissue edema depends on the adequacy of resuscitation.

In burns greater than 30 percent TBSA there is a systemic decrease in cell transmembrane potential. This decrease results from an increase in intracellular sodium concentration secondary to a decrease in sodium ATPase activity, which is responsible for maintaining the intracellular-extracellular ionic gradient. Resuscitation only partially restores the membrane potential and intracellular

sodium concentrations to normal levels, demonstrating that hypovolemia, with its attendant ischemia, is not totally responsible for the cellular swelling seen in burn shock. Membrane potential may not return to normal for many days postburn despite adequate resuscitation. If resuscitation is inadequate, cell membrane potential progressively decreases, resulting ultimately in cell death.

Moyer, Baxter, and Shires established the role of crystalloid solutions in burn resuscitation and delineated the fluid volume changes in the early postburn period. Burn edema sequesters enormous amounts of fluid, resulting in the hypovolemia of burn shock, and the edema fluid is isotonic with respect to plasma and contains protein in the same proportions as that found in blood. Thus major burns result in complete disruption of the normal capillary barrier with free exchange between plasma and extravascular extracellular compartments. Animal and later clinical studies demonstrated that the extracellular fluid (ECF) volume could be effectively restored to within 10 percent of normal within 24 h using only crystalloid. This became the basis for the Baxter (Parkland) formula (4 mL/kg of body weight per percentage TBSA burned over the first 24 h) (Table 7-2). The associated mortality rate was comparable with that obtained with a colloid-containing resuscitation formula.

Moncrief and Pruitt characterized the hemodynamic alterations in burn shock with and without fluid resuscitation. Their efforts culminated in the Brooke formula modification, which specified 2 mL/kg per percentage TBSA burned in the first 24 h (see Table 7-2). Fluid needs were estimated initially according to the modified Brooke formula, but the actual volume for resuscitation was based on clinical response. In their study, resuscitation permitted an average decrease of about 20 percent in both ECF and plasma volume, but no further loss accrued in the first 24 h. In the second 24 h postburn, plasma volume restoration occurred with the administration of colloid. Cardiac output, initially low, rose over the first 18 h postburn despite plasma volume and blood volume deficits. Peripheral vascular resistance rose during the initial 24 h but decreased as cardiac output improved. When plasma volume and blood volume loss ceased, cardiac output rose to supranormal levels, where it remained until healing or grafting occurred.

Resuscitation from Burn Shock The primary goal of fluid resuscitation is to replace fluid sequestered as a result of thermal injury. The critical concept in untreated burn shock is that massive fluid shifts can occur even though total body water remains unchanged. What actually changes is the volume of each fluid compartment, with intracellular and interstitial volumes increasing at the expense of plasma volume and blood volume. The edema formed

TABLE 7-2
FORMULAS FOR ESTIMATING TOTAL RESUSCITATION FLUID NEEDS IN ADULTS IN THE FIRST 24 h

	Electrolyte	Colloid	D_5W
Colloid formulas			
Evans (1952)	Normal saline 1 mL/kg/% burn	1 ml/kg/% burn	2000 mL
Brooke (1953)	Lactated Ringer's 1.5 mL/kg/% burn	0.5 mL/kg/% burn	2000 mL
Slater (1991)	Lactated Ringer's 2000 mL	Fresh frozen plasma 75 mL/kg	
Crystalloid formulas			
Parkland (Baxter, 1974)	Lactated Ringer's 4 mL/kg/% burn	After 24 h	
Modified Brooke (1981)	Lactated Ringer's 2 mL/kg/% burn	After 24 h	
Hypertonic sodium solution			
Monafo (1973)	Lactated Ringer's + 100 mEq/L Na lactate; maintain urine output 0.5 mL/kg/h		
Warden (1992)	Lactated Ringer's + 50 mEq/L $NaHCO_3 \times 8$ h; then LR; maintain urine output 0.5 mL/kg/h		
Dextran formula	Dextran 40 in saline 2 mL/kg/h $\times$ 8 h		
Demling (1987)	LR to maintain urine output 0.5 mL/kg/h Fresh frozen plasma 0.5 mL/kg/h $\times$ 18 h beginning at 8 h		

SOURCE: Adapted from Warden GD: Burn shock resuscitation. *World J Surg* 16:16–23, 1992.

is augmented by the resuscitation process. The National Institutes of Health consensus summary on fluid resuscitation in 1978 was not in agreement with regard to a specific formula, but there was consensus on two major issues: general guidelines to be used during the resuscitation process and type of fluid. The volume infused should be the *least* amount of fluid necessary to maintain adequate organ perfusion and should be titrated continually to avoid under-or overresuscitation. Replacement of the extracellular salt lost into the burned tissue and into the cells is essential for successful resuscitation.

Crystalloid Resuscitation Crystalloid, in particular lactated Ringer's solution with a sodium concentration of 130 mEq/L, is the most popular resuscitation fluid. Proponents of the use of crystalloid solution argue that other solutions, specifically colloids, are no better, and certainly more expensive, than crystalloid for maintaining intravascular volume after thermal injury. Even large proteins leak from the capillary after thermal injury, negating any theoretical advantage from colloid. Capillaries in nonburned tissues may maintain relatively normal protein permeability characteristics. The quantity of crystalloid needed depends on the parameters used to monitor resuscitation. If a urinary output of 0.5 mL/kg of body weight per hour indicates adequate perfusion, approximately 3 mL/kg per percentage TBSA burned will be needed in the first 24 h. If 1 mL/kg/h is optimal, considerably more fluid will be needed, and more edema will result. In major burns, severe hypoproteinemia usually develops with crystalloid resuscitation regimens. The hypoproteinemia and interstitial protein depletion may result in more edema formation.

Hypertonic Saline The resuscitation of burn patients with salt solution containing 240–300 mEq/L of sodium rather than lactated Ringer's solution (130 mEq/L) guided by urine output as the indicator of adequate resuscitation may result in less edema and smaller total fluid requirements at least in the first 24 h. A shift of intracellular water into the extracellular space occurs as the result of the hyperosmolar solution. Extracellular edema increases as intracellular fluid decreases, giving the external appearance of less edema. Several studies have reported that this intracellular water depletion does not appear to be deleterious, but the issue is controversial. Gunn and associates, in a prospective, randomized study of patients with 20 percent TBSA burns, evaluated hypertonic sodium lactate versus lactated Ringer's solution and were not able to demonstrate decreased fluid requirements, improved nutritional tolerance, or decreased body weight gain percentage. If a hypertonic solution is used, hypernatremia ($Na > 160$ mEq/L) should be avoided.

Colloid Resuscitation Plasma proteins generate the inward oncotic force that counteracts the outward capillary hydrostatic force. Without plasma proteins under normal conditions, plasma volume could not be maintained. Thus protein replacement was an important component of early formulas for burn management. Because of the marked alteration in capillary permeability with acute burn injury, however, it is not clear how much oncotic force plasma proteins exert during resuscitation from burn shock. Demling demonstrated that restoration and maintenance of plasma protein content have no effect on plasma volume until at least 8 h postburn. Since nonburned tissues appear to regain normal permeability shortly after injury and hypoproteinemia may accentuate the edema, administering protein between 8 and 24 h postburn may offer some advantage to patients.

Albumin solutions are clearly the most oncotically active colloid solutions. Fresh frozen plasma contains all the protein fractions that exert oncotic and nononcotic functions. The optimal amount of protein is controversial. Demling uses between 0.5 and 1 mL/kg/percentage TBSA burned of fresh frozen plasma during the first 24 h, beginning at 8–10 h postburn. He argues that older patients, patients with burns and concomitant inhalation injury, and patients with burns in excess of 50 percent TBSA develop less edema and better maintain hemodynamic stability if fresh frozen plasma is used during resuscitation. In the young pediatric burn patient with major burn injury, colloid replacement is frequently administered because serum protein concentration decreases so rapidly.

Dextran Dextran is a colloid consisting of glucose molecules that have been polymerized into chains to form high-molecular-weight polysaccharides. This compound is available commercially in a number of molecular sizes. Dextran 40 (average molecular weight of 40,000 and called *low-molecular-weight dextran*) improves microcirculatory flow by decreasing red blood cell aggregation. Demling reported that the net fluid requirements for maintaining vascular pressure at the baseline levels with dextran 40 are about half those noted with lactated Ringer's alone during the first 24 h postburn.

Special Considerations in Burn Shock Resuscitation

Pediatric Patients Resuscitation must be more precise for children than for adults with a similar burn. Children have a limited physiologic reserve, and they require proportionately more fluid for

burn shock resuscitation than adults with similar thermal injury. On average, fluid requirements for children approximate 5.8 mL/kg/percentage TBSA burned. Children with relatively small burns of 10–20 percent TBSA also commonly require intravenous resuscitation. The Cincinnati Shriners Burns Institute begins with the Parkland formula and adds the estimated maintenance fluid requirement to calculate the expected total volume for the first 24 h (Table 7-3):

4 mL/kg/percentage TBSA burned + 1500 mL
maintenance fluid per m^2 of body surface

Inhalation Injury Inhalation injury accompanying thermal trauma increases the magnitude of total body injury and requires increased volumes of fluid and sodium to achieve resuscitation. Patients with documented inhalation injury require, on average, 5.7 mL/kg/percentage TBSA burned as compared with 3.98 mL/kg/percentage TBSA burned in patients without inhalation injury.

Choice of Fluids and Rate of Administration All the solutions reviewed are effective in restoring tissue perfusion. Most patients with burns under 40 percent TBSA with no pulmonary injury can be resuscitated with isotonic crystalloid fluid alone. In patients with massive burns, young pediatric patients, and patients with burns complicated by severe inhalation injury, a combination of fluids can be used to achieve the desired goal of tissue perfusion while minimizing edema. Such a regimen starts with modified hypertonic saline solution (180 mEq/L lactated Ringer's + 50 mEq/L $NaHCO_3$). After correction of the metabolic acidosis, which usually requires 8 h, lactated Ringer's is given for a second 8 h. In the last 8 h, 5% albumin in lactated Ringer's solution completes the resuscitation.

None of the resuscitation formulas can be more than a general guideline for burn shock resuscitation. In all cases the fluids should be adjusted as frequently as necessary based on the patient's response. The volume of infused fluid should maintain a urine output of 30–50 mL/h or 0.5 mL/kg/h in adults and 1 mL/kg/h in children. In children weighing more than 50 kg, the urine volume should not exceed 30–50 mL/h. Heart rate and blood pressure are not indicative of fluid volume status in the burn patient. If fluid volume status and adequacy of cardiac output are uncertain, they should be measured directly via thermodilution pulmonary artery catheterization, but a low measured filling pressure with evidence of adequate perfusion is common. Placement of a Swan-Ganz catheter to monitor burn shock resuscitation should be reserved for burn patients with limited cardiac reserve, such as the elderly or

TABLE 7-3
FORMULAS FOR ESTIMATING TOTAL RESUSCITATION FLUID NEEDS IN CHILDREN IN THE FIRST 24 h

Center	Total Amount in 24 h	Formula
Shriners Burns Institute, Cincinnati	4 mL/kg/% burn + 1500 mL/m^2 TBSA	0–8 h: Lactated Ringer's + 50 mEq/L $NaCO_3$ 9–16 h: Lactated Ringer's 17–24 h: Lactated Ringer's + 12.5 g/L albumin
Shriners Burns Institute, Galveston	5000 mL/m^2 burn + 2000 mL/m^2 TBSA	D_5 lactated Ringer's + 12.5 g/L albumin

SOURCE: Adapted from Warden GD, Heimbach DM: Burns, in Schwartz SI et al (eds): *Principles of Surgery.* New York, McGraw Hill, 1999.

patients with significant concomitant disease, or burn patients who require large volumes.

Resuscitation is considered successful when there is no further accumulation of edema fluid, usually between 18 and 30 h postburn, and the volume of infused fluid needed to maintain adequate urine output approximates the maintenance fluid volume, which is the patient's normal maintenance volume plus evaporative water loss.

Fluid Replacement Following Burn Shock Resuscitation Heat-injured microvessels may manifest increased vascular permeability for several days, but burn edema at 24 h postburn is near maximal, and the interstitial space often may be saturated with sodium. Additional fluid requirements depend on the type of fluid used during the initial resuscitation. If a hyperosmolar state has been produced, additional free water may be required to restore the extracellular space to an iso-osmolar state. If the serum oncotic pressure is low because of intravascular protein depletion, protein repletion frequently is needed. Protein requirement varies with the resuscitation used. The Brooke formula proposes 0.3–0.5 mL/kg/percentage TBSA burned of 5% albumin during the second 24 h. The Parkland formula replaces the plasma volume deficit, which varies from 20–60 percent of the circulating plasma volume, with colloid.

The total daily maintenance fluid requirement in the burn patient must account for the increased amount of evaporative water loss from the wound. In adults, the total fluid volume is estimated from the following formula:

$$\text{Total fluid (mL/m}^2\text{)} = 1500 + [(25 + \text{percent TBSA burned}) \times 24]$$

This fluid may be given intravenously or via enteral feeding. The solution infused intravenously should be 0.5 normal saline with potassium supplements. Because of the loss of intracellular potassium during burn shock, the potassium requirement in adults is about 120 mEq/day.

After the initial 24–48-h postburn period of resuscitation, urinary output is an unreliable guide to sufficient hydration. Adult patients with major thermal injuries require a urine output of 1500–2000 mL/24 h; children require 3–4 mL/kg/h. Indices of the state of hydration including body weight change, serum sodium concentration, serum and urine urea and glucose concentrations, the intake and output record, and clinical examination should be monitored closely. Other electrolytes, calcium, magnesium, and phosphate also should be monitored regularly and maintained within normal limits. For very large burns and in the pediatric burn patient,

continuous colloid replacement may be required to maintain colloid oncotic pressure. Maintaining serum albumin levels above 2.0 g/dL is desirable.

RESPIRATORY INJURY

Of the nearly 50,000 fire victims admitted to hospitals each year, smoke or thermal damage to the respiratory tree may occur in as many as 30 percent. Carbon monoxide poisoning, thermal injury, and smoke poisoning are three distinctly separate aspects of clinical inhalation injury, and although symptoms and treatment are distinct, they may coexist and require concomitant treatment.

Carbon Monoxide Poisoning As many as 60–70 percent of deaths from house fires can be attributed to carbon monoxide poisoning. Carbon monoxide (CO) is a colorless, odorless, tasteless gas that has a high affinity for iron-containing proteins. When inhaled and absorbed, carbon monoxide binds to hemoglobin, myoglobin, and other iron-containing proteins. CO interferes with oxygen delivery to tissues by at least four mechanisms. First, when bound to hemoglobin (COHb), it prevents reversible displacement of oxygen. Second, COHb shifts the oxygen-hemoglobin dissociation curve to the left, thereby decreasing oxygen unloading from normal hemoglobin at the tissue level. Third, CO inhibits the cytochrome oxidase a^3 complex, resulting in less effective intracellular respiration. Fourth, CO may bind to cardiac and skeletal muscle, causing direct toxicity and interfering with function. In addition, CO affects the CNS in a poorly understood fashion, causing demyelination and associated neurologic symptoms. Although levels of carboxyhemoglobin can be measured easily, the degree of enzymatic and/or muscle impairment may not directly correlate with these values. COHb levels less than 10 percent usually do not cause symptoms, except in some patients with limited cardiac reserves.

Carbon monoxide is reversibly bound to the heme pigments and enzymes and, despite its intense affinity, readily dissociates according to the laws of mass action. The half-life of COHb, when breathing room air, is between 4 and 5 h. On 100% oxygen, the half-life is reduced to 45–60 min. Patients burned in an enclosed space or having any suggestion of neurologic symptoms should be placed on 100% oxygen while awaiting measured carboxyhemoglobin levels.

Thermal Airway Injury The term *pulmonary burn* is a misnomer. True thermal damage to the lower respiratory tract and lung

parenchyma is extremely rare, unless live steam or exploding gases are inhaled. Air has such poor heat-carrying capacity that most of the heat is dissipated in the nasopharynx and upper airway. Mucosal burns of the mouth, nasopharynx, and larynx result in edema formation and may lead to upper airway obstruction at any time during the first 24 h postburn. Patients with the greatest risk of upper airway obstruction are those injured in an explosion (gasoline vapor, propane, butane, or natural gas) with burns of the face and upper torso and those who have been unconscious in a fire. Any patient with burns of the face should have a careful visual inspection of the mouth and pharynx, and if these are abnormal, the larynx should be visualized immediately. Red or dry mucosa or small mucosal blisters raise the possibility of airway obstruction; in patients from a closed-space fire, significant smoke poisoning may be present. The presence of significant intraoral and pharyngeal burns is a clear indication for early endotracheal intubation, since progressive edema can make later intubation extremely hazardous, if not impossible. Mucosal burns are rarely full thickness and can be managed successfully with good oral hygiene. Once the patient is intubated, the tube should remain in place for 3–5 days, until the edema subsides.

Smoke Inhalation A vast number of toxic products are released during combustion (flaming) or pyrolysis (smoldering), depending on the type of fuel that is burned, whether burning occurs in a high- or low-oxygen environment, and the actual heat of combustion. Some 280 toxic products have been identified in wood smoke. Petrochemical science has produced a wealth of plastic materials in homes and automobiles that, when burned, produce nearly all these and many other products not yet characterized. Prominent by-products of incomplete combustion are oxides of sulfur, nitrogen, and many aldehydes.

Smoke inhalation can cause direct epithelial damage at all levels of the respiratory tract from the oropharynx to the alveolus. The anatomic level at which the damage occurs depends on the ventilatory pattern, the smoke constituents (e.g., particulate concentration, particulate size, and chemical components), and the anatomic distribution of particulate deposition. Although the chemical mechanisms of injury may be different with different toxic products, the overall end-organ response is reasonably well defined. There is an immediate loss of bronchial epithelial cilia and decreased alveolar surfactant. Microatelectasis, and sometimes macroatelectasis, results and is compounded by mucosal edema in small airways, with immediate development of atelectasis that is only slowly reversible by normal ventilation. The regional hypoventilation results in

significant alveolar atelectasis, intrapulmonary shunt, and subsequent hypoxemia. Chemical irritation of the respiratory tract, particularly the upper and lower airways, causes an acute inflammatory response.

Wheezing and air hunger are common early symptoms of smoke inhalation. In a few hours, tracheal and bronchial epithelium begins to slough, and a hemorrhagic tracheobronchitis develops. The pulmonary parenchymal injury appears to be dose-dependent. In very severe cases, the hemorrhagic tracheobronchitis and small airway plugging result in severe ventilatory difficulty during the first 48 h, and patients succumb to a severe respiratory acidosis because of their inability to clear CO_2. In moderately severe cases with associated extensive burns, interstitial edema becomes prominent, resulting in adult respiratory distress syndrome (ARDS), with difficulty in oxygenation.

Concomitant cutaneous burn injury aggravates pulmonary injury independent of smoke inhalation. Mediators such as thromboxane A_2 released from burned tissue may induce a variety of changes in the lung, including pulmonary hypertension, reduced dynamic compliance, and increased lipid peroxidation. Oxidants generated as a consequence of neutrophil activation and increases in xanthine oxidase also contribute to lung injury. Decreased plasma oncotic pressure from the loss of plasma protein through increasingly permeable vessels in both burned and unburned tissue creates an abnormal oncotic pressure gradient in the lung that, when combined with pulmonary hypertension, results in transient hydrostatic pulmonary edema. These changes help explain the degree of comorbidity in cases of combined inhalation and burn injuries. Much of the variability in pulmonary response appears to be related more to the severity of the associated cutaneous burn than to the degree of smoke inhalation. Without associated cutaneous burns, the mortality from smoke inhalation is very low, the process rarely progresses to ARDS, and symptomatic treatment usually leads to complete resolution of symptoms in a few days. In the presence of burns, smoke poisoning approximately doubles the mortality from burns of any size. Pulmonary symptoms are usually present on admission, but they may be delayed for 12–24 h. The earlier the onset, the more severe is the disease.

Diagnosis Anyone with a flame burn and anyone burned in an enclosed space should be assumed to have smoke poisoning until proved otherwise. The assessment of the patient should proceed as discussed above (Emergency Room Care). In obtaining a history, emphasis should be placed on data specific to the smoke exposure and to the type of therapy instituted prior to hospitalization. Signs

of smoke inhalation should be sought in the examination of the head and neck: edema, stridor, or soot impaction suggesting smoke inhalation; wheezing or rhonchi suggesting injury to lower airways; and decreased level of consciousness due to hypoxemia, CO poisoning, or cyanide poisoning. Hoarseness and expiratory wheezes are signs of potentially serious airway edema or smoke poisoning. Copious mucus production and carbonaceous sputum are also signs of injury but are not always present. Elevated COHb levels or any symptoms of CO poisoning are presumptive evidence of associated smoke poisoning. An inappropriately low arterial PO_2 indicates the need for vigorous respiratory support. Because of the limitations of fiberoptic bronchoscopy, it is recommended that the history, clinical examination, and laboratory studies be used to make the diagnosis of inhalation injury and that the use of fiberoptic bronchoscopy be reserved for exceptional cases (e.g., expansion of lobar atelectasis or removal of obstructing intrabronchial secretions).

Treatment *Upper Airway* In the presence of increasing laryngeal edema, nasotracheal or orotracheal intubation is indicated. A tracheostomy is never an emergency procedure and should not be used as the initial step in airway management in patients with burns to the face and neck. Oropharyngeal edema often subsides sufficiently by 72 h to permit extubation. Adult patients should be able to breathe around the tube with the cuff deflated before it is removed. This assessment is difficult in children due to their smaller anatomy, the use of uncuffed endotracheal tubes, the increased incidence of postextubation stridor, and the frequent need for reintubation. The incidence of postextubation stridor in burn victims is as high as 47 percent, compared with 4 percent in elective surgical patients. The treatment of postextubation stridor includes the administration of racemic epinephrine and helium-oxygen (Heliox) mixtures.

Lower Airway Tracheobronchitis, commonly seen in smoke and toxic gas inhalation victims, produces wheezing, coughing, and retained secretions. The ventilation-perfusion mismatch present in these patients can result in mild to moderate hypoxemia, depending on the degree of underlying lung disease. High-flow supplemental oxygen should be administered routinely to supplement oxygenation and to reduce carboxyhemoglobin in cases of carbon monoxide inhalation. Further treatment for smoke poisoning is supportive, with the goal of maintaining adequate ventilation and oxygenation until the lung heals itself. Mild cases of smoke poisoning are treated with highly humidified air, vigorous pulmonary toilet,

and bronchodilators as needed. More severe cases may require mechanical ventilation. For patients requiring prolonged endotracheal intubation, tracheostomy should be performed between 3 and 30 days after intubation. Patients with anterior neck burns who require tracheostomy should undergo excision and grafting of the area 5–7 days prior to creation of the tracheostomy. This minimizes pulmonary and burn wound infectious complications associated with the tracheostomy.

Prophylactic antibiotics are not valuable in burn-related chemical pneumonitis, and subsequent burn management and treatment of eventual bacterial pneumonia can be made more difficult if the early use of antibiotics leads to the selection of resistant organisms. Although steroids are commonly used in patients with severe asthma for their spasmolytic and anti-inflammatory action, there has been no study to date demonstrating a net benefit in smoke inhalation. One prospective study, in fact, demonstrated that mortality and infectious complications were higher in patients treated with steroids.

WOUND MANAGEMENT

The burn wound is typically treated with once- or twice-daily washing, removal of loose, dead tissue, and topical application of an antimicrobial agent. Three preparations have demonstrated effectiveness in controlling bacterial proliferation on the burn wound: mafenide acetate, silver sulfadiazine, and silver nitrate. All are equally effective in controlling burn wound infection if applied before heavy colonization is established. Mafenide acetate is the only agent able to penetrate eschar and suppress dense bacterial proliferation. It is especially effective against clostridia. The main disadvantage of mafenide acetate is its strong carbonic anhydrase inhibition, which results in bicarbonate wasting, retained chloride, and metabolic acidosis.

Excision and Grafting For many years no attempt was made to cover burns with skin grafts until the eschar had sloughed and granulation tissue was well developed, a process that could take up to 8 weeks. Several technical advances, including “safer” blood, better monitoring equipment and methods, and a better understanding of the altered physiology and increased metabolic demands of burn patients, have made it possible to stabilize the patient within a few days of the injury. Now, rather than waiting for spontaneous separation, the eschar is removed surgically and the wound is closed before invasive infection occurs. An aggressive surgical approach to large and small burns has produced a number of advantages. Early

wound closure shortens hospital stay and duration of illness. Although studies at first did not demonstrate dramatic differences in cosmetic and functional results, as surgeons have become more experienced, both improved function and appearance have resulted. This is particularly true with burns of the face, hands, and feet.

More burn centers are practicing early excision and grafting, and thus it is becoming the treatment of choice for all deep dermal and full-thickness burns. The procedure is still limited by difficulty in diagnosing burn depth, by limited donor sites, and by the difficulties involved in excision of three-dimensional areas, such as the perineum, ears, and nose. Evidence supports the following conclusions:

1. Small (<20 percent TBSA) full-thickness burns and burns of indeterminate depth (deep partial versus full thickness), if treated by an experienced surgeon, can be excised and grafted safely with a decrease in hospital stay, cost to the patient, and time away from work or school.
2. Early excision and grafting dramatically decrease the number of painful debridements required by all patients.
3. Patients with burns between 20 and 40 percent TBSA will have fewer infectious wound complications if treated with early excision and grafting.
4. In animals with experimental burns, the depressed immune response and hypermetabolism associated with burns can be ameliorated by early burn wound removal.

Technical Considerations Excisional procedures should be performed as early as possible after the patient is stabilized. This allows the wound to be closed before infection occurs and, in extensive burns, allows donor sites to be recropped as soon as possible. Cosmetic results are better if the wound can be excised and grafted before the intense inflammatory response associated with burns becomes well established. Any burn projected to take longer than 3 weeks to heal is a candidate for excision within the first postburn week. Wound excision is adaptable to all age groups, but infants, small children, and elderly patients require close perioperative monitoring.

Wound Excision Excision can be performed to include the burn and subcutaneous fat to the level of the investing fascia (fascial excision) or by sequentially removing thin slices of burned tissue until a viable bed remains (sequential excision). Fascial excision ensures a viable bed for grafting but takes longer, sacrifices potentially viable fat and lymphatics, and leaves a permanent cosmetic defect. Sequential (or tangential) excision can create massive blood loss

and risks grafting on a bed of uncertain viability. It sacrifices minimal living tissue, however, and leads to a far superior cosmetic result than fascial excision. Current practice reserves fascial excision for patients with fourth-degree burns and patients with such massive burns that they can afford no graft loss.

Donor Sites For years donor sites have been treated superficially. They are covered with either dry, fine-mesh gauze or gauze impregnated with a dye or other antimicrobial agent. Over the next 2–3 weeks, they desiccate. The gauze usually separates from the wound spontaneously, but it can remove substantial areas of new epithelium. Now, with aggressive programs of early excision and grafting, donor sites are a priority. Early wound closure may spare the patient the painful daily debridement of the burn, but with burn pain diminished, patients now concentrate on donor-site pain.

There are hundreds of dressings available for donor-site and after-grafting wound care. Unfortunately, there appears to be no optimal donor dressing. All dressings—including the traditional gauze dressings—seem to work, and differences in healing times are only 1–2 days. Comfort levels and ease of care are the most significant factors in choosing a dressing.

Healed donor sites are not free of complications. In addition to hypertrophic scarring and changed pigmentation, patients may be troubled by blistering for several weeks. Blisters are self-limiting and are usually treated with bandages or ointments until they reepithelialize. Infections occur in about 5 percent of patients. Infection is treated with systemic antibiotics and continuously moist dressings or silver sulfadiazine.

Skin Substitutes The next major step in burn care is likely to be an artificial skin that will be readily available, perform barrier function (epidermis), and provide the structural durability and flexibility of the dermis. It must be permanent, affordable, not susceptible to hypertrophic scarring, provide normal pigmentation, and grow with developing children. Progress toward this goal has been substantial over the past decade. Cultured epidermal autograft (CEA) consists of a thin sheet of keratinocytes grown from a biopsy of a patient's unburned skin. It can only provide a barrier function, so at best it may be a temporary measure that might permit survival in a patient with massive burns. More promising is a dermal substitute consisting of collagen that is covered with a thin epidermal graft at the time of placement on the wound. It provides a matrix for the ingrowth of native fibroblasts, epidermal cells, and macrophages, resulting in a pseudodermis. At least two products are available commercially.

NUTRITIONAL SUPPORT

The hypermetabolic responses in patients with burns can be among the most intense in clinical medicine. All burn patients have increased resting energy expenditure and accelerated rates of protein (primarily skeletal muscle) breakdown that are related to the severity of the injury, i.e., to the size of the burn. The goals of nutrition support are to provide sufficient calories to match energy expenditure and protein to minimize the draft on muscle protein. Patients with burns involving 50 percent TBSA or more may require $1\frac{1}{2}$ to 2 times their normal (preburn) caloric needs, with 25 percent of those calories provided as protein. For a more complete discussion of nutritional support assessment and techniques, see Chapters 1 and 2.

Enteral nutrition is much the preferred modality. Patients with small burns (<20 percent TBSA) often can meet their nutritional needs with a high-protein, high-calorie diet, provided that they can feed themselves and that they have effective pain control. Those with larger burns, those unable or unwilling to eat, or those with preexisting malnutrition often require exogenous nutritional support. This is best provided via small-bore nasal feeding tubes passed into the duodenum or jejunum, since small bowel motility is usually preserved, even in large burns. In many burn centers, enteral nutrition is begun during resuscitation. If the airway is protected, this often may be done through the nasogastric tube and the feeding tube placed later. The techniques, benefits, and difficulties of enteral nutrition are discussed elsewhere. Intravenous nutrition is provided only when the patient's needs cannot be met via the enteral route.

Energy expenditure can be minimized by blunting stressful stimuli. Because of the apparent change in the hypothalamic set point of thermal neutrality, burn patients require higher ambient temperatures for comfort. In an ambient environment that is comfortable for uninjured patients, the burn patient feels cold, and this will increase the energy expenditure to generate heat. The temperature of comfort is approximately 30.5°C (87°F), 5 degrees higher than that of normal subjects. Keeping burn patients warm decreases their metabolic rate and corresponding energy requirements, even if they have fever. Thermal blankets, radiation reflectors, and heat lamps may be required to maintain the patient's comfort. Pain and anxiety that accompany wound manipulation and other patient care procedures accentuate metabolic expenditure. Administration of narcotics or other analgesics and sedatives reduces the metabolic rate.

Human growth hormone increases nitrogen retention when administered with adequate calories and nitrogen. In patients with large burns, it has improved survival and reduced hospital stay by accelerating the rate of donor-site healing, reducing the time between sequential skin-grafting operations. Other anabolic agents (e.g., oxandrolone) also may be of benefit. Lack of activity also promotes muscle wasting and atrophy. Vigorous physical therapy promotes preservation of muscle bulk and must be provided on a daily basis to all patients requiring prolonged hospitalization. Patients in skeletal traction or air-fluidized beds are relatively immobile and lose lean body mass as a result. Simple isometric exercises, however, usually can be done and will reduce the rate of disuse atrophy. Wound care and expeditious wound closure are the most effective measures for limiting the injury and its metabolic sequelae.

INFECTION

Considerable morbidity and mortality in burned patients are related to infection. Thermal injury causes severe immunosuppression that is directly related to the size of the burn.

Wound Infection All burn wounds become contaminated soon after injury with the patient's endogenous flora or with resident organisms in the treatment facilities. Microbial species colonize the surface of the wound and may penetrate the avascular eschar. This event is without clinical significance. Bacterial proliferation may occur beneath the eschar at the viable tissue–nonviable tissue interface, leading to subeschar separation. In a few patients, microorganisms may breach this barrier and invade the underlying viable tissue, producing systemic sepsis. Burn wound infection can be focal, multifocal, or generalized. The likelihood of septicemia increases in proportion to the size of the burn wound. With the use of currently available topical antimicrobial agents and an early and aggressive surgical approach to the burn wound, burn wound sepsis is much less common.

Pneumonia With improved resuscitation and modern patient support techniques, severely burned patients are surviving longer in critical care units, and the respiratory tract has become the most common locus of infection. A diagnosis of pneumonia is confirmed by the presence of characteristic chest radiograph patterns and the presence of offending organisms and inflammatory cells in the spu-

tum. After inhalation injury, early infiltrates usually represent chemical pneumonitis and not infectious pneumonia, but the damaged lung tissue commonly becomes infected. Prophylaxis with antibiotics should not be used, however, because it does not reduce the incidence of pneumonia and selects resistant organisms. Colonization of the upper airway of patients requiring intubation and mechanical ventilation should not be confused with a respiratory tract infection. For the diagnosis of bronchopneumonia, analysis of sputum samples may be adequate. If there is concern about the identity of the organism, bronchoscopy should be used.

Suppurative Thrombophlebitis Suppurative thrombophlebitis occurs in up to 5 percent of patients with major burns. It is associated with the use of intravenous catheters, especially if the catheters have been inserted by cut-down techniques. The incidence increases with the duration of vein cannulation. This complication can be reduced or eliminated by the placement of catheters in high-flow veins, such as the femoral, subclavian, or internal jugular veins, and by changing insertion sites every 48–72 h.

ELECTRICAL AND CHEMICAL BURNS

Electrical Burns

Electrical burns are thermal burns from very high intensity heat and from electrical disruption of cell membranes. As electric current meets the resistance of body tissues, it is converted to heat in direct proportion to the amperage of the current and the electrical resistance of the body parts through which it passes. The smaller the size of the body part, the more intense is the heat and the less the heat is dissipated. Fingers, hands, forearms, feet, and lower legs are frequently totally destroyed. Areas of larger volume, like the trunk, usually dissipate enough current to prevent extensive damage to viscera unless the entrance or exit wound is directly on the abdomen or chest. High-voltage (>1000 V) injuries are often deep and destructive. While cutaneous manifestations of electrical burns may appear limited, massive underlying tissue destruction may be present.

Disruption of muscle cells releases cell fragments and myoglobin into the circulation to be filtered by the kidney. Myoglobinuria is evident by the ruddy or brown color of the urine. If this condition is untreated, the pigments may precipitate in the renal tubules and lead to permanent kidney failure. Cardiac damage, such as myocardial contusion or infarction, may be present, or the conduction system may be deranged. Even with injuries resulting from

high-voltage currents, however, normal cardiac function on admission generally means that subsequent cardiac dysrhythmia is unlikely.

The nervous system is particularly sensitive to electricity. The most severe brain damage occurs when current passes through the head, but spinal cord damage is possible whenever current has passed from one side of the body to the other. Myelin-producing cells are susceptible, and delayed transverse myelitis can occur days or weeks after injury. Conduction remains normal through existing myelin, but as the old myelin wears out, it is not replaced, and conduction stops. Damage to peripheral nerves is common and may cause permanent functional impairment.

Acute Care Resuscitation needs are usually far in excess of what would be expected on the basis of the cutaneous burn size, and associated flame and/or flash burns often compound the problem. The infusion rate of resuscitation fluid should be adjusted based on the patient's response. If myoglobinuria is present, the infusion rate should be increased to promote a urine flow twice that of the usual target, i.e., 60–100 mL/h in adults, in an attempt to flush the pigments through the kidney. If the urine does not appear to become less pigmented, mannitol may be administered, and bicarbonate should be administered to try to alkalinize the urine. This increases the solubility of the pigments.

Every patient with an electrical injury must have a thorough neurologic examination as part of the initial assessment. Persistent neurologic symptoms may lead to chronic pain syndromes, and so-called posttraumatic stress disorders are much more frequent after electrical burns than after thermal burns. Cataracts are a well-recognized complication of electrical contact burns. They occur in 5–7 percent of patients followed, they are frequently bilateral, and they can occur even in the absence of contact points on the head. They often occur within a year or two of injury. Electrically burned patients should undergo a thorough ophthalmologic examination during the admissions phase of acute care.

Wound Management There are two situations in which early surgical treatment is indicated for patients with electrical burns. Massive deep tissue necrosis may lead to acidosis or myoglobinuria that does not improve with standard resuscitation techniques. In this case, major debridement and/or amputation may be necessary on an emergency basis. More commonly, the deep tissues swell, and a compartment syndrome develops. Careful monitoring, including measurement of compartment pressures, is mandatory, and escharotomies and fasciotomies should be performed at the slightest suggestion of progression.

Chemical Burns

Chemical burns are most commonly caused by strong acids or alkalis. In contrast to thermal burns, chemical burns cause progressive damage until the chemicals are inactivated by reaction with the tissue or diluted by flushing with water. Individual circumstances vary, but acid burns may be more self-limiting than alkali burns because alkalis combine with cutaneous lipids to create soap and thereby continue "dissolving" the skin until they are neutralized. Chemical burns should be considered deep dermal or full-thickness burns until proved otherwise. A full-thickness chemical burn may appear deceptively superficial at first, causing only a mild brownish discoloration of the skin. The skin may appear to remain intact during the first few days postburn and only then begin to slough spontaneously.

Acute Care Any involved clothing should be removed immediately, and the burns should be flushed thoroughly with copious amounts of water, beginning at the scene of the accident. Chemicals will continue to burn until removed, and washing for at least 15 min under a running stream of water may limit the overall severity of the burn. No thought should be given to searching for a specific neutralizing agent. Delay deepens the burns, and neutralizing agents may cause burns themselves, since they frequently generate heat while neutralizing the offending agent. Powdered chemicals should be brushed off skin and clothing. Unless the characteristics of the chemical are well known, the treating physician is advised to call the local poison control bureau for specifics in treatment, in case there is a possibility of toxicity.

REHABILITATION AND CHRONIC PROBLEMS

Rehabilitation

Inpatient Therapy Maintaining function and preventing the complications of prolonged immobility are the specific goals of the rehabilitative treatment of burn patients. Daily assessment of the patient's range of motion, ambulation, and functional status is necessary to determine the effectiveness of ongoing treatment plans and to make modifications as needed. In most burns of extremities, the position of maximal comfort promotes the formation of scar contractures. Compliance is a major factor in a successful rehabilitation program, so the burn therapist and the entire burn team must gain the patient's trust, understanding, and confidence. Burn teams

should include physical and occupational therapists and a play therapist who can engage children in physical activities.

Occupational and physical therapy begin on the day of admission. Burned extremities are elevated and actively exercised to minimize edema and reduce the need for escharotomy. Stable patients are initially placed in chairs. Ambulation begins when it can be tolerated. Excessive use of analgesics and antianxiety drugs impedes a successful mobilization program. Active exercises maintain muscle mass and strength. Passive exercises are used most often in debilitated patients and patients whose state of awareness is clouded. Passive exercises must be planned carefully, because overzealous activity may lead to tendon disruption, muscle tears, heterotopic ossification, and traumatic release of scar contractures.

All second- and third-degree burns produce permanent scarring. Some scars in healed second-degree burns are barely noticeable, whereas deeper burns, even when grafted, may develop bulky hypertrophic scar tissue. Scar hypertrophy can be retarded by pressure applied to the developing scar. In the burn center, pressure is usually applied with elastic bandages or a generic tubular elastic stocking.

Outpatient Therapy Many functional deficits persist after burn patients have been discharged. Outpatient therapy and long-term follow-up should be continuous. For many patients, the burn center outpatient facility provides their only access to primary care. Some patients may require complex physical training devices and special attention to retain or restore range of motion, strength, and stamina. After the surface of the burn scar stabilizes, the patients may be fitted for custom-made compression garments. These require regular refitting. Adults may wear these garments for 6 months or more, whereas small children may require up to 4 years of compression therapy before scar maturation is complete. Patients may develop follicular infection in the burn wound several months after injury. These plugged follicles usually disappear once hair erupts through the overlying epithelium. Severe itching and vague but intense neuritic pain are long-lasting and are poorly responsive to antipruritic medications and analgesics.

Psychosocial Support Burned patients display a variety of psychological responses to their injury, including anxiety, depression, denial, withdrawal, and regression. Withdrawal and regression are especially common in children, who may refuse to participate in treatment regimens. Nearly half of older children and adults develop posttraumatic stress disorder after thermal injury, which is characterized by recurrent and intrusive recollections of the initial injury, avoidance of circumstances that invoke memories of the

event, loss of interest in daily activities, feelings of isolation, hyperalertness, memory impairment, and sleep disturbances. Noncompliance with burn therapy is a serious outward manifestation of a patient's attempt to avoid recollections of the traumatic event. Even though burn patients rarely seek treatment for psychological problems, psychosocial support is critical for optimal recovery and should be provided for the duration of the course of treatment and follow-up. Initially this is provided by the burn team and the patient's family. Later, patients should have the opportunity to participate in a burn support group composed of other burn survivors. Even long after their physical wounds have healed, these courageous patients continue to help and support each other and new burn victims and their families. They have learned that burn injuries are never completely cured or forgotten.

For a more detailed discussion, see Warden GD, Heimbach DM: Burns, chap.7 in *Principles of Surgery,* 7th ed.

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CHAPTER

8

WOUND CARE AND WOUND HEALING

GENERAL CONSIDERATIONS

Classification of Wounds

Wounds are classified into two general categories: *acute* and *chronic.* Acute wounds repair through an orderly process that results in anatomic and functional integrity. By contrast, chronic wounds have failed to proceed through the orderly and timely process or have proceeded through a repair process without establishing an anatomic or functional result.

Types of Wound Closure

Primary closure approximates the acutely disrupted tissue with sutures, staples, or tape. With time, the synthesis, deposition, and cross-linking of collagen and other proteins provide the tissue with strength and integrity.

In *delayed primary closure,* approximation of the wound is delayed for several days after the wound has been created. This is indicated to prevent infection in wounds in which there has been a significant bacterial contamination, foreign bodies, or extensive tissue trauma.

Spontaneous closure, or *secondary wound closure,* occurs when the margins of the open wound move together by a biologic process of contraction. Partial-thickness wounds heal by the process of epithelialization that occurs first by migration and the mitosis of epithelial cells.

Mechanisms Involved in Wound Healing

Three distinct biologic mechanisms are involved in all healing processes. They include *epithelialization,* which is the process by which keratinocytes migrate and divide to resurface the skin or mucosa. *Contraction* is the mechanism whereby there is spontaneous closure of full-thickness skin wounds or constriction of tubular

organs. *Connective tissue matrix deposition* is the process whereby fibroblasts are recruited to the site of injury and produce a new connective tissue matrix.

Phases of Healing

Under normal conditions, the phases of healing are divided into four specific events that actually overlap and have complex interactions. There is not a "lag phase" in the healing process.

Coagulation Injury causes hemorrhage and damage from blood vessels and lymphatics. Vasoconstriction occurs almost immediately. Vasoactive compounds initiate the process of diapedesis, the passage of intravascular cells through the vessel walls into the extravascular space of the wound. Platelets derived from the hemorrhage form a hemostatic clot and release clotting factors to produce fibrin, which is hemostatic. Fibrin forms a mesh for further migration of inflammatory cells in fibroblasts. Platelets also produce essential cytokines that modulate the events of wound healing.

Inflammation The inflammatory phase is characterized by the sequential migration of leukocytes into the wound. Inflammatory cells regulate the connective tissue matrix by specific messengers.

Fibroplasia During this phase, fibrous protein collagen is synthesized and cross-linked, and there is deposition of collagen and other matrix proteins that provide the healed wound with strength and integrity. Within 10 h after injury, there is evidence of increased wound collagen synthesis. After 5–7 days, collagen synthesis peaks and then declines gradually.

Remodeling During this phase, acute and chronic inflammatory cells diminish, angiogenesis ceases, and fibroplasia ends. The equilibrium between collagen synthesis and degradation is restored. The complex interactions of various processes during normal dermal wound healing are shown in Figure 8-1.

Cytokines in Wound Healing

Cytokines are "wound hormones." They may be *endocrine*, like somatomedin or insulin-like growth factor and circulate in the bloodstream to a distant target cell. Others are *paracrine,* produced by one cell and affecting an adjacent target cell. Examples of this are transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF). *Autocrine* factors are secreted by a cell and

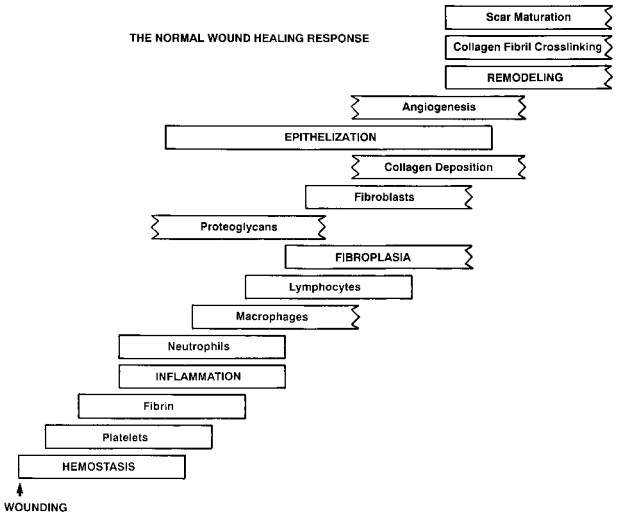

FIGURE 8-1 Sequence of events in wound healing. (Modified from: Mast BA: The Skin, in Cohen IK, Diegelmann RF, Lindblad WJ (eds): *Wound Healing: Biochemical and Clinical Aspects,* chap 22. Philadelphia, WB Saunders, 1992, with permission.)

then act on a receptor in the same cell. Finally, *intracrine* factors are produced by a cell and remain active in the same cell. Cytokines regulate cell proliferation and are also chemotactic, stimulating cells to migrate to the wound site. In addition, they direct the cells to produce specific components needed for matrix repair, including proteins, enzymes, proteoglycans, and attachment glycoproteins.

Extracellular Matrix Metabolism

The extracellular matrix has a number of cell types and components that interact with one another. Collagen is the major component of the extracellular matrix of all soft tissues, tendons, ligaments, and bones.

Synthesis Collagen is composed of three polypeptide chains, and each chain is formed in an orderly sequence. A key step in the

formation is hydroxylation that requires hydroxyproline and cosubstrates. A lack of ascorbic acid or oxygen will compromise collagen production and result in insufficient wound strength. Collagen cross-linking occurs to form fibrils and fibers of collagen. The enzyme responsible for this step may be inhibited by β-aminopropionitrile (BAPN) and D-penicillamine.

Degradation For normal wound healing, collagen must be degraded as well as produced. This is initiated by metalloproteinases synthesized by inflammatory cells, fibroblasts, and epithelial cells.

Ground Substance This is made up of proteoglycans and glycosaminoglycans that occupy a significant amount of space in the extracellular matrix. They function as "shock absorbers."

Wound Contraction

Contraction is one of the most powerful mechanical forces in the body. Contraction may result in a contracture that is a fixed deformity and often a functional disability. All attempts to use pharmacologic agents to control contraction of wounds have failed. Splinting a wound open will not prevent contracture. In an attempt to surgically correct contractures, plastic surgical procedures can result in recurrent contractures. Often it is preferable to correct the defect by placing a flap that contains both skin and subcutaneous tissue. In correcting a mature contracture, a skin graft may be used to fill the defect.

Epithelialization

While the collagen-rich dermis provides the strength attributed to skin, the epidermis provides the barrier that protects the host from the external environment. Partial-thickness wounds heal by the process of epithelialization. It incorporates both *migration* and *mitosis*. Migration is initiated in the deeper hair follicles and the sweat glands. The blood and tissue fluids contain fibronectin and vitronectin that support epithelial migration. Several growth factors stimulate keratinocyte migration and mitosis.

Nutrition

If caloric protein intake stops for 24 h, collagen synthesis ceases. Inadequate nutrition inhibits the immune response, and opsonization of bacteria is ineffective. The lack of ascorbic acid is the most common cause of wound-healing deficiency. Ascorbate is neces-

sary for the metabolism and synthesis of collagen. In a scorbutic patient, scar tissue breaks down before there is healing of the normal skin.

Trace amounts of iron are needed for prolyl hydroxylation. Calcium and magnesium are required for collagenase activity and protein synthesis. All the essential amino acids are needed for wound healing. An adequate supply of oxygen is needed for wound healing.

Immunosuppression

Only a small number of immunosuppressed patients manifest clinical wound-healing problems. A direct relationship between a leukocyte defect and healing has not been reported. The wound complications found in acquired immune deficiency syndrome (AIDS) patients have not been defined. Chemotherapeutic anticancer drugs inhibit wound healing.

Genetic Disorders of Connective Tissue

Osteogenesis Imperfecta This is a congenital form of osteopenia due to mutations in the genes for Type I collagen. There is an increased propensity for bones to break under minimal stress. There is also dermal thinning and increased bruisability. Patients also have difficulty with excessive diaphoresis. Children with osteogenesis imperfecta have a higher incidence of hernias, but these can be corrected successfully by operation.

Ehlers-Danlos Syndrome This is characterized by joint laxity, skin hyperextensibility and fragility, poor wound healing, and vascular rupture. Due to connective tissue weakness, adolescent males are at an increased risk during their normal growth development. Adolescent females are at higher risk during the hormonal changes of menstruation. A number of vascular complications include arteriovenous fistulas, varicose veins, arterial rupture, and true and false aneurysms.

Marfan's Syndrome This is characterized by tall stature, arachnodactyly, lax ligaments, myopia, scoliosis, pectus excavatum, and often dissecting aneurysms of the root and ascending portions of the aorta. Wound healing is more complicated in these patients.

Epidermolysis Bullosa This is characterized by blistering and ulcerations. It is thought to be due to excessive production of matrix metalloproteinases by fibroblasts. Most of these ulcers heal

spontaneously, but in the more severe forms the epithelium does not regenerate adequately, and inflammation and scarring ensue. Dermal incisions and tissue injury must have meticulous care to limit the amount of blistering in these patients. Phenytoin decreases collagenase activity and has been used to treat patients.

A number of factors may alter wound healing. They are listed in Table 8-1.

SPECIFIC WOUND-HEALING PROBLEMS

Gastrointestinal Tract

Anatomy The inner mucosal layer is for absorption, and the outer muscularis mucosae layer is for motility. These are wrapped in a strong serosal layer, which is an extension of the peritoneum. Unlike the skin, the mucosal epithelium is only one cell thick and renews itself about every 8 days. The submucosa separates the mucosa from

TABLE 8-1
FACTORS THAT AFFECT HEALING IN SURGICAL PRACTICE

Local Factors	General Factors
Blood supply	Age
Denervation	Anemia
Hematoma	Anti-inflammatory drugs
Infection (local)	Cytotoxic drugs
Mechanical stress	Hormones
Protection (e.g., dressings)	Infection (systemic)
Surgical technique	Jaundice
Suture material and technique	Malignant disease
Type of tissue	Malnutrition
	Obesity
	Temperature
	Trauma, hypovolaemia, and hypoxia
	Uremia
	Vitamin deficiency
	Trace metal deficiency

SOURCE: Modified from Bucknall TE, Ellis H (eds): *Wound Healing for Surgeons*, London, Baillière Tindall, 1984.

the muscularis propria and is composed of several collagen types. The muscularis propria is densely packed smooth muscle.

Injury and Repair The process is determined by the depth of injury and the chronicity of the injury. If the epithelium is injured, a rapid restitution process is initiated, and the epithelial lining is restored within hours. When the injury penetrates into the submucosa, an ulcer results. If the process is acute, the collagen laid down is resorbed, and the normal architecture of the intestine is preserved. If the process is chronic, scar tissue accumulates, and stricture may occur.

Crohn's disease is characterized by inflammation in the submucosa rather than the mucosa and often extends from the mucosa to the serosa (transmural). Inflammation leads to collagen deposition and contraction, which cause stricture. In *ulcerative colitis,* the inflammation is confined to the mucosa and does not extend into the submucosa. *Radiation injury* involves the submucosa, muscularis, and serosa with fibrosis and hyalinization of the accumulated collagen.

Healing in the Gastrointestinal Tract The same basic process of repair occurs with anastomotic healing in the gastrointestinal tract as occurs in skin. During the first few days after anastomosis, there is significant turnover of collagen at the anastomotic site and in the adjacent bowel wall.

Skin

Keloids and Hypertrophic Scars These are both abnormal healing processes that occur after injury. Hypertrophic scars remain within the boundaries of the original wound and almost always regress over a period of time. By contrast, keloids extend beyond the boundaries of the original wound and usually do not regress. They usually recur after excision unless additional therapy is provided. The rate of collagen synthesis in keloid tissue is greater than in normal skin and normal scar tissue. Inhibition of transforming growth factor beta (TGF-β) may control keloids and hypertrophic scars.

Currently, the treatment of keloid and hypertrophic scars is not consistently effective. Intralesional injection of a long-lasting synthetic glucocorticoid may make the lesion softer and smaller. Radiation therapy is ineffective and has the potential hazard of the development of skin cancer.

Marjolin's Ulcer This is a squamous carcinoma in a nonhealing wound. It appears to arise from dense scar tissue of the lesion that undergoes malignant transformation.

Tendon

Tendons are mainly composed of Type I collagen, with a significant amount of proteoglycan. The central component in the healing of a tendon within a fibrous flexor sheath is the segmental blood supply to the tendon through the vincula. Early motion provides stress forces to lengthen and remodel the scar. There is no evidence to suggest that the healing of tendons can be enhanced.

Bone

The healing process begins with inflammation and formation of a hematoma. There is a transformation of the surrounding osteoprogenitor cells and migration of hematogenous cells into the fracture site. This provides the fracture with platelets, monocytes, neutrophils, fibroblasts, osteoblasts, and osteoclasts—all needed to accomplish fracture repair.

Over the course of several weeks, there is the formation of a soft callus, a local fibrocartilaginous splint of granulation tissue. This gives the fracture some stability. In 6–8 weeks, the soft callus is transformed into bone by endochondral ossification. When rigid internal fixation is used to immobilize the injury, no soft callus forms, but instead there is direct bone-to-bone healing across the injury without endochondral ossification.

Delayed union or nonunion is a failure of fracture repair. The factors indicated are usually accompanying soft tissue injury, extensive bone loss, inadequate reduction, inadequate immobilization, infection, poor blood supply to the fracture, and malignant growth at the fracture site.

When nonunion occurs, bone grafts can be used to treat the established nonunion. Osteogenesis and osteoconduction are the primary mechanisms by which bone grafts heal. This occurs primarily in vascularized bone grafts, such as fibula flaps, in which the blood supply to the graft is maintained or reconstituted with a microvascular anastomosis. *Osteoconduction* is the process by which blood vessels and cells from the surrounding tissues grow into the bone graft and act as a scaffold for laying down new bone as the dead bone is resorbed.

Cartilage

Cartilage has little propensity to heal. Superficial injuries cause minimal inflammatory response, and healing depends on the chondrocytes' activity. The chondrocyte response is usually inadequate, and a persistent structural defect in the joint surface usually remains.

Cartilage grafts are used in reconstructive and cosmetic surgery. They maintain their structure with minimal resorption over time.

Chronic Wounds

Acute versus Chronic Wounds A *chronic wound* is one that fails to heal because of some underlying pathologic condition such as pressure, diabetes, and venous stasis. With proper clinical management, most chronic wound-healing problems can be resolved.

Pathophysiology Chronic wounds arise from physical and biochemical insults of extended duration. This prolongs the inflammatory stage of wound repair and results in extensive tissue damage and impaired healing. During normal wound repair, polymorphonuclear leukocytes (PNSs) quickly respond to chemoattractants, and infiltration lasts only a few days. With the preservation of damaged or necrotic tissue, there is an excessive response by the activated PNSs, and this continues to degrade the extracellular matrix and prevent the migration of other repairative cells into the wound.

Venous Stasis Ulcers These are the result of deep venous obstruction or valvular incompetence. The resulting increase in venous pressure promotes extravasation of fluid and high-molecular-weight proteins. Ulcers typically occur superior to or near the medial malleolus and are commonly rimmed by an area of hyperproliferative keratinocytes. The extent of the ulceration can range from just below the epidermis to the fascia.

Pressure Ulcers These occur over bony prominences. Immobilized persons are at particular risk. The pressure causes cell death in the least vascularized tissues. Patients with spinal cord injury are more susceptible to pressure ulcers because they do not have a normal leukocyte response to injury below the level of denervation.

The management of pressure ulcers requires good wound care. Antibiotics should not be used unless there is systemic toxicity.

Diabetic Ulcers Chronic ulcers in diabetics typically present as foot ulcers. Pressure and tissue trauma are major promoting factors, but the neuropathy from the primary disease is the most important element. The lack of sensation results in increased mechanical stress under the metatarsal heads, heels, and callosities. This leads to intermittent or continuous ischemia, resulting in pressure ulceration. Diabetics are also prone to angiopathy that interferes with the healing response.

TABLE 8-2
WOUND DRESSINGS

Classification	Compositions	Indications	Functions	Examples
Films	Semiocclusive (semi-permeable. Polyurethane or copolymer.	Acute or chronic. Partial- or full-thickness wounds with minimal exudate. Nondraining, primarily closed wounds.	Mimic skin performance. Water vapor permeable. Water/bacterial impermeable. Retention dressing for gels. Provides moist environment for epithelialization.	Op-site, Bioclusive, Tegaderm, Blisterfilm
Hydrocolloids	Contain colloidal particles (quar, karaya, gelatic, carboxymethyl cellulose) in an adhesive mass (usually polyisobutylene).	Acute or chronic partial- or full-thickness wounds. Stage I to IV pressure ulcers.	Absorbs fluid. Debrides soft necrotic tissue by autolysis. Protects wounds. Good adhesiveness without adherence to wound. Encourages granulation. Promotes reepithelialization. Protects wounds from trauma.	Duoderm, Restore, Intrasite, Ultec, J & J ulcer dressing
Hydrogels	Contain 80–90% water. Cross-linked polymer such as polyethyleneoxide, polyvinyl pyrollidone, or acrylamide.	Acute or chronic partial- or full-thickness wound with minimal exudate. Stage I to IV pressure ulcers.	Creates moist environment. Usually requires secondary dressing. Low absorbency. Debrides minimally. Decreases pain. Does not adhere to wound.	Vigilon, Elastogel, Intrasite Gel, Span Gel, Carrington Gel

Hydroactives	Non-pectin-based dressings. A polyurethane matrix provides high and selective absorption. Matrix is a foamed gel and combines the properties of a foam and a gel.	Chronic or acute partial- or full-thickness wounds: Stage I to IV pressure ulcers.	Selective absorption, leaving growth factors (PDGF) and other peptides in the wound bed while absorbing excessive moisture. Autolytis encourages granulation and promotes reepithelialization.	Cutinova Hydro, Cutinova Foam, Cutinova Cavity, Cutinova Thin
Foams	Either hydrophilic or hydrophobic. Nonocclusive. Usually polyurethane or gel film coated. High absorbency.	Acute or chronic partial- or full-thickness wounds that are highly secreting.	Debrides. High absorbency rates. Water vapor permeable.	Lyofoam, Allevyn, Polymem
Impregnates	Fine mesh gauze impregnated with moisturizing, antibacterial, or bacteriodidal compounds. Nonadherent.	Acute or chronic partial-thickness wounds with minimal to moderate exudate.	Does not adhere to wound. Promotes reepithelialization. Requires secondary dressing.	Aquaphor-gauze, Adaptic, Biobrane
Absorptive powders and pastes	Consist of starch, copolymers, or colloidal, hydrophilic particles. Can absorb up to 100 times their weight.	Chronic full-thickness wounds with large amounts of exudate.	High absorbency. Debrides necrotic and fibrous material from wound.	Bard absorptive dressing, Duoderm granules
Calcium alginate	Nonwoven composite of fibers from calcium alginate, a celluloselike polysaccharide.	Partial- or full-thickness wounds with high exudate.	Highly absorbent. Dressing material becomes a gel to facilitate moist healing. Requires secondary dressing.	Sorbsan, Kaltostat, Carra-Sorb

Mechanisms Involved in the Healing of Chronic Ulcers
Contraction can be involved by reducing the area of the wound. Usually minimal epithelialization is required to heal chronic ulcers. Venous ulcers heal mainly by epithelialization.

Chronic Wound Care

Most chronic wounds will heal by secondary intention only if the underlying biochemical and mechanical causative factors are corrected. Compression stockings or dressings must be used to relieve venous hypertension in the case of venous stasis ulcers. Pressure must be eliminated over pressure sores. The diabetes of a diabetic patient must be controlled to ensure healing of the ulcer. Bacterial counts above 100,000/g of tissue must be reduced and nutritional deficiencies corrected. An immunocompromised patient may require systemic or topical antibiotics to prevent or control infection. Low albumin levels should be corrected.

Tissue perfusion and cellular oxygenation are important factors for chronic wound repair. There is no evidence that hyperbaric oxygen can improve the healing of most chronic wounds with the exception of osteoradionecrosis.

Wound cleansing has a limited role. The objective of wound cleansing is not sterilization but rather reduction of the microbial load. Debridement to remove damaged and necrotic tissue often helps to accelerate healing. Sharp surgical debridement is the most effective method. Whirlpool treatment has been recommended for debridement of large areas, but care must be taken when this modality is used.

WOUND DRESSINGS

A wide variety of wound dressings are available. The classification, composition, indications, and functions of dressings are summarized in Table 8-2.

MECHANICAL WOUND CLOSURE

Sutures are classified as *absorbable* or *nonabsorbable.* The nonabsorbable polypropylene suture is smooth and is advantageous when creating a subcuticular pullout suture. The absorbable polyglycolic dermal suture (PDS) is best for areas where long-term tensile strength is required. Both absorbable and nonabsorbable sutures can be used in most situations.

In addition to sutures, surgical staplers can be used to affect closures of intestines and skin. Tape strips are also helpful in supporting the wound margins. They allow early removal of skin sutures and also can be used to effect closure by themselves. Fibrin glue, a recent development, also has been applied to a variety of wounds.

FETAL WOUND HEALING

Fetal wound repair is characterized by a reduced inflammatory response. Fetal platelets have different aggregative characteristics and reduced cytokine release compared with adult platelets. Rather than collagen, the major component of the wound matrix is the glycosaminoglycan hyaluronic acid. There is a rapid turnover, remodeling, and reorganization of collagen during fetal repair. Amniotic fluid may inhibit fetal wound contraction.

For a more detailed discussion, see Cohen KI, Diegelmann RF, Yager DR, Wornum IL III, Graham M, and Crossland MC: Wound Care and Wound Healing, chap. 8 in *Principles of Surgery,* 7th ed.

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CHAPTER 9
ONCOLOGY

Approximately 90 percent of patients with malignancy undergo surgical therapy for diagnosis, primary treatment, or management of complications related to cancer. Resection is the initial curative treatment for about 75 percent of patients because cancer is assumed to be a localized disease for an interval, allowing cure after adequate surgical removal. The surgeon is responsible for the initial diagnosis and management of many types of cancer. Accurate diagnosis and staging with adequate operative removal of localized disease and palliation of symptoms when possible are the guiding principles of surgical treatment of cancer.

Management of the cancer patient is a multidisciplinary effort requiring collaboration among surgical oncologists, radiation oncologists, medical oncologists, reconstructive surgeons, and other oncologic specialists. Combinations of surgery, radiation therapy, chemotherapy, hormone therapy, and immunotherapy significantly improve cure rates above those achieved with any single therapeutic modality. As the primary coordinator in cancer management, the surgeon must fully understand the indications, risks, and benefits of surgery, adjuvant chemotherapy, hormonal therapy, and radiation therapy and the importance of reconstructive surgery.

Determining a treatment plan requires the integration of information from four areas: (1) natural history of the disease by histologic type, (2) clinical staging, (3) goals of specific treatments, and (4) indications and risks for each treatment (or combination of treatments) based on results of experience and clinical trials.

EPIDEMIOLOGY

Cancer is the most frequent cause of death in the United States, accounting for 24 percent (approximately 520,000) of deaths each year. The five leading causes of cancer death among males in the United States are lung, 32 percent; prostate, 14 percent; colon and rectum, 9 percent; leukemia and lymphoma, 9 percent; and pancreas, 5 percent. Among females, the leading causes of cancer deaths are lung, 25 percent; breast, 17 percent; colon and rectum,

10 percent; leukemia and lymphoma, 8 percent; and ovary, 6 percent. Prostate cancer is the most frequent life-threatening cancer in men, and breast cancer is the most frequent in women.

The *incidence rate* of cancer is defined by the number of new cancer cases that develop in a population of individuals at risk during a specific interval. These rates should be distinguished from *prevalence* (the number of affected persons within a population). Rates can be crude, category-specific (e.g., age, gender, or race), or adjusted (e.g., accounting for mortality from other causes). Herein resides the value of population-based registries and of high-risk registries in which persons at risk can be concentrated for study and treatment.

Vastly different incidence rates for site-specific cancers have been found. Cancer of the stomach remains a leading cause of death in Asia and eastern Europe. When natives of Japan, where gastric cancer is frequent and colorectal cancer uncommon, emigrated to Hawaii, over one generation the frequency of these cancers was reversed, a change attributed to adoption of the Western diet. Given that diet and nutrition may be characterized as an environmental factor, these differences incriminate environment-induced molecular events in human carcinogenesis. The more frequent occurrence of cancer in older persons may reflect accumulation of environmentally based genetic events as well as molecular events associated with senescence.

Recognition of internal and external environmental interactions in human carcinogenesis provides the means for risk reduction and the development of prevention strategies. Elimination of exposure to asbestos or radiation, avoidance of occupational carcinogens, and reduction of cigarette smoking remove certain carcinogens from the environment and reduce risk. Sunscreens block the carcinogenic wavelength of ultraviolet light.

BIOLOGY OF MALIGNANT TRANSFORMATION

Cellular Homeostasis To achieve homeostasis in tissues, renewable cell populations must perform four related functions; they must (1) proliferate with proper timing and fidelity of DNA content, (2) differentiate in a pattern consistent with normal function of the tissue, (3) involute in a manner such that the proliferation and involution rates are balanced, and (4) repair any damages to their DNA resulting from exposure to mutagens such as radiation, toxins, and transforming viruses. A defect in any of these functions can result in tumor formation.

Carcinogenesis Cancer results from a deregulation of critical aspects of cellular function. Without the proper constraints on these processes, neoplastic cells reproduce in great numbers, invade adjacent structures, and develop metastases. *Tumor initiation* is defined as the exposure of cells to agents that induce an inheritable genetic change, i.e., agents that are genotoxic or induce critical mutations by binding of electrophilic carcinogenic metabolites to DNA. *Tumor promotion* is the exposure of initiated cells to agents that induce their proliferation. This proliferation may allow other spontaneous mutations to occur that culminate in expression of malignant phenotype. *Tumor progression* describes successive development of increased local growth, invasion, and metastasis by transformed cells.

CANCER PHENOTYPE

Progression of a tissue to malignancy disturbs host homeostatic mechanisms, as characterized by (1) unresponsiveness to normal growth regulators, (2) invasive phenotype, and (3) evasion of immune-mediated tumor destruction. Tumors are thought to be clonal in origin (i.e., all the cells within a tumor arise from a single progenitor cell whose growth regulation has become deranged). Despite their possible clonal origin, cancers, particularly the solid tumors, are heterogeneous in character. A cancer mass includes tumor cells and their supporting blood vessels and stroma. As regions of tumor outstrip their blood supply, areas of inflammation and necrosis further contribute to tumor heterogeneity. As a result of loss of the fidelity of DNA replication, changes in the malignant cell population occur throughout the course of tumor progression. This is best demonstrated by a change in differentiation state or tumor antigen expression between primary tumors and their metastatic foci.

Progression of a tissue to malignancy involves several stages. The earliest visible evidence of neoplastic transformation is dysplasia, a condition in which epithelial tissues exhibit altered size, shape, and organization. Dysplasia is a common reaction of tissue to chronic inflammation or exposure to environmental toxins or irritants. Because dysplastic cells retain a measure of control over cellular proliferation, dysplasia is generally reversible once the inciting factor is removed. In most tissues, however, severe dysplasia is associated with progression to carcinoma if left without intervention.

The hallmark of a solid-tumor carcinoma is the ability to invade the basement membrane and spread without regard to normal tissue boundaries. *Local disease* is the term used to refer to invasive tumor that is confined to the tissue of origin. Once the basement membrane has been breached, the next barrier to tumor dissemination is the

network of draining lymph nodes. Tumor spread to the lymph nodes draining the tissue of origin is termed *regional disease.* The final stage of tumor progression is metastasis, whereby independent colonies of tumor are established in distant sites favorable to tumor growth. This type of tumor is commonly referred to as *distant disease.*

Physical Carcinogens Physical agents can induce tumor induction by two mechanisms: (1) induction of cell proliferation over an extended period of time, which increases the opportunity for events leading to transformation, and (2) exposure to physical agents that induce damage or changes in DNA. The best known agent of physical carcinogenesis is radiation. Ionizing radiation includes x-rays and gamma rays, whereas the most common form of non-ionizing radiation is ultraviolet radiation. Both types of radiation are associated with human cancers.

Chemical Carcinogens Epidemiologic studies reveal that a substantial number of compounds are associated with chemical carcinogenesis. Tobacco products remain the source of most chemically induced human cancers. Most carcinogenic chemicals are a complex mixture of molecules rather than a single pure agent. There are several main classes of chemical carcinogens, including organic and inorganic substances. Polycyclic hydrocarbons are organic carcinogens that undergo metabolism in the host to an active form. Benzo[a]pyrene, a component of cigarette smoke and smoked foods, is probably the most extensively studied polycyclic hydrocarbon. This substance is converted to its toxic metabolites through the action of the hepatic enzymes cyclooxygenase and cytochrome P-450. Inorganic carcinogens include heavy metal products of fossil fuel combustion such as nickel, cadmium, chromium, arsenic, and lead.

Viral Carcinogens Viruses can insert their genetic material into host cells and induce changes morphologically consistent with neoplastic transformation. It is now recognized that both RNA and DNA viruses are capable of inducing tumors in humans, although only a small proportion of individuals infected with a cancer-associated virus actually develop tumors. Virus-associated cancers arise after an incubation period of years to decades, suggesting that other genetic or environmental factors contribute to virally induced carcinogenesis. The contribution of oncogenic viruses to carcinogenesis may lie in the inactivation of the proteins that are essential for regulation of the cell cycle. The most common tumor viruses are listed in Table 9-1.

TABLE 9-1
TUMOR-ASSOCIATED VIRUSES

Virus	Associated Cancer
Epstein-Barr virus (EBV)	B cell lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease
Hepatitis B virus (HBV)	Hepatocellular carcinoma
Human papillomavirus (HPV) subtypes 16 and 18	Cervical cancer, squamous cell carcinoma
Human papillomavirus (HPV) subtypes 5 and 8	Squamous cell carcinoma in association with epidermodysplasia verruciformis
Human T cell leukemia virus type 1 (HTLV-I)	Adult T-cell leukemia/lymphoma (ATLL)
Human T cell leukemia virus type 2 (HTLV-II)	Chronic T-cell lymphoproliferative disorders
Kaposi's sarcoma–associated herpeslike virus (KSHV)	Kaposi's sarcoma
Human immunodeficiency virus type 1 (HIV-I)	Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, anal squamous cell carcinoma

IMMUNODEFICIENCY AND CANCER

The theory of immunologic surveillance against cancer is that immune effector cells can eliminate cells that undergo malignant transformation. According to this theory, the development of a tumor is a failure of immune surveillance in maintaining tissue homeostasis. Despite advances in the understanding of carcinogenesis, the nature of immune surveillance and the role of the immune response cells in the progression of malignancy are unclear.

States of immunosuppression are associated with an increased risk of cancer. Patients receiving long-term immunosuppressive medication for prevention of allograft rejection have an increased incidence of skin cancers and lymphoid malignancies. The coincidence of virally induced tumor formation and states of immunosuppression provides strong evidence that a normally functioning immune system acts to suppress carcinogenesis. For example, the acquired immunedeficiency syndrome (AIDS) is associated with Kaposi's sarcoma, non-Hodgkin's lymphoma, and squamous cell carcinoma.

GENETIC ALTERATIONS

The Multistep Hypothesis Cancer is fundamentally an alteration in the genes that control cellular function. Cancer susceptibility genes can be inherited at conception as germline defects. These genes affect the cell's ability to detect and repair genetic damage, alter immune surveillance for tumors, modify cellular metabolism of carcinogens, or regulate the growth of specific cell types. Carcinogenesis seems to require the successive accumulation of genetic defects that result in the altered cellular growth and differentiation characteristic of a malignant phenotype. Such genetic changes are known as the *multistep hypothesis* of cancer and have been identified in the development of colorectal cancer.

Oncogenes *Oncogenes* are genes that promote the transformation of normal cells into tumor cells. They are usually designated by three-letter names derived from the tumors or the cell line in which the oncogene was first identified. Oncogenes derived from viral genomes are labeled with the prefix *v* (e.g., v-*src*), whereas cellular oncogenes are labeled with *c* (e.g., c-*src*). Oncogenes encode proteins, sometimes termed *oncoproteins*, that alter cell cycle regulation, resulting in tumor formation. Oncogenes are divided into categories depending on the role their proteins play in cellular function. These include growth factors, growth factor receptors, cytoplasmic protein kinases, guanosine triphosphate (GTP)–binding proteins, nuclear transcription factors, and cell cycle regulators (Table 9-2).

Tumor Suppressor Genes and the Inherited Cancer Predisposition Syndromes Tumor suppressor genes keep cellular growth in check. The loss of function of one of these genes leads to tumor formation. Loss of RB1 gene function requires mutation of both copies of the gene. In familial retinoblastoma, affected individuals inherit one defunctionalizing germline mutation. Expression of the RB1 mutation phenotype requires loss of the second allele by somatic mutation, a concept known as *Knudson's "two-hit" hypothesis.* Most of the inherited cancer predisposition syndromes described to date involve inheritance of one mutant and one normal allele of a tumor suppressor gene.

p53 has been recognized as a tumor suppressor gene and identified as a germline mutation associated with Li-Fraumeni syndrome, a familial clustering of breast cancer, soft tissue sarcomas, brain tumors, osteosarcoma, leukemia, and adrenocortical carcinoma. Affected individuals develop cancer by age 70 through somatic loss of the wild-type p53 allele. Inactivation of the p53 gene is one of the most detectable genetic defects in tumors. The p53 protein plays a crucial role in preserving the integrity of the cell's genome by temporarily halting the cell cycle in response to damage, allowing adequate time for DNA repair prior to replication. In instances of severe damage, the p53 protein is capable of triggering programmed cell death, consequently eliminating damaged cells before replication can occur. Given its importance in preventing replication of a damaged genome, p53 has been labeled the "guardian of the genome"; intact p53 function is crucial for tumor prevention. Other diseases that have been linked to defective tumor suppressor genes include familial adenomatous polyposis, hereditary malignant melanoma, multiple endocrine neoplasia, and familial breast and ovarian cancer.

FUNCTIONAL ALTERATIONS IN CARCINOGENESIS

Tumor progression involves acquisition of several abilities by the malignant colony. These cells must be able to (1) invade the basement membrane and surrounding tissues through the production of proteases, (2) recruit blood vessels to support the growth of the tumor mass, (3) avoid destruction by effector cells of immune surveillance, such as natural killer (NK) cells, (4) move through tissues, a process that requires production and recruitment of cell adhesion molecules and chemotactic cytokines, and (5) travel to distant sites, adhere, and establish a new tumor colony. There are many parallels between fetal development and malignant transformation. The process of tumorigenesis involves the disruption of normal developmental programs.

TABLE 9-2
ONCOGENES

Oncogene	Associated Malignancy	Protein Function
Growth factors		
int-2	Breast carcinoma	Fibroblast growth factor
sis		Platelet-derived growth factor
Growth factor receptors		
*erb*B	Breast carcinoma	Epidermal growth factor receptor
fms		Monocyte colony-stimulating factor receptor
ret	MEN-II syndrome	Nerve growth factor receptor
trk		Nerve growth factor receptor
Cytoplasmic protein kinases		
src		Protein-tyrosine kinase
abl	CML, ALL, AML	Protein-tyrosine kinase
raf		Serine-threonine kinase

Gtp-binding proteins		
gsp		G protein α subunit
ras	Colorectal, lung, pancreatic, and prostate cancers (epithelial tumors)	GTP/GDP-binding protein
Nuclear transcription factors		
jun		AP-1 transcription factor
fos		AP-1 transcription factor
myc	Burkitt's lymphoma, neuroblastoma, small cell lung cancer, colorectal cancer	DNA-binding protein
*erb*A		Thyroid hormone receptor
Cell cycle regulators		
bcl-2	Non-Hodgkin's lymphoma	Supressor of apoptosis
cyclin D1	Parathyroid adenoma (PRAD1), breast, esophageal cancers, lymphomas (*bcl*-1)	Cyclin

RELATIONSHIPS BETWEEN TUMORS AND NORMAL HOST TISSUES LOCAL INVASION

In order to become invasive carcinoma, tumor cells must cross the basement membrane and enter the surrounding stromal tissue. Tumor invasion must involve partial destruction of a barrier of collagen, glycoproteins, and proteoglycins. The process of local tumor invasion includes tumor cell adhesion, matrix dissolution, and migration.

Tumor Cell Adhesion Cell-cell adhesion is an important process for growth of normal tissues. Cells that lose contact with each other undergo involution. During carcinogenesis, the requirement for cell-cell adhesion is lost, and single cells can infiltrate local tissue. Adhesion of cells and growth regulation are mediated by *cell adhesion molecules* (CAMs), which are complex glycoproteins present on the surfaces of both epithelial and stromal cells. CAMs are divided into four main classes according to their structure and general function. These include the cadherins, the integrins, the selectins, and the immunoglobulin superfamily receptors. Following tumor cell adhesion, the process of infiltration requires matrix dissolution. Matrix lysis occurs in experimental models of tumor infiltration from 2–8 hours after adhesion. Enzymes belong to a family known as the *metalloproteinases* (MMPs) and are responsible for matrix lysis. These enzymes include interstitial collagenases, Type IV collagenases, and stromelysins. Natural protease inhibitors, known as *tissue inhibitors of metalloproteinases* (TIMPs), produced either by the host or by the tumor itself, can counteract this process. Once the basement membrane barrier is lysed, tumor cells are free to migrate into the surrounding stromal tissues.

Migration The third step of invasion is migration. Tumor cell motility involves both fixed cell surface interactions and soluble factors. Tumor cell movement is characterized by ameba-like pseudopod extension. This movement requires coordination of multiple steps, including cellular protrusion and new adhesion formation at the leading edge, as well as release of old adhesive interactions at the trailing edge. A number of cytokines stimulate motile responses in tumor cells. These include tumor cell–derived cytokines, such as autocrine motility factor, autotaxin, and scatter factor. Many adhesion molecules, particularly those found in the extracellular matrix, such as laminin, collagen, fibronectin, and thrombospondin, serve as tumor cell attractants in motility assays.

Angiogenesis *Angiogenesis*, or the formation of new blood vessels, is important for all phases of tumor progression. Without new

vessel growth, tumors would quickly outstrip their local nutrient supply and would be unable to form new colonies after metastasis. Endothelial cells in vessels near a tumor site are stimulated by angiogenesis factors to degrade the extracellular matrix. This allows migration of endothelial cells into the stroma, initiating a capillary sprout. Growth of a tumor colony beyond 1 cm^3 in size requires vascularization through angiogenesis. The locally secreted factors of angiogenesis include basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), transforming growth factors alpha and beta (TGF-α and -β), angiogenin, tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8).

The development of angiogenic potential in a tumor may be an important indicator of its biologic behavior. For example, the presence of increased vascularity in early breast cancer specimens indicates a higher chance of tumor recurrence as well as increased presence of lymph node metastasis. These observations raise the possibility that antiangiogenesis agents, such as analogues of the fungus-derived angiogenesis inhibitor fumagillin, might prove beneficial in the treatment of malignancy.

Metastasis Metastatic tumors develop as clones arising from a heterogeneous primary tumor. Tumor cell metastases require multiple host-tumor interactions that probably begin early in the growth of the primary tumor. The metastatic cell must be able to break away from the original tumor population, invade through the basement membrane into a blood vessel, travel and adhere to a distant site, and induce angiogenesis. These activities require coordinating the processes of proteolysis, motility, adhesion, growth factor responsiveness, and angiogenic activity. Since all these processes are naturally occurring functions of growth and development, the basic defect of metastasis must lie in the aberrant regulation of these processes.

Metastasizing tumors have a predilection for selected organ sites. In human beings, colon tumors frequently metastasize to the liver, renal cell carcinoma to the lung, melanoma to the lung and brain, prostate cancer to bone, and ocular melanoma to the liver. Selection of a metastatic site by a particular tumor is probably governed by the adhesion and growth factor characteristics of the metastatic site and the requirements of the metastatic tumor.

The role of the regional lymphatics in the spread of cancer is controversial. It is now thought that the properties of the tumor cells themselves, rather than the filtration capacity of the lymph nodes, determine whether neoplastic cells are trapped within nodes

or allowed to disseminate. The regional nodes also may be involved in the initiation of systemic immunity to tumors. For example, adoptive transfer of lymphoid cell populations derived from regional lymph nodes has been shown to induce tumor allograft immunity in normal animals.

Metastasis is a multistage process in which tumor cells acquire more and more autonomy regarding growth factor and adhesion requirements. A complex process with no universally applicable mechanism, metastasis depends on the characteristics of the tumor (the "seed") and the microenvironment of its implantation site (the "soil").

INTRACELLULAR SIGNAL TRANSDUCTION

Binding of a ligand to a cell surface receptor results in an intricate cascade of intracellular reactions ultimately inducing transcription of appropriate cellular genes. This complex process is known as *intracellular signal transduction.* Most oncogenes or tumor suppressor genes encode proteins essential for intracellular signal transduction. Oncogenes can be roughly divided into groups according to their cellular function, e.g., the cytoplasmic protein kinases, transcriptional regulators, GTP-binding proteins, and regulators of programmed cell death (apoptosis).

Growth factor receptors are also known as *tyrosine kinases.* Binding of a growth factor on the extracellular domain results in phosphorylation of the intracellular portion of the receptor. This triggers recruitment of intracellular substrates, which trigger a cascade of kinase activity and cytoplasmic enzymes. These kinases mediate the reactions that bridge the gap between the cell membrane and the nucleus, resulting in induction of transcription in stimulation of the cells that progress from G_1 to S phase.

Cell Cycle Control Cells take their cues for proliferation and differentiation not only from external sources such as growth factor receptors but also according to an internal program. The cell cycle encompasses the progression from G_1 phase through mitosis and is coordinated by nuclear proteins called *cyclins.* The passage of a cell through the cell cycle is tightly regulated by a network of controls that act on the transcription of cyclin genes, the degradation of cyclin proteins, and the modification of cyclin-dependent kinases by phosphorylation. It is now recognized that the cell cycle is a dynamic process that includes periods of arrest of cell proliferation when DNA damage occurs, presumably to allow time for DNA repair to occur. Provisions are made within the cell cycle program for apoptosis in circumstances in which the cell's genome has undergone irreparable damage. *Cyclin-dependent kinases* (CDKs)

coordinate the cell cycle. Multiple CDKs have been described that govern progression of the cells from G_1 to mitosis.

Defects in the cell cycle control points are known to be associated with carcinogenesis. At the transition of G_1 to S phase, the Rb protein is an important control point. Loss of function of the Rb protein leads to unregulated entry of a cell into S phase. The p53 gene product is also known to be a regulator of cell cycle activity. The protein product of p53 gene activates p21, a protein that inhibits all the cyclin-CDK complexes. A cell with deficient p53 will enter S phase without sufficient DNA repair and will replicate uncorrected mutations.

Regulation of Apoptosis In order for tissues to maintain a normal state, cells subject to renewal must involute so that the proliferation and involution rates are balanced. This programmed cell death is known as *apoptosis.* Defects resulting in loss of normal apoptosis are associated with tumor formation. The *bcl*-2 oncogene was identified in follicular lymphomas and found to promote cell survival rather than proliferation. BAX, a protein identified by its association with the *bc*-2 gene product, counteracts the survival-promoting effects of *bcl*-2. Most mechanisms that induce apoptosis involve the BAX/*bcl*-2 interchange. Transcription of BAX protein is inducible by p53. Other regulators of apoptosis include TNF-R1 and insulin-like growth factor-1 (IGF-1).

SURGICAL MANAGEMENT OF PRIMARY TUMORS

General Considerations Some types of cancer involve some role for the surgeon, either by diagnosis, clinical staging, operative resection, pathologic staging, palliation, or management of medical conditions. Knowledge of clinical and pathologic staging is important, and accurate diagnosis and assessment of the extent of tumors are essential to appropriate treatment. Surgical resectability is determined by the tumor's relation to and degree of invasion into and around vital structures. Invasive and noninvasive radiologic studies are extremely helpful in outlining the goals of operative management and defining the operative approach. Studies to preclude metastases are indicated when they are cost-effective and would substantially alter surgical treatment.

The surgeon has a major role in disease prevention and patient/family counseling. The extent of an operation may be related to the presence of additional precancerous lesions or to a strong family history of site-specific cancers.

An important but often underemphasized goal of cancer management is restoring the patient's physical, emotional, social, and employment status. The rehabilitation for a woman with breast cancer might be directed toward minimizing scarring and swelling of the tissues in the chest and arm, regaining strength and mobility of the shoulder after axillary lymphadenectomy, and restoring contour and symmetry of the breast. For some women, an external prosthesis is satisfactory; other women significantly benefit from breast reconstructive surgery.

Clinical Diagnosis A complete history and physical examination are indispensable before further judgments can be made. Symptoms generally correspond to the sites involved, but nonspecific symptoms, such as night sweats and weight loss, may be the initial manifestations of an underlying neoplastic tumor.

The patient's past medical history often lends clues to the diagnosis. Diethylstilbestrol (DES) use by the patient's mother during pregnancy, thymic irradiation for asthma, skin irradiation for acne in childhood, and a history of chronic inflammatory bowel disease are historical factors known to be associated with the development of cancer. Smoking, alcohol ingestion, and exposure to asbestos or aniline dyes can be related to tumor development.

Inquiry into family history may reveal findings that support an initial diagnosis or influence the extent of surgical treatment. Without a thorough history, genetically influenced diseases may be missed.

Laboratory and Radiologic Studies Complete blood count, coagulation profile, serum biochemistry profile, and chest x-ray are baseline studies that are useful in determining the prognosis in patients with malignant disease. Serum markers such as carcinoembryonic antigen (CEA), CA19-9, beta-human chorionic gonadotropin (β-HCG), and alpha-fetoprotein (AFP) are useful in the management of patients with specific tumors. Elevated plasma levels are correlated with increasing tumor size, stage, and the extent of positive lymph node metastases in patients with large-bowel cancer.

Surgical Pathology Accurate pathologic diagnosis is extremely important in the proper surgical treatment of cancer patients. Determinations of the presence of cancer, the histologic grade, the site of the primary or metastatic foci, and surgical resection margins provide critical information.

Fine-needle aspiration cytology is a valuable technique for diagnosis of palpable masses in the breast and thryoid, as well as palpable suspicious nodes in the neck, axilla, or groin. Aspiration cy-

tology cannot be completely depended on for grading of solid tumors, for subdividing types of lymphoma, or for accurate diagnosis after radiation treatment, but a positive diagnosis greatly facilitates diagnostic and treatment planning.

When an accurate diagnosis of tumor type and grade is necessary, an incisional or excisional biopsy is required. Care should be taken in the planning of a surgical biopsy so as not to jeopardize later surgical extirpation. In general, large soft tissue masses that are deeper than the superficial fascia are best sampled by incisional biopsy. Small (<2 cm) superficial lesions can be managed by excisional biopsy with a view toward further treatment depending on tumor size, grade, and depth of invasion.

Decision for Operation A decision for curative operation presupposes that the tumor is localized or confined regionally, that the area of the tumor can be encompassed by regional excision, that evidence of distant metastases cannot be found, and that the tumor is appropriately treated by operation. In principle, an en bloc resection should be performed, encompassing the primary tumor, regional lymph nodes, and intervening lymphatic channels. This principle is best illustrated by operations for large bowel cancer, in which the regional lymphatics of the colon course in one direction with the major arteries and veins.

The extent of various operations for cancer is undergoing change. The theraputic value of regional lymph node dissection has been questioned by many. Performed properly, a lymph node dissection is of clear prognostic value and can establish the database for precise staging for other adjuvant treatments.

Some surgical procedures may be performed solely for staging purposes. Examples include staging laparotomy for Hodgkin's disease. Other operations are performed solely for palliative treatment, such as bypasses around obstructed viscera. Cytoreductive surgery is controversial. This approach may be most relevant in ovarian cancer and some childhood tumors, such as neuroblastoma. Rarely is cytoreductive surgery applicable in other circumstances.

Cancer Operations

Local Resection Wide local resection that removes an adequate margin of normal tissue with the tumor mass may be adequate for certain low-grade neoplasms that do not metastasize to regional nodes or widely infiltrate adjacent tissues. Basal cell carcinomas, thin melanomas, and mixed tumors of the parotid gland are examples of such neoplasms. Some normal tissue surrounding the tumor should be excised to prevent local recurrence.

Radical Local Resection Neoplasms, such as soft tissue sarcomas and esophageal and gastric carcinomas, may spread widely by infiltration into adjacent tissues. In such cases it is necessary to remove a wide margin of normal tissue with the neoplasm. The greater the width of normal tissues between the plane of dissection and the tumor, the greater is the likelihood of a complete local excision.

If an incisional biopsy procedure was performed previously, a segment of skin and the underlying muscles, fat, and fascia must be removed far beyond the limits of the original incision because tumor cells may have been implanted in the incision during the initial operation.

Malignant neoplasms are not well encapsulated. A pseudocapsule composed of a compression zone of neoplastic cells may surround the tumor. This apparent encapsulation offers a great temptation for simple enucleation, because the tumor may be easily dislodged from its bed. The surgeon must cut through normal tissue at all times and should never disrupt the neoplasm during its removal. Dissection should proceed with meticulous care to avoid tumor cell spill. The surgeon should resect as far as possible from the gross extent of the tumor on all sides, including the deep aspect. Skin, subcutaneous fat, and some muscles may have to be sacrificed, but usually this causes little functional loss. Sacrifice of tumor-involved major vessels, nerves, joints, or bones may be necessary to obtain a curative result.

Radical Resection with En Bloc Excision of Lymphatics Since many neoplasms commonly metastasize by way of the lymphatics, operations have been designed to remove the primary neoplasm and the regional lymph nodes draining that area in continuity with all the intervening tissues. Conditions are best suited for this type of operation when the collecting nodes of the lymphatic channels draining the neoplasm lie adjacent to the primary site or when there is a single avenue of lymphatic drainage that can be removed without sacrificing vital structures. Modified radical mastectomy and radical total gastrectomy are examples of en bloc regional lymph node dissection. En bloc removal of the involved nodes offers the best chance for cure and provides significant palliation and local control.

Lymphadenectomy General principles common to lymph node dissection (LND) at various anatomic sites include the following: (1) The surgeon must thoroughly understand the anatomy of the lymph nodes in each area of the body as well as lymphatic drainage. (2) Goals of LND must be clearly defined as cure, control of local

disease, or staging. (3) Incomplete LNDs generally are not acceptable, except when the goal of surgery is strictly palliative. (4) The incision providing access to regional lymph nodes should be placed to minimize the risk of dividing lymphatic vessels that contain malignant cells. (5) Closed-suction drains are important for evacuation of blood and serum and for minimizing the risk of seroma formation. The incidence of wound infection increases if drains are kept in longer than 10 days.

Elective Lymph Node Dissection Removal of regional lymph nodes without clinical evidence of metastasis is designated *elective lymph node dissection.* It is not clear whether cure rates are improved if lymph nodes are removed before they become palpable. Nonetheless, knowledge of tumor and regional lymph nodes affects staging, treatment, and prognosis. Breast and melanoma patients frequently have significant alterations in therapy depending on the status of regional lymph nodes. Furthermore, a comparison of experimental results from different institutions depends on accurate staging when therapy is initiated.

Selective Lymph Node Dissection Morton and colleagues recently described a promising technique for detection of the regional draining lymph nodes most likely to contain metastatic tumor cells spreading from a primary cutaneous melanoma. Their technique of intraoperative lymphatic mapping and selective sentinel LND is currently under investigation in a phase III multicenter trial for melanoma and is also being applied to breast carcinoma and other neoplasms. Initially, the technique relied on injection of a vital blue dye at the tumor site and visual tracking of this dye along the lymphatics to the nodal basin. Sentinel node mapping has been facilitated by adding a radiolabeled isotope to the dye and monitoring its path by a handheld gamma probe.

RADIATION THERAPY

Ionizing radiation is effective in the management of a wide variety of malignant tumors and is part of the treatment for 50–60 percent of patients with cancer. The radiation oncologist should be involved in the selection of patients and their evaluation before, during, and after treatment.

With radiation, tumors can be destroyed while anatomy is preserved. Often function and cosmesis can be preserved if the anatomy is intact before treatment. Concurrent medical problems have less influence on radiation therapy than on surgical or chemotherapy.

The differential effect of radiation therapy on tumors and normal tissues results in a favorable therapeutic ratio in most clinical situations. Radiation can, however, have immediate and delayed side effects on normal tissues. The incidence and severity of late sequelae, which may progress over many years, are highly dependent on treatment technique. The appearance of late sequelae may be the unfortunate consequence of treatment techniques long abandoned.

Physical Basis Ionizing radiations are characterized by their capacity to ionize atoms and molecules in an absorber such as tissue. Electromagnetic radiations can be produced artificially in kilovoltage radiation therapy units and linear accelerators by impinging energetic electrons on a target. The energy of the resulting x-rays is related to the energy of the accelerated electrons as they reach the target material. According to quantum physics, x-rays and gamma rays also can be represented as particles called *photons.* Other types of particulate radiations (e.g., protons, neutrons, pi mesons, and helium ions) are produced by very powerful linear accelerators, or *cyclotrons,* and have been used therapeutically, primarily in investigative settings. Because the basic physical mechanisms of action of all ionizing radiations are the same, the different effects observed with equal physical doses result from differences in spatial or temporal distributions.

Clinical specification of radiation doses is derived from direct measurements of absorbed doses within the patient (using thermoluminescent dosimeters) or from doses calculated within a tissue phantom that simulates the human being. Phantom measurements are adapted for precise clinical application through the use of computer programs. Recent technological advances have made it possible to correct for tissue inhomogeneities (air cavities and bone) within the treatment volume using computed tomography (CT)–based treatment planning. Doses of radiation are quantified in gray units (Gy), with 1 Gy = 100 rad = 1 joule per kilogram of the absorber and 1 cGy = 1 rad.

In some clinical situations, brachytherapy, or the direct placement of radioactive sources within tissue, may permit delivery of tumor doses higher than those achievable with external-beam radiation therapy. Because the dose delivered is inversely proportional to the square of the distance from the source, very high doses can be delivered to tissues immediately adjacent to the implant with relative sparing of surrounding normal tissues. High-dose-rate (HDR) remote afterloaded brachytherapy, a new delivery technique that is gaining greater clinical acceptance, involves the delivery of several grays in minutes. Low-dose-rate (LDR) brachytherapy may require

several days of hospitalization, but HDR brachytherapy can be delivered in a fractionated manner as an outpatient procedure. In HDR remote afterloading, a high-activity source is driven to a predetermined series of positions for specified periods. Because of the small source size, smaller-diameter catheters can be applied to interstitial and intraluminal sites, such as the bronchus, esophagus, and bile duct, which previously could not be easily treated with LDR techniques. This computer-operated remote afterloading technique optimizes the dose distribution. These brachytherapy techniques have led the radiation oncologist into the operating room and into closer cooperation with the surgeon.

Biologic Basis *Radiosensitivity* is the susceptibility of cells to injury by ionizing radiation. This injury may cause reproductive cell death by interrupting the cell's capacity to replicate indefinitely. Radiation can kill cells by interfering with critical cell functions unassociated with cell replication. Differences in the rapidity and completeness of response of human tumors and normal tissues must be based on factors such as the capacity to repair sublethal damage, tissue oxygenation, cell cycle time and distribution, and repopulation.

Radiocurability is the ability of radiation to control a tumor permanently, allowing survival of the host. Tumor type, size, and site have a greater influence on radiocurability than cellular radiosensitivity. *Radioresponsiveness*, or the rapidity of a tumor's response to radiation, may not correlate well with radiocurability. Epidermoid carcinomas of the oral cavity and adenocarcinomas of the breast and prostate may be radiocurable despite relatively slow responses to radiation. Undifferentiated carcinomas tend to respond rapidly to radiation treatment but usually are not cured because of widespread tumor dissemination.

Normal tissues have a greater capacity to repair injury than do tumor cells. *Fractionation*, or the division of a radiation dose into multiple smaller doses, allows recovery of this damage between radiation fractions. Because of their greater repair capacity, slowly dividing normal tissues usually are spared more than tumor cells by the use of relatively small fraction sizes, but rapidly dividing stem cell populations, such as bone marrow and mucosal surfaces, have less capacity for repair. Clinicians have been investigating the use of altered, hyperfractionated schedules that use two or three small fractions per day in an effort to further decrease late normal tissue complications without increasing the overall duration of treatment.

Radiation-induced cell killing can be modified in other ways. Because molecular oxygen must be present for maximal cell killing by ionizing radiation, tumor cellular hypoxia can decrease the

effectiveness of radiation therapy by as much as a factor of 3. This "oxygen effect" may explain the postirradiation persistence of tumor cells when there is necrosis or fibrosis.The intrinsic radiosensitivity of cells can be increased by altering the target DNA, such as by replacing thymidine with halogenated pyrimidine analogues during cell replication. Unfortunately, such methods are not selective for tumor cells and may not improve the therapeutic ratio.

Clinical Basis Irradiation may be the only anticipated treatment for some cancers or may be combined with surgery and/or chemotherapy for others. The intent of treatment may be curative or palliative. It is important that all such specialists are involved before initiation of therapy. Close cooperation from the beginning of therapy often can improve treatment outcome significantly. For example, careful marking of the margins of a tumor during surgery can help the radiation oncologist define a more accurate target volume and decrease the morbidity of therapy. Awkward placement of a surgical incision can dramatically increase the volume, complexity, and morbidity of subsequent irradiation. In some cases, the radiation oncologist can obtain valuable information by observing the operative field. The potential for local and regional tumor control with radiation is closely related to tumor size and the primary site. In most cases, radiation dose is limited by the tolerance of surrounding normal tissues. Surgical tumor debulking procedures that leave gross residual disease are sometimes necessary to relieve tumor-related symptoms; however, they may increase tumor hypoxia and decrease the tolerance of adjacent normal tissues.

The primary tumor site predicts biologic behavior and dictates which normal tissues will be affected by treatment. Small tumors of the glottic larynx, for example, rarely spread to regional lymph nodes, and more than 90 percent of these tumors are cured with moderate doses of radiation to a small local field. Large tumors of the cervix can be controlled locally with minimal risk of serious morbidity because of the high radiation tolerance of the uterus and vagina and the ability to deliver high doses with intracavitary therapy. By contrast, carcinomas of similar size in the upper abdomen are rarely controllable with radiation therapy alone because surrounding normal tissues such as liver, kidney, bowel, and spinal cord limit the deliverable doses of external-beam radiotherapy. Intraoperative radiotherapy (the delivery of external-beam radiotherapy directly to a tumor exposed during an operation) is currently being investigated as a possible means of increasing the radiation dose that can be delivered in such situations.

Combination Modalities Radiation therapy alone is curative in many clinical situations. Aggressive local or regional treatment

yields high cure rates in many types of head and neck cancer, gynecologic malignancies, anal cancer, prostate cancer, Hodgkin's disease, and other neoplasms. In other cases, radiation is used in combination with surgery or chemotherapy. Radiation and surgery may be directed to the same site, e.g., when resection of a cancer of the hypopharynx is followed by irradiation or when irradiation of a soft tissue sarcoma in an extremity is followed by surgery. Combined modalities may decrease the morbidity associated with either modality alone. Local tumor excision plus radiation therapy is an alternative to mastectomy for breast cancer. Treatment of soft tissue sarcomas with wide local excision and preoperative or postoperative irradiation achieves local control rates comparable to amputation but with preservation of the limb.

Postoperative radiation improves local and regional control rates in most postoperative situations. Even when the survival benefit of postoperative radiation is uncertain, treatment may be indicated to prevent local recurrence.

Side Effects Any effective anticancer therapy can produce undesirable and occasionally dangerous side effects. Acute radiation-induced side effects can be distressing but usually can be managed conservatively and are almost always self-limited. The nature of these effects depends on the tissues included within the target volume. The clinically important late sequelae of radiation therapy may not be apparent until months or even years after completion of treatment. The risk of second malignancies induced by ionizing radiation is small. In studies of more than 2000 patients with head and neck cancer and 2000 patients with cancer of the breast, no increase in the incidence of second cancers could be demonstrated in patients treated with radiotherapy.

MANAGEMENT OF CANCER AT DISTANT SITES

General Principles of Treatment The treatment of a patient with advanced cancer depends on the number and sites of metastases, their rate of growth, types of and responses to previous treatment, and the patient's age, overall condition, and desires. For example, vigorous treatment might be appropriate for a slowly growing solitary metastasis, but only symptomatic treatment or none at all might be used in a debilitated patient with multiple metastases. The option of no treatment is particularly important in patients who are asymptomatic, terminally ill, or very old. Quality of life is maintained in this instance, and treatment can be instituted when the patient develops symptoms.

The number of organs or tissues containing metastases is the most significant factor predicting survival in patients with distant disease. For example, the median survival is 7 months for melanoma patients with metastasis to one site, 4 months for those with metastases to two sites, and only 2 months for those with metastatic disease at three or more sites. The locations of the metastases is also important.

Defining the Goals, Benefits, and Risks of Treatment The first goal of treatment is relief of symptoms. Treatment to relieve symptoms is worthwhile, especially when the benefit of symptom relief exceeds the risk of toxic effects and morbidity. Its efficacy can be monitored by subjective and objective assessments of the symptoms caused by the metastases.The second goal of treatment is to prolong life. This has not been achieved in most patients with metastatic cancer.

Surgery

In selected patients with slowly growing neoplasms, curative resection of metastatic lesions may be indicated, especially if the metastasis is solitary. Observation for several weeks or months sometimes provides relevant information about the rate of tumor growth and the possibility of metastases emerging at other sites. All patients considered for curative resection must undergo an extensive workup to rule out metastatic spread. Magnetic resonance imaging (MRI) of head, CT of the chest, abdomen, and pelvis, and a bone scan may be applicable. Newer whole-body imaging studies, such as positron emission tomographic (PET) scanning, eventually may replace conventional radiologic techniques.

Surgical procedures are sometimes indicated for palliative benefits, to relieve symptoms or reduce the severity of disease, or to prolong a comfortable life without attempting cure. A palliative operation that improves quality of life is justified when it can be done safely without great discomfort to the patient. Surgery that only prolongs a miserable existence does not benefit the patient. Some examples of palliative surgical procedures are colostomy and gastrojejunostomy to relieve obstruction, chordotomy to control pain, cystectomy for infected, bleeding tumors of the bladder, amputation for painful infected tumors in the extremities, and simple mastectomy for carcinoma of the breast, even in the presence of distant metastases.

Radiation Therapy

Irradiation has a role in the treatment of patients with advanced cancer, particularly those with symptomatic lesions. It is used as

palliative treatment for patients with bone or brain metastases and for symptomatic lesions located in the skin, subcutaneous tissues, or lymph nodes. Radiation therapy using high-energy beams relieves the pain of bone metastases, often within 1 week.

Chemotherapy

Chemotherapy is the systemic or regional delivery of defusible pharmocologic agents that can destroy or arrest tumor cells capable of proliferation. Currently available drugs are not selected for tumor cells; they affect all dividing and some quiescent cells. Chemotherapy attempts maximal tumor cell kill with minimal and acceptable toxicity to normal host tissues. Cells and tissues with the highest growth fraction will be most affected.

Anticancer drugs may kill tumor cells, but the majority act by preventing cell division and cell proliferation. Most drugs affect one or more components of the cell cycle. DNA synthesis can be prevented by blocking the availability of purine and pyrimidine nucleotide precursors. DNA may be damaged by cross-linking with unstable alkyl groups. DNA transcription can be prevented by direct binding of drug to DNA. Mitosis can be arrested through binding of tubulin and prevention of mitotic spindle formation. Drug combinations often are based on the complementary effects of phase-specific agents on rapidly dividing cells and non-cell-cycle-specific agents on dividing and nondividing cells.

Alkylating Agents Alkylating agents are non-cell-cycle-specific drugs that contribute an unstable alkyl group to cross-link nucleic acids (primarily DNA). The major effect is on cells in G_1 or mitosis. Cyclophosphamide, cisplatin, dacarbazine, and ifosfamide are examples of clinically useful alkylating agents. Nitrosoureas are a subgroup of alkylating agents with increased lipid solubility and better CNS penetration.

Antimetabolites These agents interfere with DNA and RNA synthesis and are phase specific for the synthesis phase of the cell cycle. An exception is 5-fluorouracil, which is phase specific and cell cycle specific. These drugs are most active in rapidly proliferating tumors such as the hematologic malignancies but also have wide applicability in many solid tumors. Some antimetabolites bind to rate-limiting enzymes and the synthesis pathways. For example, leucovorin (folinic acid) potentiates the antitumor effect of 5-fluorouracil by stabilizing the covalent bond of 5-FdUMP to the enzyme thymidylate synthase.

Plant Alkaloids These agents inhibit mytosis by binding microtubules and causing arrest in metaphase. They include the derivatives of the periwinkle plant, e.g. vinblastine, vincristine, and vindesine. These alkaloids have antitumor activity against Hodgkin's and non-Hodgkin's lymphomas, acute leukemias, and a variety of solid tumors.

Antibiotics These drugs are isolated from mircoorganisms and appear to interfere with the synthesis and/or function of nucleic acids. Examples include doxorubicin, bleomycin, mitomycin C, and dactinomycin.

Dose and Timing To achieve maximal tumor cell kill, the highest tolerated dose is given over the shortest possible time. The dosage is based on the maximal tolerated dose (MTD) derived from clinical studies and must be tailored to a patient's performance status, medical illness, or organ dysfunction.

Drug dosing is most reliably calculated in terms of body surface area, milligrams per square meter (mg/m^2). A dose in milligrams per kilogram can be converted to yield the milligrams per square meter dose by multiplying by a factor of 40.

The interval between doses depends on a drug's toxicity. For most chemotherapeutic agents with bone marrow toxicity, leukopenia and thrombocytopenia become evident on a complete blood count by day 9 or 10 and are most pronounced between days 14 and 18. Recovery usually begins by day 21 and is approximately 90 percent by day 28. This provides the rationale for a 28-day course or cycle of marrow-suppressive agents.

Induction chemotherapy is the use of chemotherapy as the sole form of treatment for advanced disease. These patients usually are not candidates for surgery or radiation. *Adjuvant chemotherapy* is the use of regional or systemic chemotherapy after locoregional tumor elimination by surgery or radiation therapy. Adjuvant therapy attempts to eliminate residual micrometastatic disease and usually is limited to patients at moderate to high risk for local or distant recurrence. Responses can only be evaluated by monitoring rates of recurrence, disease-free survival, and overall survival. *Neoadjuvant or primary chemotherapy* is the use of chemotherapy as the first treatment for localized solid tumors such as breast, gastrointestinal, and extremity sarcomas. It has several advantages. First, it may reduce the size of large or locally advanced tumors, allowing a safer resection that spares surrounding normal tissues, as in breast-conservation surgery, anal sphincter preservation with middle to low rectal tumors, and limb preservation with extremity sarcomas. Second, tumor responsiveness to chemotherapy can be determined

while grossly or radiologically visible tumor is still present; agents that produce an initial complete or major partial response will be continued postoperatively. On the other hand, unsuccessful neoadjuvant chemotherapy can delay locoregional interventions, and tumor progression during this time may preclude safe resection or require sacrifice of additional normal surrounding structures to obtain adequate resection margins. Preoperative chemotherapy may confuse pathologic staging of resected tissues, complicating future treatment decisions and prognosis.

The clinical response to chemotherapy for visible, palpable, or radiologically measurable tumors is determined by the change in tumor mass. A *partial response* is generally 50 percent greater reduction in summed measurable tumor mass. Each tumor mass is measured as the product of the two greatest perpendicular diameters. A partial response is occasionally subdivided into minor responses (less than 50 percent size reduction) and major responses (more than 50 percent size reduction but less than a complete response). A *complete response* requires total disappearance of tumor on physical examination and radiologic studies for at least 4 weeks. A complete clinical response is likely to be followed by early relapse if chemotherapy is not continued long enough to eliminate any micrometastatic disease. *Tumor progression* is defined as a greater than 50 percent increase in summed measurable tumor mass. *Stable disease* indicates no change in tumor mass, size reduction less than a partial response, or any increase in size less than progression.

Side Effects and Toxicity Some degree of drug toxicity during the administration of chemotherapy is not only expected but often is desirable because it indicates a cellular damage response. The maximal tolerated dose of most chemotherapeutic agents is sought to achieve the highest tumor cell kill. Patterns of organ toxicity have been well described for the different classes of drugs. The degree of toxicity depends on drug concentration, duration of exposure, and host response. Anticipated drug toxicity is based on the nonspecific damage caused by most chemotherapeutic agents to rapidly proliferating normal tissues such as bone marrow.

Biologic Therapy

Biologic therapy is the administration of any biologic molecule or multimolecular complex and includes immunotherapy and gene therapy. *Immunotherapy* assumes that cancer progression results from failure of the host immune defenses to recognize and reject the tumor. Biologic agents augment the immune response with the

goal of blunting tumor progression. Theoretically, the immune system may be activated or reactivated to attack and destroy tumor specifically, leaving normal tissue largely unaffected. Implicit in the ability of the immune system to recognize and attack neoplastic cells is the existence of immunogenic tumor-associated antigens. Evidence that human tumors are immunogenic comes primarily from investigations using melanoma, which is one of the most immunogenic solid tumors. Blood from melanoma patients contains antibodies against tumor antigens as well as cytotoxic T cells (CTLs) that can destroy tumor cells in vitro. Clinical studies indicate that approximately 3–15 percent of all cutaneous melanomas are first diagnosed as lymphatic or visceral metastases without evidence of a primary tumor, which suggests that the immune system has caused complete regression of the primary melanoma. T-lymphocytes play a critical role in the rejection of solid tumors in these models. In addition to the adoptive specific immunity afforded by T-lymphocytes, natural killer (NK) cells can lyse a wide variety of tumor and virus-infected cells without the antigen-specific receptors used by T or B cells. Rapidly emerging advances in the basic mechanisms of cell-mediated immunity provide new strategies for biologic therapy based on the prospect that the host immune system may be manipulated either in vivo or ex vivo to reject neoplastic outgrowth. Molecular biology and cell cloning enable investigation of a new level of the biology of host-tumor relationships and development of biologic agents to administer to cancer patients.

Recombinant Cytokines Several cytokines are currently in use for biotherapy of cancer. Trials using recombinant interferon-alpha (IFN-α) for metastatic melanoma show a major response rate of about 23 percent (range 14–28 percent). Interleukin-2 (IL-2), the T-cell growth factor, induces a major response, particularly in patients with metastatic melanoma and metastatic renal cell carcinoma, but not in patients with breast cancer, colon cancer, or lymphoma. The treatment of melanoma was significantly changed when Kirkwood and associates reported that high-dose IFN-α-2b significantly prolonged both relapse-free and overall survival rates after surgical resection of high-risk primary melanoma [American Joint Committee on Cancer (AJCC) Stage IIB] or regional lymph node metastases (AJCC Stage III). This important study was the first randomized, controlled trial to show a significant benefit of adjuvant therapy in prolonging relapse-free and overall survival of high-risk melanoma patients. On the basis of the results of the study, the Food and Drug Administration approved IFN-α-2b for postoperative adjuvant therapy in melanoma patients at high risk of

systemic recurrence. The intravenous administration of the cytokines is not without significant toxicity, however, and it is clear that they trigger a cascade of effects that results in other lymphocyte activities as well as the direct effects of IL-2 on other tissues. Some of the side effects are similar to those seen with septic shock. Concern over the toxicity of intravenously administered cytokines has promoted the development of methods to target cytokines and reduce systemic effects. Cytokines are administered aggressively and frequently because of their short half-life in the blood. Combination biologic therapy is now in clinical trials for treatment of most major human cancers. The multiagent concept is plausible because (1) multiple immune abnormalities are most likely to occur in cancer patients, (2) there is heterogeneity in immune response (nature of lymphocytes, role of antibody, presence of macrophages) relative to the site of the metastases, and (3) combinations of agents with different mechanisms of action are more likely to augment individual aspects of immune response additively or synergistically in a diverse population of cancer patients. For example, combinations of IL-2 and IFN-α elicit a higher rate and more durable response time for metastatic melanoma than either cytokine alone. Combinations of tumor antigen, lymphokines, and cyclophosphamides are intended to activate tumor-specific immunity, promote effector T-cell proliferation, and downregulate suppressor T cells. *Biochemotherapy* uses cytokines such as IL-2 and IFN-α in combination with chemotherapeutic agents such as 5-fluorouracil with the goal of enhancing antitumor activity. Various biochemotherapeutic regimens are being examined in patients with metastatic colorectal cancer, lung cancer, renal cell carcinoma, and melanoma. Cytokines also have been used as supportive therapy to allow higher doses of chemotherapy. For example, granulocyte-macrophage colony-stimulating factor (GM-CSF) has been administered with erythropoietin to allow acceleration and dose escalation of chemotherapy with cyclophosphamide, epidoxorubicin, and 5-fluorouracil in patients with advanced breast cancer.

Immunotherapy Immunotherapy is a logical adjunct for the treatment of subclinical microscopic disease after definitive cancer surgery, radiation therapy, or chemotherapy for the following reasons: (1) patients who have only small foci of cancer cells remaining after destruction of the major tumor bulk are the most likely to benefit from immunotherapy because the tumor mass that must be destroyed is smallest at that time, (2) the specificity of the immune response provides a possible therapeutic tool that has selectivity for small numbers of cancer cells not possible with any other therapeutic modality, (3) patients with disease in earlier stages are more

likely to respond to immunotherapeutic maneuvers because the cancer patient's general immune competence is greatest when the disease is localized and is often impaired after metastasis, and (4) immunotherapy should complement rather than interfere with currently available methods of cancer therapy. Because both irradiation and chemotherapy are immunosuppressive, the use of immunotherapy in combination with these therapeutic modalities must be controlled carefully.

Active Specific Immunotherapy (Cancer Vaccines) The clinical use of cancer vaccines was initiated at the turn of the century, prompted by the success of vaccines against infectious disease. Unlike vaccines against infectious disease, which are administered prophylactically, cancer vaccines are generally administered after the advent of disease. Both types of vaccine use attenuated whole cells, cell walls, specific antigens, or nonpathogenic strains of living organisms to stimulate the patient's immune system to fight the disease. The specific goals of active immunotherapy with cancer vaccines are to overcome the immunosuppression produced by tumor-derived factors, to stimulate specific immunity that will destroy tumor cells, and to enhance the immunogenicity of tumor-associated antigens (TAAs). Several observations support the potential value of active specific immunotherapy for the treatment of cancer. These include (1) vaccine-induced immunity against cancer in animal models, (2) the regression and eradication of tumors injected directly with immunostimulants, (3) occasional regression of non-injected tumors after the intralesional injection of bacille Calmette-Guérin (BCG), and (4) the development of antitumor antibodies.

Adoptive Immunotherapy In *adoptive immunotherapy,* immune lymphoid cells are transferred to a recipient to mediate tumor destruction. Rosenberg and colleagues pioneered the study of adoptive immunotherapy using lymphokine-activated killer (LAK) cells, which are cytolytic lymphocytes generated in the presence of IL-2. These cytolytic cells can kill a wide range of fresh and cultured human cancer cells but not normal cells. Clinical trials using autologous LAK cells and systemically administered IL-2 produced clear, objective responses in some patients with bulky metastatic cancer. Some evidence suggests that LAK cells may be more important in renal cell carcinoma than in melanoma. Subsequently, the method was developed for isolating tumor-infiltrating lymphocytes (TILs) from human melanoma and renal cell carcinoma; after proliferation ex vivo in the presence of IL-2, the TILs were returned to the patients and IL-2 therapy administered concurrently. In preliminary studies, response rates of up to 40 percent were obtained. TIL-

based immunotherapy is an active area of research, and TILs also are being investigated in conjunction with gene therapy.

Nonspecific Immunotherapy Certain substances, such as mixed bacterial toxins and fractions of the tubercle bacillus, nonspecifically enhance host resistance to most viral, fungal, and bacterial agents. Although the exact mechanism is unknown, these agents appear to stimulate immune response to a wide variety of antigens, including tumor antigens. Interest in a nonspecific immunotherapy was revived more than 20 years ago using attenuated bovine tuberculosis bacillus (bacille Calmette-Guérin, BCG). Some tumor regressions were observed, but consistent responses in any one treatment group were difficult to achieve. Other nonspecific agents include *Corynebacterium parvum, Bordetella pertussis,* MTP-PE, methanol-extractable residue of BCG, bacterial endotoxins, and polynucleotides. Another form of nonspecific immunotherapy involves the use of agents capable of restoring depressed immune responses. Several agents have been proposed, including thymic hormones, such as thymosin, and the antihelmintic drug levamisole.

Passive Immunotherapy The systemic use of tumor-specific antiserum is laden with theoretical and practical problems. Passive immunotherapy is effective only in suppressing small numbers of tumor cells and must work in concert with host effectors (e.g., complement, macrophages, antigen-dependent cellular cytotoxicity) to effect a cytotoxic action on target cells. In addition, only antibodies of certain classes and subclasses can interact effectively with certain cellular effectors. Most of the better characterized human tumor-specific antisera are murine monoclonal antibodies that, because of their antigenicity, have limited applications in human beings. Immunotoxins are tumor-specific antibodies that are attached to toxic molecules. This concept uses the antibody molecule to preferentially localize anticancer agents in the vicinity of tumors. It obviates the need for the host to supply effector cells or complement to mediate tumor destruction. Monoclonal antibodies are preferred to heterologous antiserum because they permit the use of homogeneous purified antibodies of defined specificity. A wide range of toxic molecules has been tested in vitro and includes radioactive isotopes, traditional cancer drugs, and plant and bacterial toxins.

Gene Therapy Gene cloning has introduced a new era of biologic therapy that will have an impact on human clinical trials in the coming years. A novel approach is transfection of human TILs with genes for producing cytokines, such as tumor necrosis factor (TNF). The ability to transfect cytokine genes into human TILs

suggests adaptive cellular therapy with genetically transfected cells capable of producing high concentrations of tumor necrosis factor or other lymphokines at the tumor site. This would deliver high concentrations of cytokine to the tumor site while sparing the vascular compartment of the otherwise deleterious effects of high-dose, systemic cytokine. Gene transfection also may be used to augment the immunogenicity of tumor vaccines. Other approaches to gene therapy of cancer are antisense oncogene and tumor suppressor gene therapy, which attempt to correct genetic disorders of cancer by suppressing the abnormal expression of proliferative genes.

Management of Distant Metastases at Specific Sites

Lung, Pleura, and Mediastinum Two of the most common initial sites of metastasis are the lungs and pleura. A standard chest x-ray is sufficiently sensitive and cost-effective for screening all cancer patients and frequently will reveal hilar and mediastinal adenopathy in those with pulmonary metastases. Although pulmonary tomograms or CT scans have too low a yield and too high a cost to be justified when the chest x-ray is normal, they are of value in evaluating suspicious chest lesions or in determining whether the metastatic disease seen on the chest x-ray is present elsewhere in the chest. CT scan can identify lesions as small as 3 mm, but it is not indicated unless the presence of pulmonary metastases would alter the treatment plan or unless a better definition of lesions is required for entry into a research protocol. Bronchoscopy with biopsy may be considered when the etiology of a pulmonary lesion is in doubt. A scalene lymph node biopsy is indicated for palpable nodes. Mediastinoscopy is indicated if the chest x-ray or CT scan reveals abnormal mediastinal nodes that are accessible through the instrument. Thoracentesis or pleural biopsies may be helpful when evaluating effusions. Fine-needle biopsy of a pulmonary lesion under CT scan guidance may be useful in selected instances to establish the histologic diagnosis. Video-assisted thoracoscopy is increasingly used both diagnostically and therapeutically in the staging and treatment of lung cancer. This technique permits visualization of the entire visceral, parietal, and mediastinal pleural surfaces and excisional or incisional biopsy for establishing diagnosis. If the diagnosis remains in doubt, an exploratory thoracotomy may be necessary, especially for a solitary lesion, because some patients will have potentially curable primary lung cancer. The treatment approach is determined by the location and number of thoracic metastases and by the patient's overall status. Criteria for resection include absence of metastases at other

sites, control of the primary tumor, potential for complete resection, and a long tumor doubling time. CT scans should be obtained preoperatively because the number of lesions demonstrated by CT scanning is often greater than that shown by chest x-ray. Lung parenchyma should be conserved during resection. Most metastases occur just below the pleura, and a wedge of tissue removed by segmental resection suffices. Stapling, electrocautery, and laser surgery can be useful. Lobectomy and pneumonectomy usually are not indicated. Patients who are ineligible for surgery, such as those with multiple slowly growing tumors, might be monitored but receive no treatment while they are asymptomatic.

Tumor Doubling Time The growth rate of a tumor can be expressed by the time the tumor doubles in volume. The *tumor doubling time* (TDT) is an accurate and reproducible measure of biologic aggressiveness that can be used to determine the indications for surgical resection. TDT represents the balance between the intrinsic proliferative rate of the tumor cell and the patient's immune defense mechanisms. TDT measurement is especially useful in treating patients with pulmonary metastases because neoplasms tend to be peripherally located and discretely identified on chest radiographs. It is quite easy to obtain accurate serial chest x-rays that can be used to measure the changing diameters of the lesion. The greater and lesser diameters are averaged and then plotted against time on semilogarithmic paper. The slope of the line drawn between any two points represents the rate of tumor growth. The horizontal distance between any two doubling points represents the TDT in days. TDT may vary from 8–600 days, but most tumors double in 20–100 days. Patients with a short TDT have aggressive, fast-growing metastatic lesions; patients with a long TDT might have nonaggressive lesions that would be responsive to surgery. TDT is an important prognostic tool for selecting surgical candidates. Patients with pulmonary metastases can be divided into three survival groups according to TDT. Those patients with TDTs of less than 20 days are not recommended for surgery; it is likely to be ineffective and will not result in long-term survival. Patients with a TDT of 20–40 days are not ineligible for surgery, particularly if a slowing of TDT is observed after preoperative chemotherapy; their long-term survival rates are not much improved by surgery alone. Patients with a TDT of 40 days or more can have long-term survival after resection of the pulmonary lesion. Sarcoma patients with a TDT of more than 40 days were found to have significant palliation from pulmonary resection and remained free of disease for as long as 5 years; patients with a TDT of less than 20 days did not significantly benefit from resection of metastatic lesions.

Liver, Biliary Tract, and Spleen Hepatic metastases can occur in many patients with metastatic disease, especially those with gastrointestinal malignancies and breast cancer. There are no reliable and accurate tests for early detection of liver metastasis and no common symptoms and physical signs. The patient might experience decreased appetite with loss of weight followed within weeks by general lassitude and debility. A history and physical examination and serum liver chemistries with appropriate tumor markers are the most cost-effective screening tests. Elevated levels of lactate dehydrogenase or alkaline phosphatase in the presence of normal or only slightly elevated levels of serum glutamic-oxaloacetic transaminase or bilirubin suggest liver metastasis. Suspected liver metastasis should be confirmed by ultrasonography or dynamic CT scan. Radionuclide liver scanning and hepatic arteriography are used less frequently. Abdominal CT scans are more accurate and reliable than ultrasonography and radionuclide liver scans for evaluation of liver masses. PET scans also are increasingly useful in detecting metastatic disease. Hepatic metastases are not detected by radiologic tests until they are more than 1 cm in diameter. Angiography is used only when the differential diagnosis cannot be established by noninvasive techniques, when the information gained would affect the treatment decision, or when hepatic resection is contemplated. Biopsy usually is not necessary to confirm the diagnosis of liver metastasis. In the few instances in which biopsy confirmation is essential to treatment decisions, a needle biopsy can be performed percutaneously with CT or ultrasound guidance or by laparoscopy or during laparotomy. Some patients with isolated liver metastases from colorectal cancers can benefit from surgical resection. Those patients with a solitary metastasis or metastases located in one lobe are often treated successfully with resection, and approximately 25 percent will survive for 5 years. Most liver metastases are not amenable to surgical excision. Systemic chemotherapy or hepatic arterial chemotherapy is the most common intervention for patients with nonresectable hepatic metastasis, and response rates vary. Cryosurgery might offer effective palliative treatment for patients with nonresectable primary or metastatic hepatic malignancies; in certain cases, extended survival has been reported with the potential for cure. Other treatments include hepatic artery embolization, chemoembolization, radiation therapy, and alcohol injection.

Brain and Spinal Cord Many cancers, particularly breast cancer, lung cancer, and melanoma, metastasize to the brain, a common cause of death. Headache and mental deficits are the most common symptoms of brain metastasis. The most common physi-

cal sign of brain metastasis is a focal neurologic deficit; seizures are common. The best tests for diagnosing intracerebral metastasis are MRI and CT with contrast enhancement. MRI, a technique that depends on the intrinsic paramagnetic properties of biologic tissue, is generally the preferred test to detect and stage brain and spinal metastases. The accuracy and sensitivity of these scans make it unnecessary, in most cases, to perform a radionuclide brain scan or electroencephalogram unless there are some equivocal findings. The mainstay of initial treatment is corticosteroids, the most effective of which is dexamethasone (up to 100 mg/day). Dexamethasone reduces edema around the tumor and temporarily helps to relieve symptoms in the majority of patients. Chemotherapy is not usually effective for brain metastasis. Surgical excision followed by cranial irradiation is the treatment of choice for a solitary, surgically accessible metastasis. Tumor excision by means of a craniotomy is safe and may be considered in some patients who have disease at other sites plus symptomatic brain metastases because their estimated life span can exceed 3 months, and their neurologic status usually improves. Patients treated with open brain surgery and fractionated radiotherapy have a better outcome than those treated with radiation alone, but many patients do not have surgically accessible cerebral metastases. In these patients, stereotactic radiosurgery using the "gamma knife" may offer the best chance of prolonged survival.

Bone Bone metastases are common in patients with advanced breast or prostate cancer but infrequent in patients with gastrointestinal cancers. They are medullary in location and destructive in nature. The pain from bony metastases is typically nocturnal at first, becoming persistent, progressive, and localized, and it can become quite severe. Bone metastases are frequently diagnosed in symptomatic patients, but occasionally they are seen incidentally on radiographs (e.g., rib metastases on routine chest x-ray) or a bone scan prompted by an elevated serum alkaline phosphatase level in the absence of liver metastasis. They are generally osteolytic in appearance on radiography and provoke little if any bone formation, but some patients with prostate cancer have osteoblastic bone metastases. The radionuclide bone scan is the initial test for evaluating suspected bone metastases. Its sensitivity is reportedly 50–80 percent greater than radiographs alone, but bone scan abnormalities are nonspecific and must be correlated with radiographic study (e.g., x-ray or CT scan) and patient history (e.g., fractures, trauma, arthritis, etc.) to distinguish between benign and malignant causes. A bone biopsy might be necessary to establish the diagnosis before instituting treatment. The treatment of bone metastases

depends on the degree of symptoms, the location and magnitude of the lesions, and the patient's life expectancy. The goals of therapy are to relieve pain and maximize ambulation. Symptomatic metastases frequently involve non-weight-bearing bones, particularly the spine and ribs. In these cases, irradiation of the lesions usually provides relief. The radiation fields should be restricted to those lesions responsible for the symptoms. Symptomatic bone lesions only occasionally respond to systemic chemotherapy, but bone metastases from breast cancer sometimes respond well to hormonal therapy. Symptomatic metastases in weight-bearing bones (e.g., the femur) require special consideration. If the lesion is large, and if there is evidence of cortical destruction, prophylactic stabilization and irradiation are sometimes used when the patient's life expectancy is at least 2 months. Alternatively, the lesion might be treated with radiation alone, but the patient must be closely monitored for evidence of pathologic fracture. Unless the surgical risk is high or the patient's expected life span is short, pathologic fracture of a weight-bearing bone should be stabilized. Patients with fractures of the vertebrae that have compressed the spinal cord require prompt treatment to avert paralysis. The treatment may require decompressive laminectomy and postoperative irradiation or irradiation alone depending on the extent of the disease and the patient's overall medical condition.

PSYCHOLOGICAL MANAGEMENT AND REHABILITATION

The physician can ease the cancer patient's fear of the disease by free and open communication. Psychological support and education are necessary for the patient to deal with any disability that can result from therapy. Examples include training in the care of a stoma following curative surgery for colonic and rectal cancer and referral to lay groups associated with the American Cancer Society for counseling the anxious patient with an altered body image resulting from mastectomy. It is impossible to predict the exact course of any malignant tumor. Patients with a poor prognosis are occasionally cured by aggressive therapy, and spontaneous regressions are sometimes observed in patients with metastases. In contrast, some patients with apparently localized disease can die of disseminated cancer in a few months. Uncertainty about the future is one of the most difficult adjustments that cancer patients and their families face. It is reassuring to emphasize that the chances for cure improve each month after successful treatment of the primary neoplasm, particularly for tumors such as squamous cell carcinoma of the

lung or oropharynx. Other, more slowly growing neoplasms, such as carcinoma of the breast and malignant melanoma, can recur after disease-free intervals of 10–20 years, although the chances of recurrence also decrease with time. Recognition that cancer is a chronic disease is an important aspect of management. Long-term, consistent follow-up provides opportunities for reassurance and usually can ensure detection of recurrence at an early stage. Some patients suspect the worst but do not want to hear the truth from their physician. However, a lie is never appropriate, even if requested by the family. Untruths often create barriers between patients and their families that can lead to psychological isolation of patients, who are unable to discuss their fears and anxieties with those they need most. Gentle and optimistic truth is generally the best approach, even when primary cancer therapy has failed and the patient is judged incurable. Realistic and consistent support is actually more important to the patient and family at this stage of the disease than earlier. There is increasing evidence that patients tolerate the process of dying much better when sustained by the physician's continuing concern and active support. Some incurable patients are unable to accept the realities of the situation. In this case, it is essential that a responsible family member be informed. The duration of the incurable patient's life is so uncertain that predictions should be avoided. If, as frequently happens, the relatives insist on some estimate, a combined minimum-maximum prognosis, such as from 6 months to 2 years, will help the family accept this uncertainty. The basic aim in caring for the patient with advanced cancer is to prolong useful life, but not useless suffering. The patient should be permitted to die with dignity when active therapy can no longer be of benefit.

For a more detailed discussion, see Daly JM, Bertagnolli M, DeCosse JJ, and Morton DL: Oncology, chap. 9 in *Principles of Surgery,* 7th ed.

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CHAPTER

10

TRANSPLANTATION

Transplantation is the process of taking a graft—cells, tissues, or organs—from one individual—the donor—and placing it into another individual—the recipient or host. If the graft is placed into its normal anatomic location, the procedure is called *orthotopic transplantation* (e.g., heart transplants, liver transplants). Transplantation between genetically different members of the same species is referred to as *allogeneic transplantation*, such as transplantation of tissues or organs between two different strains of experimental animals (e.g., rat strain ACI to Lewis). In human beings, all transplants except those between identical twins are allotransplants. Failure of graft to "take" is the result of immunologic rejection, mediated by the recipient's lymphocytes.

TRANSPLANT IMMUNOLOGY AND IMMUNOSUPPRESSION

An *epitope* is the molecular unit of specific immune recognition. It is a carbohydrate or peptide moiety with a defined stereochemical configuration. Antigen is used to describe an epitope containing molecules that can be bound by one of two types of lymphocyte receptors: the *T-cell receptor* (TCR) of T cells or the *antibody* (or *immunoglobulin*) of B cells. The degree to which an allograft shares regulatory molecules of the immune system with the recipient is referred to as the *histocompatibility* of the graft. This is a description of the similarity of a cluster of genes on chromosome 6 known as the *major histocompatibility complex* [MHC, known as *human leukocyte antigen* (HLA) in human beings]. Two different classes of MHC gene products are produced, *class I* and *class II*. The importance of MHC gene products stems from their *polymorphism*. Because MHC is polymorphic, it can serve as an antigen to another individual. Antigens derived from different MHC molecules within the same species are called *alloantigens*. *Isografts* are organs transplanted between identical twins and are immunologically inconsequential. *Xenografts* are organs transplanted from one species to another.

Overview of Immunity

Immunity has two distinct but complementary branches to combat disease: innate and acquired immunity. The hallmark of acquired immunity is specific recognition and elimination of nonself. The pathogen is recognized as a specific entity, not just as nonself, and a record is retained for more rapid response to future encounters, a phenomenon known as *immunologic memory.* Antigen recognition is mediated by lymphocytes, T cells, and B cells. T cells protect the cells of the body against alterations by mutation or viral infection (cellular immunity) and bind peptide antigens that have been processed by the body's cells. B cells provide protection against extracellular infectious organisms and foreign material (humoral immunity) and recognize antigens in their native unprocessed state. Parenchymal cells express class I MHC molecules. Class I molecules display peptides from within, e.g., peptides from normal cellular processes or from viral replication, which are bound by T cells expressing an adhesion molecule with special affinity to class I, the CD8 molecule. Hematopoietic cells also express class II MHC molecules. These molecules display peptides that have been phagocytized from surrounding extracellular spaces and bind to T cells complemented by an adhesion molecule with affinity to class II, the CD4 molecule. B cells bind soluble antigens and secrete soluble forms of their receptor, known as *antibodies,* to bind these foreign molecules. Material that is bound by an antibody is opsonized (flagged) for destruction by cells of the innate arm of immunity — phagocytic cells lacking the ability to distinguish self from nonself — primarily macrophages, monocytes, and polymorphonuclear leukocytes (PMNs). Antibody-bound surfaces activate a destructive enzymatic cascade known as the *complement system.* This leads to destruction of the membrane to which the complement is bound and further opsonization. The entire immune process is facilitated by a means of amplifying the response of one cell to one antigen. *Cytokines* [known as *interleukins* (ILs)] are polypeptides that are released by many cell types and activate or suppress adjacent immune cells (Table 10-1). The immune response to an allograft is the result of incompatibility between the recipient's receptor repertoire and the donor's MHC polymorphisms. Effector mechanisms that have evolved to counteract viral, fungal, and bacterial infections, as well as those in place to prevent malignancy and autoimmunity, all come into play after transplantation. Rejection, like physiologic immunity, can be divided into humoral and cellular mechanisms. Humoral rejection of a graft can be the result of antibodies existing in circulation prior to exposure or antibodies acquired after exposure. Cellular rejection is the result of T-cell incompatibility between the donor and recipient.

Genetic and Structural Characteristics of Transplant Antigens

The antigens primarily responsible for human allograft rejection are those encoded by the HLA region of chromosome 6. The polymorphic proteins encoded by this locus that directly affect transplant rejection are class I molecules (HLA-A, -B, and -C) and class II molecules (HLA-DR, -DP, and -DQ). The blood group antigens of the ABO system also must be considered polymorphic transplant antigens, and their biology is critical to humoral rejection. Class I is expressed as a single MHC-encoded transmembrane heterodimeric protein. The critical structural feature of class I molecules is the presence of a groove. Within this groove, a nine-amino-acid peptide, formed from fragments of proteins being synthesized in the cell's endoplasmic reticulum, is mounted for presentation to the body's T cells. Class I molecules are found on all nucleated cells except neurons. The structural features of class II molecules are strikingly similar to those of class I molecules. The groove of class II is filled with a peptide derived from endocytosed proteins (as opposed to proteins formed by the cell, as is the case for the groove of class I). Class II molecules are found primarily on cells of the innate immune system, particularly phagocytes, such as dendritic cells, macrophages, and monocytes, but can be upregulated to appear on other parenchymal cells by cytokines released during an immune response or injury. The TCR accessory molecule CD8 selectively binds to class I, whereas the accessory molecule CD4 binds to class II. In this way T cells geared toward the initial recognition of intruders and subsequent amplification of the immune response (CD4+ helper T cells) are targeted to bind the cells with the ability to capture and present these antigens. Similarly, T cells that survey the body's parenchyma for signs of entrenched intracellular pathogens and destroy infected cells (CD8+ cytotoxic T cells) are outfitted to perform this duty.

RECEPTOR

T-Cell Receptor (TCR) The formation of the TCR is fundamental to an understanding of alloreactivity and self nonreactivity. T cells are formed in the fetal liver and bone marrow and migrate to the thymus, where they accquire a single TCR with a single specificity through genetic rearrangement. Developing T cells also express CD4 and CD8, increasing the binding repertoire of the population to include either class I or class II MHC molecules. To avoid the release of self-reactive T cells, developing cells undergo a process after recombination known as *thymic selection.* Cells initially interact with the MHC-expressing cortical thymic epithelium.

TABLE 10-1
PROPERTIES OF SOME HUMAN CYTOKINES

Cytokine	Alternative Name	Source(s)	Target Cell Type(s)	Action(s)
IFN-α and IFN-β	—	Activated T cells, endothelial cells, macrophages, fibroblasts	Activated T and B cells, NK and LAK cells	Induces antiviral state, antitumor activity, induces fever, increases class I and II MHC expression, stimulates activated B-cell differentiation and proliferation and NK cell activity, inhibits T and LAK cell activity
IFN-γ	—	Activated T cells, LAK cells	Activated and resting B and plasma cells, NK, endothelial, and LAK cells, macrophages	Induces antiviral state, antitumor activity, induces fever, increases class I and II MHC expression, stimulates activated B-cell differentiation and proliferation and NK and LAK cell activity, activates macrophages and endothelial cells, stimulates IgG2a isotype switch

TGF-β	—	T cells, macrophages, NK cells	Monocytes, fibroblasts	Chemotactic for fibroblasts and monocytes, induces extracellular matrix remodeling, repair, and fibrosis, induces B-cell differentiation and isotype switching, T-cell proliferation and angiogenesis
TNF	—	Activated T cells, LAK cells, macrophages	Resting T cells, activated T and B cells, plasma, stem, and endothelial cells, eosinophils, fibroblasts, macrophages	Induces antiviral state, antitumor activity, induces fever, increases class I MHC expression, activates macrophages, granulocytes, eosinophils, and endothelial cells, chemotactic and angiogenic activity
IL-1	Endogenous pyrogen	Activated T and B cells, LAK cells, endothelial cells, macrophages, fibroblasts	Resting T and B cells, activated T and B cells, plasma, stem, and endothelial cells, eosinophils, fibroblasts, macrophages	Induces antiviral state, antitumor activity, induces fever, stimulates activated B-cell differentiation and proliferation, activates and stimulates proliferation of T cells, activates granulocytes and endothelial cells, stimulates hematopoiesis

TABLE 10-1 (CONTINUED)
PROPERTIES OF SOME HUMAN CYTOKINES

Cytokine	Alternative Name	Source(s)	Target Cell Type(s)	Action(s)
IL-2	T-cell growth factor	Activated T cells, LAK cells	Activated T cells, activated and resting B cells, NK and LAK cells, macrophages	Activates macrophages, T, NK, and LAK cells, stimulates differentiation of activated B cells, stimulates proliferation of activated B and T cells, induces fever
IL-3	Multi-CSF	Activated T cells	Stem, activated B, eosinophil	Stimulates hematopoiesis, activated B-cell proliferation, and eosinophil activity
IL-4	B-cell stimulating factor-1	Activated T cells	Activated T cells, activated and resting B cells, plasma LAK cells, macrophages	Activates macrophages, T and B cells, stimulates differentiation of activated B cells, stimulates proliferation of activated B and T cells, induces IgE receptors on B cells, stimulates IgE and IgG1 isotype switch
IL-5	B-cell growth factor-2	Activated T cells	Activated and resting B cells, plasma cells, eosinophils	Stimulates IgA isotype switch and eosinophil activity
IL-6	B-cell stimulating factor-2, interferon-β_2	Activated T cells, endothelial cells, fibroblasts, macrophages	Activated T, resting B, and stem cells	Activates T cells, stimulates activated B-cell differentiation and activated T- and B-cell proliferation

IL-7	—	Activated T cells	Activated T and resting B cells	Stimulates activated T-cell and resting B-cell proliferation
IL-8	—	Activated T cells	Granulocytes	Stimulates granulocyte activity, chemotactic activity
IL-9	—	Activated T cells	T cells	Stimulates T-cell proliferation
IL-10	—	Macrophages, B and T cells	Macrophages, B and T cells	Inhibits macrophage cytokine release, induces B-cell differentiation and isotype switching, induces class II expression, T-cell stimulation
IL-11	—	Bone marrow stromal cells	Hematopoietic stem cells	Stimulates megakaryocyte and B lineage stem cell maturation
IL-12	—	NK cells and macrophages	T cells	Induces T-cell maturation and cytotoxic activity
G-CSF	—	Endothelial cells, fibroblasts, macrophages	Granulocytes	Stimulates granulocyte activity and hematopoiesis
M-CSF	—	Macrophages	Macrophages	Activates macrophages
GM-CSF	—	Endothelial cells, fibroblasts, activated T cells	Stem cells, granulocytes, macrophages, eosinophils	Activates macrophages, stimulates granulocyte and eosinophil activity and hematopoiesis

Cytokines are secreted polypeptides that mediate autocrine and paracrine cellular communication but do not bind antigen. They include those compounds previously termed interleukins and lymphokines. IFN=interferon; TGF=transforming growth factor; TNF=tumor necrosis factor; IL=interleukin; CSF=colony stimulating factor; LAK=lymphokine activated killer; NK=natural killer.

SOURCE: Based on the consensus cytokine chart of the British Cytokine Group (Burke F, Naylor MS, et al: The cytokine wall chart. *Immunol Today* 14:165, 1993.)

If binding does not occur to self MHC, the cells are useless to the individual because they would be unable to bind and function in the periphery. All nonbinding cells undergo *apoptosis*, or programmed self-destruction, a process called *positive selection.* Cells surviving positive selection then move to the thymic medulla and lose either CD4 or CD8. If binding to self MHC in the medulla occurs with an unacceptably high affinity and apoptosis results, this is called *negative selection.* Any foreign peptide encountered alters the affinity that has been preordained in the thymus, resulting in T-cell activation. MHC molecules that were not part of the T cell's thymic education will bind the TCR with unacceptable affinity and lead to activation. This phenomenon defines alloreactivity.

ANTIBODY

Antibody, also called *immunoglobulin* (Ig), is formed in B cells much the way TCR is in T cells, although maturation occurs in the bone marrow, not in the thymus, and continues in the periphery. Antibodies have a basic structure of four chains, two of which are identical heavy chains and two of which are identical light chains. The heavy-chain usage defines the Ig type as being either IgM, IgG, IgA, IgE, or IgD. The Fc portion is bound by Fc receptors on phagocytic cells of the innate immune system, facilitating phagocytosis, followed by destruction of the antigen and processing of antigenic peptides. The Fc portion of IgM and some classes of IgG also serves to activate complement. IgG becomes the most significant soluble mediator of opsonization and is the dominant antibody resulting from allostimulation. To avoid a vigorous humoral rejection of the graft, screening for these antibodies must be done before transplantation.

Biology of Transplant Antigen Recognition and Destruction

T-Cell Activation T cells can respond to transplant antigens directly, through TCR binding to foreign MHC molecules expressed on transplanted tissues, or indirectly, by encountering antigen-presenting cells (APCs) that have phagocytosed fragmented allograft tissues and processed the antigens for expression on self MHC. The TCR transmits its signal to the cell by initiating the activity of intracytoplasmic protein tyrosine kinases (PTKs) associated with the TCR-associated transmembrane protein complex called CD3 (Fig. 10-1). After calcium-dependent activation and nuclear transcription, interleukin-2 (IL-2) is then released and binds to the T cell in an autocrine loop. In addition to TCR engagement,

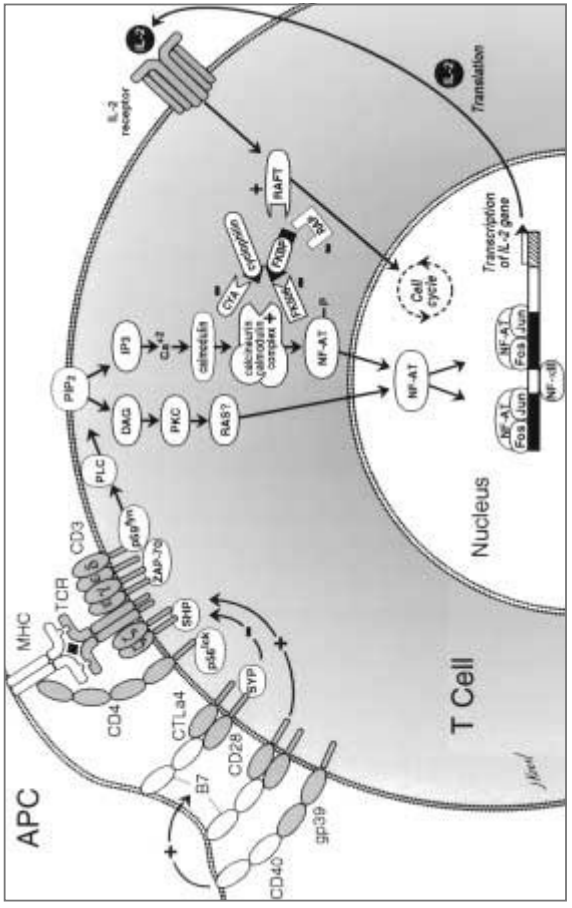


FIGURE 10-1 T-cell receptor activation through its interaction with MHC and adhesion molecules and the mechanism of action of selected immunosuppressants. The TCR binds to an MHC molecule (class II is shown). This event is stabilized by an accessory molecule (CD4 or CD8, depending on the MHC class). The costimulatory molecule gp39 upregulates the expression of the APC costimulation molecules B7, shifting the balance of negative regulation by CTLa4 to positive regulation by CD28. This potentiates signal transduction and activation of NF-AT, which in turn induces IL-2 synthesis. IL-2 works in an autocrine loop to force the cell into a division cycle. Cyclosporine (CyA) and tacrolimus (FK506) both block this signal transduction by blocking the calcineurin/calmodulin-potentiating proteins cyclophilin and FK-binding protein, respectively. Rapamycin (RAP) blocks the IL-2 receptor signal transduction by blocking the interaction of RAFT and FK-binding protein.

a second confirmatory signal is required for T-cell activation. Costimulation can control whether a TCR signal results in activation or quiescence. This control has a role in self-tolerance.

T-Cell Amplification Once activation occurs, cytokines, particularly IL-2 and interferon-γ (IFN-γ), create a potent milieu, recruiting other T cells into the response and potentiating clonal expansion.

T-Cell–Mediated Cytotoxicity T cells assume one of two roles: that of an amplifier or that of a cytotoxic effector. The amplification role generally is performed by CD4+ cells, because these cells are most suited for communication with class II–expressing APCs. Cytotoxicity is best mediated by CD8+ cells, because they bind to the MHC of all nucleated cells. The mechanisms of direct T-cell–mediated destruction of microorganisms or non-MHC-expressing tissue are poorly defined.

B-Cell Activation and Clonal Expansion B cells recognize antigen in its native form without the requirement for processing and presentation on MHC molecules. Surface antibody cross-linking by antigen leads to B-cell proliferation and differentiation into a plasma cell. Like the T cell, the threshold for B-cell activation is high. This can be lowered by costimulation signals received by the transmembrane complex CD19/CD21. B cells also can internalize antigens bound to surface antibody and process them for presentation to T cells. As such, B cells can bind antigen in circulation and initiate a T-cell response to deal with antigen incorporated into tissues of the body. Antigen exposure generally leads to B-cell affinity maturation and isotype switching and produces high-affinity IgG antibodies. Naturally occurring antibodies are low-affinity IgM antibodies and respond to a broad array of carbohydrate epitopes found on many common bacterial pathogens. Natural antibody is responsible for ABO antigen responses.

Antibody-Mediated Cytotoxicity Antibody facilitates the destruction and removal of antigenic cells. Once bound to an antigen, antibody serves as an anchoring site for the complement component C1q and subsequent activation of the *classical complement activation cascade.* Antibody also can serve as an opsonin directly. Most phagocytic cells have receptors for the Fc portion of IgG and actively engulf antibody-coated targets in a process known as *antibody-dependent cellular cytotoxicity* (ADCC). Antibody binding to the endothelium, and the subsequent activation of complement, also alters the activation status of the endothelial cell. This leads to cellular retraction and exposure of the underlying matrix, which in

turn potentiates platelet activation and aggregation. Endothelial activation also alters its usually anticoagulant environment in favor of a procoagulant one. The result is microvascular thrombosis, a hallmark of the two antibody-mediated graft rejections: hyperacute rejection and acute vascular rejection.

Clinical Rejection Syndromes

Rejection has been classified as hyperacute, acute, and chronic. Only acute rejection can be reversed successfully. Although hyperacute rejection is mostly preventable, chronic rejection is a difficult problem.

Hyperacute Rejection *Hyperacute rejection* (HAR) is caused by presensitization of the recipient to an antigen expressed by the donor. It develops in the first minutes to hours after graft reperfusion. Antibodies bind to the donor tissue. This initiates complement-mediated lysis and induces a procoagulant state, resulting in immediate graft thrombosis. Exposure usually is in the form of prior transplant, transfusion, or pregnancy. Prevention is through preoperative screening via the lymphocytotoxic crossmatch and ABO typing. A delayed variant of HAR known as *vascular rejection* also is mediated by humoral factors.

Acute Rejection *Acute rejection* is caused primarily by T cells and evolves over a period of days to weeks. It can occur any time after the first 5 postoperative days but is most common in the first 6 months and is inevitable without immunosuppression directed against the T cell. T cells bind antigen via their TCR either directly or after phagocytosis of donor tissue and re-presentation of MHC peptides by self APCs. This leads to cell activation, resulting in a massive infiltration of the graft by T cells, with destruction of the organ. Any mismatch puts the patient at risk for T-cell–mediated graft destruction and mandates T-cell–specific immunosuppression. Treatment of rejection leads to successful restoration of graft function in 90–95 percent of patients, and failure to treat results almost uniformly in graft loss.

Chronic Rejection Unlike acute and hyperacute rejection, *chronic rejection* (CR) is poorly understood. Onset is insidious over a period of months to years, and chronic rejection is untreatable. Heightened immunosuppression is not effective in reversing or retarding the progression of chronic rejection. Histologically, CR, regardless of the organ involved, is characterized by parenchymal replacement by fibrous tissue with a relatively sparse lymphocytic infiltrate. Those organs with epithelium show a dropout of the

epithelial cells and endothelial destruction. Chronic rejection requires retransplantation.

Immunosuppression

Without some attenuation of the immune system, all allografts eventually would be destroyed. For all organs, the events occurring at the time of transplantation are the most critical in establishing the state of immune unresponsiveness necessary for long-term graft survival. Immunosuppression is extremely intense in the early postoperative period and subsequently tapers. Initial conditioning of the recipient's immune system is known as *induction immunosuppression.* Medications used to prevent acute rejection for the life of the patient are called *maintenance immunosuppressants.* All have side effects that increase the risk of infection and malignancy. Immunosuppressants used to reverse an acute rejection episode are called *rescue agents.* They are the same as the agents used for induction therapy.

Corticosteroids Corticosteroids remain a central tool in the prevention and treatment of allograft rejection. Higher doses of steroids also are used as a rescue agent to treat acute cellular rejection. Although steroids have a desirable immunosuppressive effect, they can contribute significantly to the morbidity of transplantation. Glucocorticosteroids bind to an intracellular receptor after nonspecific uptake into the cytoplasm and form a receptor-ligand complex that enters the nucleus and ultimately prevents the function of NF-κB, a key activator of proinflammatory cytokines. In doing so, steroids prevent the primary mechanism by which lymphocytes amplify their responsiveness. The adverse effects of steroid therapy are numerous and include a suppressed hypothalamic-pituitary-adrenal axis, impairment of glucose tolerance, delayed wound healing, salt and fluid retention that may exacerbate hypertension, and central nervous system (CNS) effects such as insomnia, depression, nervousness, and euphoria. Chronic side effects of corticosteroids include Cushing's syndrome (i.e., central obesity, acne, striae, hirsutism, and altered facies), cataracts, muscle wasting, and growth retardation in prepubertal children. Patients show an increased propensity toward peptic ulceration. Osteoporosis results from the combined effects of the inhibition of bone matrix formation and intestinal absorption of calcium.

Antiproliferative Agents *Azathioprine* The antimetabolite azathioprine is a part of many maintenance immunosuppressive protocols. The derivatives of azathioprine inhibit DNA synthesis by

alkylating DNA precursors and inducing chromosomal breaks. They inhibit the enzymatic conversion of inosine monophosphate (IMP) to adenosine monophosphate (AMP) and guanosine monophosphate (GMP). The effects of azathioprine are relatively nonspecific; it acts not only on proliferating lymphocytes and PMNs but also on all rapidly dividing cells. Azathioprine effectively inhibits rejection when given as a maintenance agent but, unlike steroids, has no value as a rescue or induction agent.

Mycophenolate Mofetil Mycophenolate mofetil (MMF, RS-61443) is a potent immunosuppressive agent approved for use in adults; it is a noncompetitive, reversible inhibitor of IMP dehydrogenase. Physiologic purine metabolism requires that GMP be synthesized for subsequent synthesis of guanosine triphosphate (GTP) and deoxyguanosine monophosphate (dGTP). GTP is required for RNA synthesis and dGTP for DNA synthesis. GMP is formed from IMP by IMP dehydrogenase, and therefore, MMF prevents a critical step in RNA and DNA synthesis. Of major importance is the presence of a "salvage pathway" for GMP production in most cells except lymphocytes (hypoxanthine-guanine phosphoribosyl transferase—catalyzed GMP production directly from guanosine). MMF exploits a critical difference between lymphocytes and other body tissues, including PMNs, to produce relatively selective immunosuppressive effects.

Calcineurin Inhibitors *Cyclosporine* Borel demonstrated the T-cell–specific immunosuppressive properties of cyclosporin A, a cyclic endecapeptide isolated from the fungus *Tolypocladium inflatum Gams.* Cyclosporine's mechanism of action is mediated primarily through its ability to bind to cytoplasmic protein cyclophilin, blocking the calcium-dependent phosphorylation and activation of the transcription-regulating factor NF-AT. This prevents the transcription of the IL-2 gene critical for T-cell activation. Cyclosporine reversibly inhibits T-lymphocyte–mediated immune responses, but it does not prevent antigen recognition by T cells, and its effects can be overcome with exogenous (or in the case of an ongoing rejection episode, ambient) IL-2. Cyclosporine works as a maintenance agent and is ineffective as a rescue agent.

Cyclosporine causes dose-related nephrotoxicity, an idiosyncratic reaction producing hemolytic uremic syndrome; hyperkalemia also may result. Long-term use causes a 30 percent reduction in renal function; hypertension also is a common adverse effect but usually can be treated effectively. Cyclosporine frequently causes neurologic side effects consisting of tremors, paresthesias, headache, depression, confusion, somnolence, and rarely, seizures.

Hypertrichosis of the face, arms, and back is seen in about 50 percent of patients. Gingival hyperplasia also may occur.

Tacrolimus Tacrolimus (FK506) is a macrolide produced by *Streptomyces tsukubaenis.* Tacrolimus, like cyclosporine, blocks the effects of NF-AT, prevents cytokine transcription, and arrests T-cell activation. Tacrolimus is 100 times more potent in blocking IL-2 and IFN-γ production than cyclosporine. Like cyclosporine, the effects of tacrolimus are relatively T-cell specific, but in addition to its role as a maintenance agent, tacrolimus has shown promise as a rescue agent. The side effect profile of tacrolimus is similar to that of cyclosporine with regard to renal and hepatic toxicity. Neurotoxicity, in the form of tremors and mental status changes, is somewhat more pronounced, as is its diabetogenic effect. Cosmetic side effects are reduced substantially.

Antilymphocyte Globulin *Antilymphocyte globulin* (ALG) is a polyclonal serum against human lymphocytes. Thymocytes rather than lymphocytes are sometimes used, and this is designated as *antithymocyte globulin* (ATG); ATGAM is the most widely used preparation. ATGAM targets the T cell by coating multiple epitopes on this cell type and promoting their clearance through complement-mediated lysis, opsonin-induced phagocytosis, and internalization of key surface receptors. One side effect is severe thrombocytopenia, which may result from cross-reactivity with platelets and may limit the use of the drug. Major side effects are rare; the most common symptoms are the result of transient cytokine release after antibody binding. Chills and fevers occur in up to 20 percent of patients. Thrombocytopenia and leukopenia do require an alteration in treatment. Because antilymphocyte preparations profoundly inhibit T lymphocytes, they also suppress cell-mediated immunity. The use of ALG has been associated with an increase in the reactivation and development of primary cytomegalovirus (CMV) infections. In addition to CMV infections, herpes simplex virus (HSV), Epstein-Barr virus (EBV), and varicella infections may occur more frequently after therapy with antilymphocyte preparations.

Monoclonal Antibodies Monoclonal antibodies have very specific targets. OKT3 is the murine monoclonal antibody to the signal-transduction subunit on human T cells (CD3). There are several ways in which OKT3 is thought to have its effect. Because OKT3 binds to the CD3 determinant, it prevents signal transduction of the TCR antigen-binding event and arrests amplification of a rejection episode. After the administration of OKT3, there is a rapid decrease in the number of circulating T lymphocytes. This is partially a re-

sult of opsonization and clearance by the reticuloendothelial system of the OKT3-lymphocyte complex. Another way in which OKT3 exerts its effect is by downregulation of the TCR complex, producing a "blind" T cell incapable of binding to antigen. In addition to interfering with the generation of cytotoxic T cells and the modulation of cell surface proteins, OKT3 blocks the cytotoxic activity of already activated T cells through inappropriate activation and degranulation. This is perhaps its most important function, but it leads to substantial side effects. Administration of OKT3 leads to a profound systemic cytokine release syndrome that can result in hypotension, pulmonary edema, and rarely, fatal cardiac myodepression. In approximately 2 percent of patients, the inflammatory response manifests itself as aseptic meningeal inflammation. Administration of high-dose methylprednisolone prior to OKT3 administration is required to blunt this adverse response, but rarely is the response averted altogether. The syndrome abates with subsequent dosage as the target cells available for degranulation are consumed or exhausted. The adequacy of dosage is determined by the percentage of CD3+ cells using flow cytometry. The presence of less than 10 percent CD3+ cells is associated with therapeutic efficacy. OKT3 was first used as a rescue agent to treat rejection. It is vastly superior to conventional steroid therapy in reversing rejection and improving allograft survival, but its side effects and the limiting nature of the antimurine antibody response have served to limit its use to the treatment of steroid-resistant rejection. OKT3, like other antilymphocyte preparations, causes a high reactivation rate of CMV. EBV infection leading to lymphoproliferative disorders is also associated with its use.

PANCREAS

Diabetes is now the leading cause of renal failure in the United States and commonly contributes to blindness, debilitating neuropathies, and accelerated atherosclerosis. Numerous studies have demonstrated the beneficial effect of intensive glucose control on arresting the development and progression of end-organ complications. It might be possible to prevent or ameliorate systemic complications of diabetes by achieving more precise glucose control. Alternative methods of insulin replacement therapy are under investigation, but none has been successful enough to warrant more widespread application.

Indications Type I insulin-dependent diabetics younger than 45 years of age are potential candidates (Table 10-2). For major organ

TABLE 10-2

CRITERIA FOR SELECTION OF CANDIDATES FOR SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION AND SOLITARY PANCREAS TRANSPLANTATION

Simultaneous Pancreas-Kidney Transplant	Solitary Pancreas Transplant
Type I diabetes mellitus	Type I diabetes mellitus
End-stage renal disease	Two or more end-organ complications, including peripheral/autonomic neuropathy, retinopathy, vasculopathy
Absence of significant coronary artery disease	Hypoglycemic unawareness and/or hyperlabile diabetes
Age under 45–50 years	Minimal to no evidence of early diabetic nephropathy or normal renal transplant function
Functional vision	
No major amputations	
Compliant	

transplant necessitating long-term immunosuppression, contraindications include untreated malignancy, active infection, and human immunodeficiency virus (HIV) seropositivity. Pancreas transplantation is performed in three different sets of circumstances: pancreas transplantation alone (PTA) in the nonuremic diabetic with minimal or no evidence of diabetic nephropathy, pancreas transplantation after successful kidney allografting (PAK), and pancreas transplantation performed simultaneously with a kidney transplant (SPK) in the uremic patient. Approximately 90 percent of pancreas transplants performed in the United States are SPK transplants.

Operative Procedure The pancreatic duct carrying the exocrine secretions can be drained by two methods, into the bladder or directly into the small bowel. Advantages of bladder drainage include the ability to use urinary amylase determinations as a screening test for rejection, avoidance of an enteric anastomosis and spillage of bowel contents, and reduced potential for peripancreatic infections. Advantages of the enteric drainage technique include avoidance of the postoperative urologic complications that occur in up to 30 percent of patients, avoidance of chronic dehydration and the need for bicarbonate replacement, and early removal of the Foley catheter. The pancreatic graft harvested en bloc with the liver is first separated. The recipient operation begins with a midline transabdominal incision. The pancreas usually is placed into the right iliac fossa, and the kidney, if transplanted simultaneously, is implanted on the left side. The venous anastomosis is performed first. This can be achieved by anastomosing the portal vein of the pancreas graft to the distal inferior vena cava or to a completely mobilized iliac vein. The arterial anastomosis is then performed between the reconstructed donor iliac artery Y graft and the common iliac artery. If bladder drainage is chosen, a pancreatic duodenocystostomy is performed in a side-to-side anastomosis to the dome of the bladder with two layers of running absorbable sutures. If enteric drainage is performed, the duodenal segment is sutured to the ileum in a side-to-side manner.

Postoperative Management Rejection occurs with greater frequency after pancreas and simultaneous pancreas-kidney transplantation than after isolated renal transplantation. This difference requires management that balances aggressive immunosuppression against the risks of infection. Acute rejection is the rule rather than the exception after pancreas transplantation, occurring in 70–80 percent of patients, and primarily. Pancreas rejection more commonly occurs with kidney rejection. There is no ideal screening test for rejection of the pancreas allograft.

Complications Despite improvements in technique, preservation, and patient selection, surgical complications are not uncommon and threaten the survival of the graft and the patient. Proper management of complications is critical to a successful outcome. The development of a urologic complication is most frequent after SPK transplantation performed with bladder drainage. A metabolic acidosis is present postoperatively in approximately 80 percent of patients after pancreas transplantation with bladder drainage and usually is a result of excessive urinary loss of bicarbonate-containing exocrine fluids. Oral replacement should be initiated to maintain a serum bicarbonate level of at least 22–25 mg/dL. This problem usually stabilizes and diminishes over time and only infrequently requires conversion from bladder to enteric drainage. Enteric conversion is used for treatment of persistent urologic and electrolyte problems.

Results Between 1987 and 1995, over 4500 cadaver donor pancreas transplants were performed in the United States and reported to the International Pancreas Transplant Registry. The 1-year patient survival rate is more than 90 percent, and the 1-year pancreas graft survival rate (as measured by insulin independence) is more than 75 percent. The addition of a pancreas to a kidney transplant does not adversely affect patient or kidney graft survival rates in uremic diabetic patients. Long-term kidney function is not negatively affected by a simultaneous pancreas transplant.

Effect of Pancreas Transplantation on Secondary Complications of Diabetes The major benefit of a pancreas transplant over a kidney transplant alone is enhanced quality of life.

INTESTINE

Potential Candidates Most potential candidates for intestinal transplantation are patients with short-bowel syndrome. Different disease processes can lead to short-bowel syndrome, but adults and children generally develop this syndrome after extensive intestinal resections. Common indications for intestinal transplantation in adults are Crohn's disease, mesenteric thrombosis, and trauma. Necrotizing enterocolitis, intestinal pseudo-obstruction, gastroschisis, volvulus, and intestinal atresia are indications in children.

Operative Procedures There are three methods of intestinal transplantation, the choice depending on the disease and sequelae that occur in combination with the short-bowel syndrome. For pa-

tients without liver failure, isolated intestinal grafting is preferred; patients with liver failure receive a combined liver-intestine transplant. In a small number of patients, a multivisceral procedure is performed that includes grafting of the liver, stomach, pancreas, duodenum, and small intestine with or without the colon.

Immunology The two major immunologic problems after intestinal transplantation have been graft-versus-host disease (GVHD) and host-versus-graft disease (rejection). To prevent GVHD, sufficient immunosuppressive therapy must be administered. Clinically, there has been a low incidence of GVHD. The prevention of rejection after intestinal transplantation is more difficult. The introduction of tacrolimus significantly improved the outcome after intestinal transplantation.

Diagnosis of Rejection The earlier rejection is detected, the more effective might treatment be in reversing the rejection process and minimizing damage to the grafted organ. Rejection is detected primarily by clinical symptoms and graft histology. These symptoms include fever, abdominal pain, elevated white blood cell count, ileus, increased stomal output, gastrointestinal bleeding, and positive blood cultures. Intestinal biopsies may show evidence of cryptitis, shortening of villi, mononuclear infiltrate, or even mucosal sloughing.

Results The International Intestinal Transplant Registry reported results on 178 intestinal transplants performed worldwide since 1985. The results of tacrolimus-based immunosuppression were superior to those of cyclosporine-based immunosuppression. The 1- and 3-year actuarial graft survivals were 65 and 29 percent for isolated intestine, 64 and 38 percent for liver-intestine, and 51 and 37 percent for multivisceral transplants, respectively.

LIVER

Indications Liver transplantation is indicated for the treatment of irreversible liver failure from acute or fulminant disease or, more commonly, chronic liver disease. Fulminant hepatic failure frequently has an unknown cause but may be secondary to viral hepatitis, Wilson's disease, hepatotoxins, or alcoholic hepatitis. Outcomes for liver transplantation in patients with fulminant hepatic failure have a worse prognosis than in patients with chronic liver disease because the former are generally more unstable and have more comorbid conditions. Survival rates of 70 percent at

1 year are expected for patients transplanted for fulminant disease (Table 10-3). Posthepatitic cirrhosis resulting from hepatitis B or C is associated with the risk of recurrence of viral hepatitis and cirrhosis in the transplanted liver. Strategies to prevent recurrence of hepatitis B have included administration of hepatitis B hyperimmune globulin, interferon, and lamivudine. Hepatitis C also has been associated with frequent recurrence of disease in the transplanted liver and often is unresponsive to interferon therapy. Liver transplantation for primary biliary cirrhosis is associated with a high success rate, but the primary disease may recur and is difficult to distinguish from chronic rejection. Primary sclerosing cholangitis should be treated with liver transplantation before cholangiocarcinoma develops. Patients with alcoholic liver disease account for 75 percent of liver failure in the United States, comprising the

TABLE 10-3
CAUSE OF LIVER FAILURE IN ADULT RECIPIENTS AT UNIVERSITY OF WISCONSIN

Laënnec's cirrhosis
Sclerosing cholangitis
Primary biliary cirrhosis
Secondary biliary cirrhosis
Hepatitis, A/B/C, non A/B/C, acute, chronic
Autoimmune hepatitis
Cryptogenic cirrhosis
Hepatocellular malignancy
Cholangiocarcinoma
Fibrolamellar hepatoma
Wilson's disease
α-1-antitrypsin deficiency
Acute fulminant liver failure, unknown etiology
Hemochromatosis
Chemically induced cirrhosis
Congenital hepatic fibrosis
Biliary atresia
Polycystic liver disease
Sarcoidosis
Amyloidosis
Budd-Chiari syndrome
Caroli's disease
Cystic fibrosis
Steatosis

largest group of patients who could potentially benefit from liver transplantation. A period of abstinence and evidence of family and social support are required before the candidate can be eligible for transplantation. Comorbid features, such as alcoholic cardiomyopathy, also must be excluded. Numerous metabolic defects and many inborn errors of metabolism, with their primary defect in the liver, also can be corrected by liver transplantation (Table 10-4). Liver transplantation for cancer is controversial, and the results are poor. Five-year patient survival rates around 40 percent are reported, which is better than the outcome without transplantation.

Preoperative Evaluation The signs and symptoms of liver failure should be evaluated in detail in patients being considered for liver transplantation. Hepatic encephalopathy is determined by clinical examination and often is paralleled by serum ammonium levels. Patients with stage IV coma must be managed aggressively to prevent cerebral edema or hemorrhage, common causes of death in patients with end-stage liver failure. Coagulopathy associated with liver failure is associated with an elevated international normalized ratio (INR) unresponsive to vitamin K replacement. Thrombocytopenia is common and usually is caused by hypersplenism

TABLE 10-4
CAUSES OF LIVER FAILURE IN CHILDREN

Biliary atresia
Hepatitis, acute fulminant A/B/C, non A/B/C
Hepatitis, chronic B/C, non A/B/C
Hepatitis, neonatal
α-1-antitrypsin deficiency
Cystic fibrosis
Tyrosinemia
Cryptogenic cirrhosis
Short gut syndrome/total parenteral nutrition
Acute fulminant failure
Hepatoblastoma
Allagile syndrome
Caroli's disease
Congenital hepatic fibrosis
Crigler-Nijjar syndrome
Histiocytosis X
Ornithine transcarbinase deficiency
Wilson's disease

related to underlying portal hypertension. Patients with bleeding should be treated with administration of fresh frozen plasma and platelet transfusions. Gastrointestinal bleeding related to underlying portal hypertension, if associated with Child's class B or C liver failure and liver fibrosis or cirrhosis, constitutes an indication for liver transplantation. Variceal bleeding before transplantation should be controlled with a combination of medical, radiologic, and, if necessary, surgical therapy. Ascites resulting from portal hypertension may be severe and require medical treatment with diuretics and paracentesis. Hepatorenal failure, a fatal condition before the advent of liver transplantation, is reversible after liver transplantation. Other correctable causes of underlying kidney dysfunction must be excluded before hepatorenal failure is diagnosed. If hepatorenal failure has caused renal function to deteriorate acutely over a period of days or weeks, renal function can be expected to return to normal after liver transplantation. Biliary obstruction in patients with primary biliary cirrhosis is associated with fatigue, and severe itching should prompt liver transplantation. Patients with primary sclerosing cholangitis who develop recurrent bouts of cholangitis requiring hospitalization should be considered for early liver transplantation to avoid the septic complications of cholangitis. Patients with liver failure are immunocompromised. Spontaneous bacterial peritonitis may present with evidence of generalized sepsis and peritonitis and can be treated with antibiotics. Other causes of peritonitis, such as a perforated viscus, must be excluded. Patients with liver failure develop a hyperdynamic state, with elevated cardiac output and low systemic vascular resistance.

Contraindications Contraindications to liver transplantation are summarized in Table 10-5.

Immunologic Considerations Graft failure in liver transplantation usually is not because of immunologic rejection in compliant patients but more frequently is because of primary nonfunction, re-

TABLE 10-5
CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Severe cardiopulmonary disease, uncompensated
Disseminated cancer
Multisystem organ failure
Infection outside the liver
Noncompliance with medical therapy
Severe neurologic impairment

currence of original disease (hepatitis or primary biliary cirrhosis), or biliary and vascular complications.

Donor Procedure, Procurement, and Preservation The liver can be procured from a brain-dead donor as part of an en bloc procurement with the pancreas (Fig. 10-2) or as an isolated liver procurement. Care must be taken to preserve anomalous arteries, such as a right hepatic artery arising from the superior mesenteric artery or an accessory left hepatic artery arising from the left gastric artery.

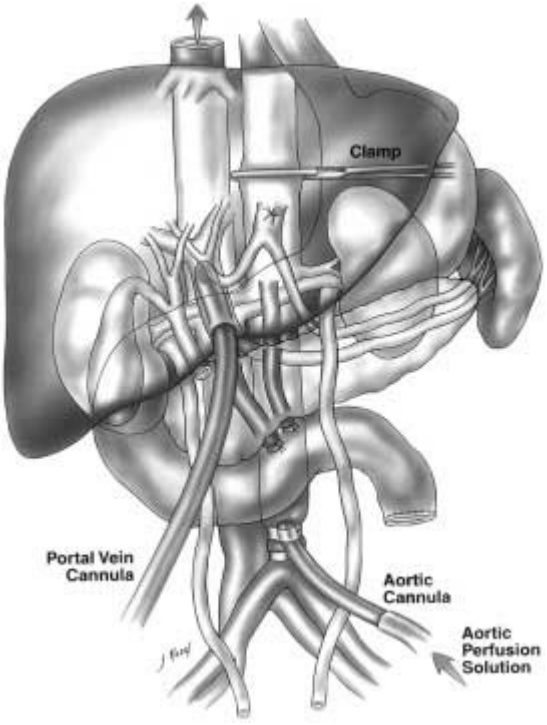


FIGURE 10-2 Procurement of the donor liver involves arterial perfusion of UW solution via an aortic cannula with cross-clamping of the supraceliac aorta and concomitant perfusion of the portal vein via a separate cannula. En block procurement with the pancreas, duodenum, and spleen is performed routinely, and the pancreas and liver are then separated on the back table.

Recipient Operative Procedure Orthotopic liver transplantation begins with native hepatectomy (including removal of a segment of the intraabdominal inferior vena cava), followed by implantation of the donor liver (Fig. 10-3). Because this technique requires occlusion of the inferior vena cava and portal vein simultaneously during the entire anhepatic phase, this method was found to result in hemodynamic instability in a significant proportion of adult patients. Venovenous bypass was developed to return blood from the inferior vena caval and portal venous circuits to the superior vena cava. A donor liver procured from an adult may be reduced in size as necessary for transplantation to a pediatric recipient. An additional modification is the split-liver technique, which uses the entire liver for two recipients; the right and left lobes are used for different patients. Application of these surgical techniques to the left lateral segment of a live donor has resulted in successful living-related liver transplantation, typically from a parent to a child with

FIGURE 10-3 Conventional orthotopic liver transplantation includes division of the donor hepatic artery, portal vein, common bile duct, and infrahepatic and suprahepatic inferior vena cava with subsequent anastomosis of these from the donor, as shown here. The bile duct anastomosis shown is performed over a T-tube stent. The donor celiac axis is anastomosed end-to-end to the proper hepatic artery or to an arterial graft anastomosed to the recipient aorta.

liver failure. Reconstruction of the common bile duct in liver transplantation involves an end-to-end anastomosis of donor-to-recipient bile ducts. This has been performed over a T tube, although using an internal stent or no stent at all has become popular. If the recipient common bile duct is inadequate or unsuitable for any reason, a Roux-en-Y choledochojejunostomy is performed. The donor hepatic artery is reconstructed by anastomosing the donor celiac axis to the recipient hepatic artery. If the recipient hepatic artery is compromised (including intrinsic or extrinsic stenosis of the celiac axis), a donor iliac artery graft is placed on the aorta in the supraceliac or infrarenal position and used as a conduit to the donor celiac artery.

Postoperative Management The immediate postoperative management of liver transplant patients includes optimizing the patient's physiology and conditions that favor good liver function. Maintenance immunosuppression in liver transplant recipients relies principally on cyclosporine or tacrolimus. Tapering doses of steroids also are used. Azathioprine or mycophenolate mofetil also have been used as maintenance agents. Acute rejection episodes after liver transplantation are common, but graft loss from rejection is rare. An elevation in liver enzyme levels, particularly canalicular enzymes [gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin], that is not explained by bile duct obstruction or hepatic artery thrombosis should prompt percutaneous liver biopsy because the diagnosis of rejection is best made histologically.

Complications Primary nonfunction of the liver is manifested by a high INR, low fibrinogen level, and high ammonia level in the first several days posttransplant. Primary nonfunction must be treated with urgent retransplantation, but livers that demonstrate initial poor function typically recover after a period of days. Portal vein thrombosis is a rare complication of liver transplantation but requires immediate diagnosis and operative intervention. Hepatic artery thrombosis has an incidence of approximately 5 percent in adult liver transplantation and a higher incidence in pediatric liver transplantation. Because the biliary tree depends on hepatic artery blood flow, hepatic artery thrombosis results in ischemic changes of the bile ducts, resulting grossly in sloughing of the biliary epithelium and leading to plugging and obstruction of the bile ducts. If uncorrected, this leads to biloma formation and eventually liver abscess and sepsis. The management of hepatic artery thrombosis includes retransplantation or observation (because some patients tolerate this complication without ill effects). Bile leaks after liver

transplantation must be corrected immediately because they lead to peritonitis, sepsis, and graft loss. Recurrence of original disease may be a problem after liver transplantation in particular groups of patients. These include patients with primary biliary cirrhosis, which is difficult to differentiate from chronic rejection. Hepatitis B and C are likely to recur after liver transplantation but will not necessarily lead to cirrhosis of the transplanted liver. If alcoholism recurs after liver transplantation, it is considered a contraindication to retransplantation. Posttransplant lymphoproliferative disorder (PTLD) may arise in liver transplant recipients as a side effect of overimmunosuppression. Particularly at risk are pediatric recipients, especially those treated with high-dose immunosuppression for recalcitrant rejection. The primary treatment of PTLD is reduction of immunosuppressive therapy.

Results Patients in better medical condition at the time of liver transplantation have better outcomes, which has prompted earlier referral of patients with liver failure. Combined patient and graft survival rates for U.S. centers are shown in Figure 10-4. Certain

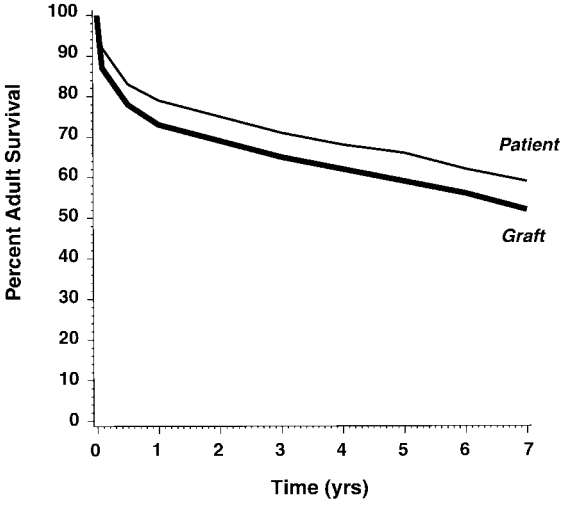


FIGURE 10-4 Combined data for U.S. liver transplant centers for the period 1987–1993 on current patient and graft survival rates for adults.

indications, such as primary biliary cirrhosis in adults and biliary atresia in children, are associated with higher-than-average success rates.

THORACIC ORGANS

Heart Transplantation

Preoperative Considerations *Recipient Selection* Rigid adherence to recipient selection criteria is important in achieving the excellent results observed in cardiac transplantation. The United Network for Organ Sharing (UNOS) heart transplant waiting list contains over 2800 patients, with about 300 new patients added to the list each month. Donor organ availability permits only 150–160 cardiac transplants each month. The average length of time on the waiting list has increased to over 300 days for outpatients, contributing to the 15–20 percent mortality rate among patients on the waiting list.

Indications Generally accepted indications for cardiac transplant evaluation are listed in Table 10-6. Patients who suffer from severe cardiac disability despite maximal medical therapy but who are

TABLE 10-6
GENERAL INDICATIONS WARRANTING CONSIDERATION FOR ADULT CARDIAC TRANSPLANTATION

Severe cardiac disability despite maximal medical therapy
History of recurrent hospitalizations for congestive heart failure
New York Heart Association functional class III or IV
Peak metabolic oxygen consumption < 15 mL/kg/min
Symptomatic cardiac ischemia refractory to conventional treatment
Unstable angina not amenable to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty with left ventricular ejection fraction $< 30\%$
Recurrent symptomatic ventricular arrhythmias
Exclusion of all surgical alternatives to cardiac transplantation
Revascularization for significant reversible ischemia
Valve replacement for critical aortic valve disease
Valve replacement or repair for severe mitral regurgitation

otherwise healthy are considered for cardiac transplantation. Most cardiac transplant recipients suffer from end-stage, inoperable coronary artery disease or idiopathic cardiomyopathy and often require multiple hospitalizations. Other diagnoses include defined cardiomyopathy (e.g., viral, postpartum, familial), congenital anomalies, and valvular disease. Disabling symptoms typically include those associated with congestive heart failure (e.g., dyspnea, orthopnea, generalized edema, and weakness), although recurrent symptomatic ventricular arrhythmias and severe ischemic symptoms (i.e., unstable angina) are observed frequently. Cardiac transplant candidates generally fall into the New York Heart Association's (NYHA) functional classes III and IV. Formerly, a left ventricular ejection fraction (LVEF) of less than 20 percent was relied on as a key indicator of severe cardiac dysfunction requiring transplantation, but refinements in medical management, particularly aggressive vasodilator therapy, have rendered this parameter less representative of severe patient disability or predictive of imminent death. Peak oxygen consumption, a function of peak cardiac output and peripheral oxygen extraction, correlates well with functional class and is an independent predictor of outcome in heart failure patients. Prospective studies have shown that patients with severely reduced peak oxygen consumption ($<$ 15 mL/kg/min, approximately 50 percent of normal) have a 1-year mortality rate exceeding 50 percent.

Contraindications (Table 10-7) Active infection and malignancy are absolute contraindications to transplantation in view of the lifelong immunosuppression required. Acute transient infections must be thoroughly cleared before transplantation; chronic infective agents, including chronic hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), preclude transplantation. Chronic conditions predisposing to serious infection, including symptomatic cholelithiasis, severe diverticulitis, active peptic ulcer disease, and cerebral/pulmonary embolization, should be evaluated and treated before transplantation. With the exception of fully resected squamous cell carcinoma of the skin, patients with previous malignancies should not be listed for cardiac transplantation less than 5 years after the malignancy has been considered cured. Severe, fixed pulmonary hypertension has been confirmed as a significant independent risk factor for early mortality after orthotopic cardiac transplantation because of a heightened incidence of acute post-transplant right ventricular failure.

Evaluation and Management of Patients Awaiting Cardiac Transplantation *Candidate Evaluation and Listing* Patients

TABLE 10-7
CONTRAINDICATIONS TO ADULT CARDIAC TRANSPLANTATION

Absolute contraindications
Advanced age (> 65 years)
Significant, irreversible pulmonary, hepatic, or renal dysfunction
Severe obstructive or restrictive lung disease (e.g., FEV_1 < 1.5 L, DLCO < 50% predicted)
Severe hepatic failure
Severe renal insufficiency (e.g., creatinine clearance < 40 mL/ min, albuminuria > 500 mg/24 h)
Severe pulmonary hypertension (e.g., pulmonary vascular resistance ≤ 5 Wood units)
Unresolved, recent malignancy
Significant systemic disease
Diabetes mellitus with significant end-organ dysfunction
Severe peripheral or cerebral vascular disease
Psychiatric illness or history of medical noncompliance
Potentially reversible contraindications
Active infection
Active peptic ulcer disease
Diverticulitis
Symptomatic cholelithiasis
Current tobacco, alcohol, or drug use
Cachexia
Morbid obesity (≥150% predicted ideal body weight)

suitable for cardiac transplantation are categorized and listed on the basis of clinical status, time on the waiting list, body size, and ABO blood group. Heart failure and clinical deterioration refractory to parenteral support necessitate mechanical intervention in the form of intraaortic balloon pump (IABP) counterpulsation or ventricular assist system (VAS) placement. Complications observed in left VAS-supported patients include bleeding (40 percent), infection (20–75 percent), and right ventricular failure (10–30 percent).

Donor Selection and Management *Criteria* Donors must have sustained irreversible brain death, usually as a result of blunt or penetrating head trauma or intracranial hemorrhage. Suggested criteria for cardiac donors and guidelines for recipient matching

developed by the American Heart Association in 1992 are listed in Table 10-8.

Absolute contraindications for donation include severe coronary or structural disease, prolonged cardiac arrest, prior myocardial infarction, a carbon monoxide hemoglobin level greater than 20 percent, arterial oxygen saturation of less than 80 percent, metastatic malignancy (sometimes excluding primary brain and skin cancers), and positive HIV status.

Donor-Recipient Matching Donor-recipient matching parameters include ABO compatibility and body size.

TABLE 10-8
SUGGESTED CRITERIA FOR CARDIAC DONORS AND GUIDELINES FOR RECIPIENT MATCHING

Age less than 40 years (may be extended by certain centers under certain circumstances)
Negative serologies for HIV and hepatitis B
No active severe infection or malignancy with possibility of metastases (i.e., most extracracial malignancies disqualify person as donor)
No evidence of significant cardiac disease or trauma
Very low probability of coronary artery disease (coronary angiograms may be required to ascertain its absence)
Normal or acceptable ventricular function after intravascular volume normalization; dopamine less than 10 μg/kg/min
Blood type (ABO) compatibility with recipient
Donor body weight usually between 80 and 120 percent of recipient's body weight
If required, negative prospective cytotoxic T cell crossmatch. A retrospective crossmatch is performed in most centers
Anticipated allograft ischemic time less than 4–5 h

SOURCE: O'Connell JB, Costanzo MR, et al: The American Heart Association position paper on cardiac transplantation from the Committee on Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Cardiac transplantation: Recipient selection, donor procurement, and medical follow-up. *Circulation* 86:1061–1079, 1992. (Reproduced with permission. Copyright 1992, American Heart Association.)

Operative Procedures *Procurement* The chest is entered through a median sternotomy (Fig. 10-5). The superior and inferior vena cavae are divided, then the heart is cooled, and cardioplegia solution is infused. When the heart is fully arrested, cooled, and perfused with cardioplegia solution, it is elevated from the pericardial well, and each of the pulmonary veins is divided at its pericardial reflection. The pulmonary artery is divided at the level of the bifurcation, and the aorta is divided at the level of the innominate artery. The explanted heart is placed into cold sterile saline and stored until implantation.

Orthotopic Transplantation The recipient operation is performed via a median sternotomy under cardiopulmonary bypass and moderate hypothermia.

Heterotopic Transplantation This is rarely performed.

Postoperative Management *Early Postoperative Period* Precautions are taken to minimize patient contact with objects or persons harboring active infectious agents. A primary objective in the immediate postoperative period is to maintain adequate perfusion in the recipient while minimizing cardiac work. Approximately 10–20 percent of transplant recipients have some degree of transient sinus node dysfunction, often manifested as sinus bradycardia that usually resolves within a week. Because cardiac output is primarily rate dependent after transplantation, the heart rate should be maintained between 90 and 110 beats/min during the first few postoperative days using temporary pacing or isoproterenol. The systolic blood pressure should be maintained between 90 and 110 mmHg using afterload reduction in the form of nitroglycerin or nitroprusside if necessary. Cardiac function generally normalizes within 3–4 days. Optimizing pulmonary function is another critical objective in the acute postoperative period. An initial endomyocardial biopsy is taken several days postoperatively, and a second endomyocardial biopsy and baseline coronary arteriogram are obtained approximately 2 weeks postoperatively.

Graft Physiology The grafted heart presents several unique physiologic characteristics. The denervated heart graft is isolated from normal autonomic regulatory mechanisms. The resting heart rate is higher because vagal tone, sinus arrhythmia, and carotid reflex bradycardia are absent. The denervated heart graft develops an increased sensitivity to catecholamines, possibly from an increase in beta-adrenergic receptor density and a loss of norepinephrine uptake in postganglionic sympathetic neurons. This augmented

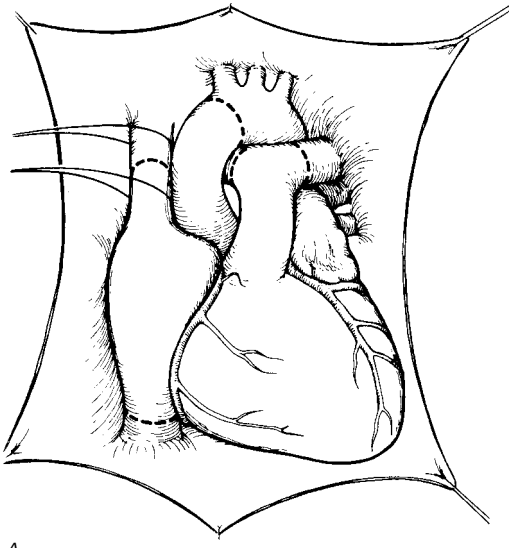
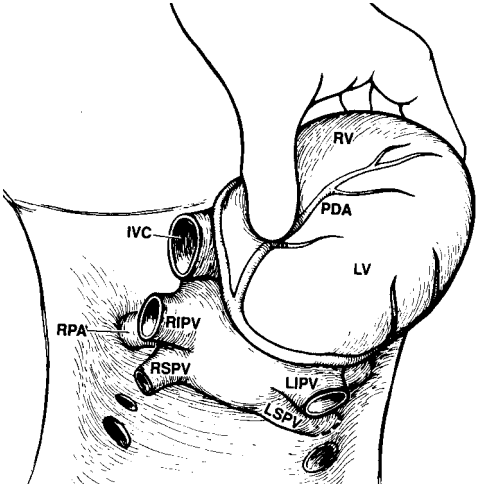


FIGURE 10-5 Donor cardiac procurement. *A.* Anticipated lines of transection of the vena cavae, aorta, and pulmonary veins. *B.* Donor heart excision, beginning with transection of the inferior vena cava (IVC) and pulmonary veins (PV; R = right, L = left, I = inferior, S = superior) and proceeding superiorly before transecting the pulmonary arteries and aorta. RPA = right pulmonary artery; RV = right ventricle; LV = left ventricle; PDA = posterior descending artery. (From: Smith JA, McCarthy PM, et al: *The Stanford Manual of Cardiopulmonary Transplantation.* Armonk, NY, Futura Publishing, 1996, with permission.)

sensitivity has an important role in maintaining an adequate cardiac response to exercise and stress. The output of cardiac allografts is at the low end of the normal range and the measured cardiac response to exercise or stress is below normal, but the response of the cardiac allograft is adequate for most activities. The atrial cuff anastomoses also result in abnormal cardiac physiology. The normal atrial contribution to ventricular end-diastolic filling is impaired by the dissociation between recipient and donor atrial contractions.



B

FIGURE 10-5 (*continued*)

Immunosuppression Conventional immunosuppression in cardiac transplant recipients consists of the triple-drug combination of cyclosporine, azathioprine, and glucocorticoids.

Postoperative Complications *Acute Rejection* Acute graft rejection is a major cause of death after cardiac transplantation. The incidence of acute graft rejection is highest during the first 3 months after transplantation. After this initial 3-month period, the incidence of acute rejection averages about one episode per patient per year. Despite attempts at developing noninvasive means to detect acute rejection in a timely manner, the endomyocardial biopsy remains the "gold standard" for the diagnosis of acute rejection. Surveillance endomyocardial biopsies allow rejection to be diagnosed before significant organ damage and dysfunction occur. Endomyocardial biopsies are repeated 10–14 days after antirejection therapy to assess efficacy.

Chronic Rejection Accelerated graft coronary artery disease (CAD) or atherosclerosis is a major limiting factor for long-term

survival in cardiac transplant recipients. Significant graft CAD resulting in diminished coronary blood flow may lead to arrhythmias, myocardial infarction, sudden death, or impaired left ventricular function with congestive graft failure. Typical angina from myocardial ischemia usually is not noted in transplant patients because the cardiac graft essentially is denervated. In a retrospective analysis of cardiac transplants from 1980 through 1993, the actuarial freedom from graft CAD at 1, 5, and 10 years was 95, 73, and 65 percent, respectively. The definitive therapy for diffuse disease is retransplantation. Effective prevention of graft CAD relies on developments in improved immunosuppression, recipient tolerance induction, improved CMV prophylaxis, and inhibition of vascular intimal proliferation.

Infection Infection is the leading cause of morbidity and mortality in post-cardiac transplantation patients. The risk of infection and infection-related death peaks during the first few months after transplantation and rapidly declines to a low persistent rate. Early infections, those occurring during the first month after transplantation, are commonly bacterial (especially gram-negative bacilli) and are manifested as pneumonia, mediastinitis, catheter sepsis, and urinary tract and skin infections. Treatment of these infections involves identification of the infective agent (e.g., cultures, antibiotic sensitivity tests), source control (e.g., catheter removal, debridement), and appropriate antibiotic regimens. In the late posttransplant period, opportunistic viral, fungal, and protozoan pathogens are more prevalent. The lungs, CNS, gastrointestinal tract, and skin are the usual sites of invasion. CMV infection is widely recognized as the most common and important viral infection in transplant patients, with an incidence of 73–100 percent in cardiac transplant recipients. It presents as a primary infection or reactivation of a latent infection, most commonly 1–4 months after transplantation. CMV infection has protean manifestations, including leukopenia with fever, pneumonia, gastroenteritis, hepatitis, and retinitis. CMV pneumonitis is the most lethal of these, with a 13 percent mortality rate, whereas retinitis is the most refractory to treatment, requiring indefinite treatment. Fungal infections are less common than bacterial or viral infections. Long-term prophylaxis typically includes nystatin mouthwash for thrush, sulfamethoxazole-trimethoprim for opportunistic bacterial and *Pneumocystis carinii* infections, and antiviral agents such as acyclovir or ganciclovir.

Neoplasm Organ transplant recipients are at significantly higher risk for developing cancer, undoubtedly because of chronic immunosuppression. Recipients are predisposed to skin cancer, B-cell

lymphoproliferative disorders, carcinoma in situ of the cervix, carcinoma of the vulva and anus, and Kaposi's sarcoma.

Retransplantation The primary indications for cardiac retransplantation are graft failure from accelerated graft atherosclerosis or recurrent acute rejection. Patients in need of retransplantation are held to the same standard criteria as initial candidates. Survival rates after retransplantation are significantly less than those achieved in primary transplant patients.

Results Actuarial 1-, 5-, and 10-year survivals are 82, 61, and 41 percent, respectively. Most patients are fully rehabilitated to New York Heart Association functional class I status.

PEDIATRIC CARDIAC TRANSPLANTATION

Cardiac transplantation is now an accepted therapeutic option for infants and children with end-stage heart disease. The leading indications in children are acquired dilated cardiomyopathy and congenital heart disease. Contraindications for transplantation in this group are similar to those in adults, with the addition of some complex venous drainage anomalies. Blood type and donor size are the most important considerations in donor-recipient matching. Actuarial 1-, 5-, and 10-year survival estimates are 75, 60, and 50 percent, respectively, with most survivors achieving the New York Heart Association functional class I. Normal somatic growth rate can be maintained in these patients, and normal cardiac chamber dimensional growth also occurs.

Lung and Heart-Lung Transplantation

Chronic obstructive lung disease has been treated effectively with single-lung transplantation and currently constitutes a major indication for this procedure.

Preoperative Considerations The indications are shown on Table 10-9.

Postoperative Complications Early morbidity and mortality after lung and heart-lung transplantation are most commonly caused by infection, graft failure, and heart failure. Mortality after 1 year is caused most commonly by obliterative bronchiolitis, infection, and malignancy. The majority of acute rejection episodes occur during the first 3 months after transplant (60–70 percent of patients in the first month). Signs of rejection include fever, dyspnea,

TABLE 10-9
INDICATIONS FOR ADULT SINGLE-LUNG, BILATERAL SINGLE-LUNG, AND HEART-LUNG TRANSPLANTATION

Single-lung transplantation
Pulmonary fibrosis
Emphysema
Bronchopulmonary dysplasia
Primary pulmonary hypertension without significant right heart dysfunction
Posttransplant obliterative bronchiolitis
Bilateral single-lung transplantation
Cystic fibrosis/bronchiectasis without cardiac decompensation
Emphysema/COPD without cardiac decompensation
Heart-lung transplantation
Severe primary pulmonary hypertension with right ventricular decompensation and/or cardiomyopathy
Severe Eisenmenger's syndrome with right ventricular decompensation or uncorrectable congenital heart disease (e.g., truncus arteriosus, large ventricular septal defect)
Intercurrent cardiac and pulmonary disease

impaired gas exchange manifested by a decrease in PaO_2, a diminished forced expiratory volume in 1 s (FEV_1, a measure of airway flow), and the development of an interstitial infiltrate on chest x-ray. Fiberoptic bronchoscopy with transbronchial parenchymal lung biopsy and bronchoalveolar lavage is used routinely to diagnose acute rejection or rule out infection.

Immunosuppression Immunosuppression protocols for lung and heart-lung transplant recipients are similar to those used in cardiac transplantation. Triple-drug therapy begins immediately after operation and is tapered according to standard protocols. Episodes of acute rejection are treated with a short course of intravenous steroid boluses. After steroid therapy, improvement often is rapid and dramatic and is considered confirmatory of rejection. Persistent rejection is treated with ATG or OKT3 monoclonal antibodies. Chronic lung allograft rejection is the greatest limitation to the long-term benefits of lung and heart-lung transplantation. Chronic lung rejection most commonly presents as obliterative bronchiolitis (OB), a pulmonary corollary to cardiac graft atherosclerosis.

Infection Bacterial, viral, and fungal infections are the leading causes of morbidity and mortality in lung and heart-lung transplant recipients. Most common are pulmonary bacterial infections involving the allograft. Absence of the cough reflex in the denervated lung, abnormal mucociliary clearance mechanisms, and deficiencies in lymphatic drainage predispose grafted lungs to infection. CMV is the most common and most clinically significant viral pathogen. The diagnosis of CMV pneumonitis, usually the most severe manifestation of CMV infection, is made from a positive viral culture or cytologic evidence obtained from bronchoalveolar lavage or transbronchial biopsy, respectively. Ganciclovir is the treatment of choice. CMV prophylaxis includes ganciclovir, acyclovir, and polyvalent immune globulin. Lung and heart-lung transplant patients also are at a higher risk for developing lymphoproliferative disease, particularly in association with EBV infection. Treatment consists of lowering immunosuppression and administering acyclovir. Fungal infections are the most infrequent and most deadly of infectious complications. *P. carinii* pneumonia has been effectively prevented in lung transplant patients since the institution of prophylaxis in the form of oral trimethoprim-sulfamethoxasole or, for sulfa-allergic patients, inhalational pentamidine. Improvements in surgical technique and posttransplant management have resulted in a relatively low incidence of airway complications after lung and heart-lung transplantation. The rates of lethal airway complications and late stricture have been reported at 3 and 10 percent, respectively. The most common airway complications are partial anastomotic dehiscence and stricture. The most common causes of death after retransplantation are infection and OB.

Results According to the International Heart-Lung Registry, the 6-year actuarial survival rate for single-lung and bilateral single-lung transplants performed worldwide from 1982 to 1995 is about 40 percent (Fig. 10-6). Most recipients are able to resume an active lifestyle without supplemental oxygen. Pulmonary function measured by spirometry and arterial blood gases is improved significantly in patients after transplantation, with a normalization of ventilation and gas exchange after 1–2 years.

KIDNEY

Renal transplants are the most common solid organ allografts performed, and transplantation has become the preferred treatment of chronic renal failure for many patients.

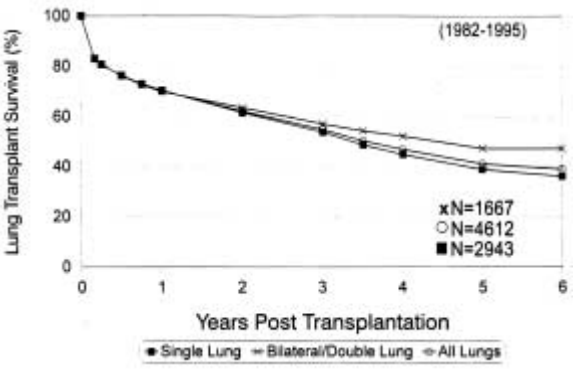


FIGURE 10-6 Actuarial survival rates of adult lung transplant recipients (1982–1995). (From: Hosenpud JD, Novick RJ, et al: The registry of the International Society for Heart and Lung Transplantation: Thirteenth official report—1996. *J Heart Lung Transplant* 15:655–674, 1996, with permission from Mosby–Year Book.)

Preoperative Management *Transplant Recipient Evaluation* Evaluation should include a careful and complete history and physical examination, with attention directed to the history of renal disease, prior surgery, and comorbid conditions, such as heart disease, peripheral vascular disease, and diabetes. Any history of cancer or recent infection should be documented. Laboratory studies should include standard chemistries, complete blood counts, urinalysis, and serologic studies for hepatitis B and C, cytomegalovirus, and HIV. A chest x-ray and electrocardiogram also are included for adult candidates. Evidence of risk factors for surgery should prompt more thorough investigations. Specific tests for associated conditions may include noninvasive cardiac studies such as an echocardiogram or a stress test, evaluation for peripheral vascular disease with noninvasive vascular studies, and pulmonary function tests for patients with a significant history of chronic pulmonary disease. Cardiac catheterization may be required for assessment of coronary disease. Urine cultures should be obtained and a urologic evaluation performed if there is evidence of urologic anatomic abnormalities or prior urologic surgeries.

Indications and Contraindications The contraindications are shown in Table 10-10.

TABLE 10-10
CONTRAINDICATIONS TO RENAL TRANSPLANTATION

Absolute
Cancer (except nonmelanotic skin cancer)
Infection
HIV
Active fungal or bacterial
Tuberculosis
Cirrhosis
Chronic active hepatitis
Active drug abuse
Relative
Ischemic cardiac disease
Aortic iliac occlusive vascular disease
Obesity
Renal disease
Sickle cell disease
Hyperoxaluria

Histocompatibility Testing The workup begins with blood group typing and HLA typing. Blood group typing is essential because renal endothelial cells express major blood group antigens, and the preformed natural antibodies to these antigens can result in hyperacute rejection. In cadaveric transplantation, absolute blood type matching is required, but type O donors are universal donors. The standard typing procedure is a lymphocytotoxic serologic test in which the potential recipient's cells are tested against a battery of sera or as monoclonal antibody preparations. These sera have been selected because of reactivity against specific HLA antigens. All cadaveric and potential living donors are HLA typed as well. Standard tests include typing for the class I antigens HLA-A, -B, and -C and the class II antigens HLA-DR, -DP, and -DQ. HLA typing can be of significant importance in living donor transplantation by allowing identification of the best match from multiple potential donors. For cadaver donor allocation, matching also has an important role. In living donor transplantation, an HLA match is correlated with short- and long-term graft survival. In cadaveric transplantation, matching is used to facilitate organ allocation. There is a correlation between the degree of HLA matching; the 1-year survival advantage for six-antigen matches over completely

mismatched cadaveric transplants is about 5 percent. Serum screening is another important histocompatibility test in renal transplantation. As a result of sensitizing events, such as blood transfusions, pregnancies, and previously failed transplants, patients may produce anti-HLA antibodies. The consequences of sensitization are the production of antibodies against specific HLA antigens. Serum screening is performed by testing a patient's serum against a panel of lymphocytes selected to represent the known HLA antigens. Sensitization is designated by the patient's panel-reactive antibodies (PRA) level, which is a reflection of the percentage of cells on the panel against which the sera react. The most important histocompatibility test in renal transplantation is the final crossmatch. This is similar to the crossmatch test performed for blood transfusions. Cells from a potential donor and serum from a recipient are incubated together. Crossmatching is performed just before proceeding with transplantation. The use of sensitive crossmatch techniques has essentially eliminated hyperacute rejection as a problem in renal transplantation.

Renal Donor *Evaluation of the Living Donor* According to recent statistics from the United Network of Organ Sharing (UNOS), there are over 30,000 patients awaiting renal transplants in the United States. The cadaveric donor pool has remained static over the past 5 years, with only 4000–5000 donors realized each year. Because of the shortage of cadaveric donors, live donors, related and unrelated, have a larger role in many renal transplant programs. The advantages of live donation are excellent immediate graft function and avoidance of posttransplant dialysis, better short- and long-term results, preemptive transplantation (i.e., avoidance of dialytic support), avoidance of waiting time for a cadaveric kidney, and in the case of HLA-identical transplants, a reduction in immunosuppressive therapy. The risks to the donor are relatively low, but there is a 1 in 10,000 risk of death and a 10 percent or less risk of morbidity. No definitive long-term morbidity has been demonstrated for live donors. The presence of diabetes, hypertension, malignancy, significant cardiopulmonary disease, a history of renal disease, and age over 65 years are the primary reasons not to proceed with live donation.

Donor Nephrectomy The donor operation is carried out through a flank incision and retroperitoneal approach. The most common complications after live donation include urinary tract infections, wound infections, and pneumothorax. More serious complications are rare. In the case of cadaveric donation, with the exception of older donors, whose liver and pancreas may not be used for trans-

plantation, retrieval of kidneys usually is part of a multiorgan procurement that includes the heart, lung, liver, pancreas, and most recently, the intestine. Figure 10-7 illustrates intraabdominal multiorgan procurement of the liver, pancreas, and kidneys.

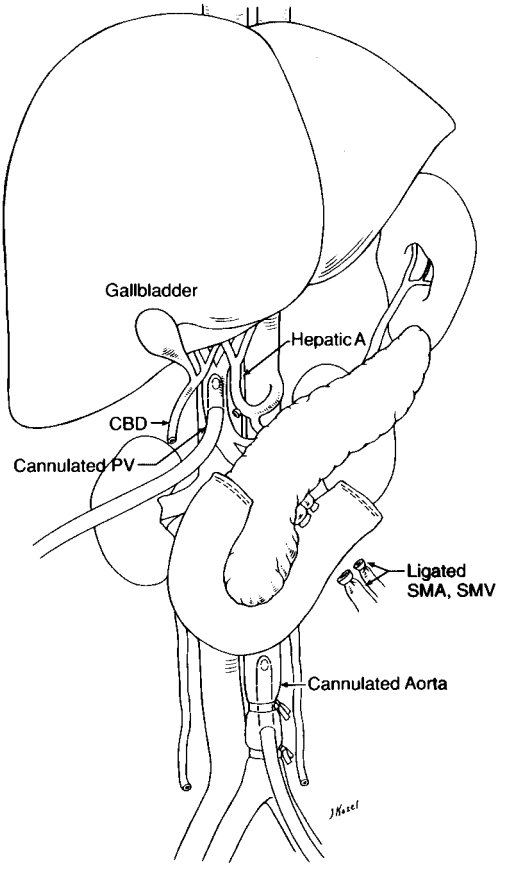


FIGURE 10-7 Multiorgan procurement of the liver, pancreas, and kidneys. Note intraaortic and portal vein cannulas for in vivo flushout.

Surgical Technique A right curvilinear incision is made, extending from the pubic tubercle to a point just medial to the iliac crest and to the tip of the eleventh rib. In the event of a second transplant, the opposite side is used. If three or more transplants are necessary, a transabdominal approach is used. The donor renal artery may be anastomosed end-to-side to the common or external iliac artery or end-to-end to the hypogastric artery. Occasionally in children the donor renal artery is sewn to the distal aorta. The renal vein is sutured to the common or external iliac vein or the distal vena cava. The ureteral anastomosis is performed most commonly on the recipient's bladder.

Postoperative Care *Immediate Care* Because early delayed graft function occurs in approximately 25 percent of cadaveric transplants, fluid replacement linked to urinary output helps to prevent fluid overload and the need for urgent hemodialysis. Diabetic patients need to have blood glucose level monitored closely, and insulin may be given via a sliding scale or an insulin drip. Patients also need to have their blood pressure monitored closely because moderate hypertension is common in the postoperative period. This results from preexisting hypertension from long-standing renal disease, postoperative pain, fluid administration, and medications that are known to cause hypertension, such as prednisone, cyclosporine, and tacrolimus (FK506).

Technical Complications Early technical complications include graft thrombosis, urine leaks, bleeding, and wound infections; late complications include lymphoceles, ureteral strictures, and renal artery stenosis. Graft thrombosis is from an arterial or venous thrombosis and in the early postoperative period is technical in origin. Urine leaks occur most commonly at the ureterovesical junction but may occur anywhere along the length of the ureter or from the renal pelvis. Technical failure results from a ureteral anastomosis that is too loose or too tight or from a bladder closure that is less than watertight. Urine leaks also occur because of distal ureteral slough from inadequate blood supply. Lymphoceles may present with swelling over the transplant, unilateral leg edema caused by iliac vein compression, and an increased creatinine level as a result of ureteral compression. Small asymptomatic lymphoceles do not require treatment, but lymphoceles that cause obstruction or venous compression must be drained.

Immunosuppression New immunosuppressive agents have permitted immunosuppression to be tailored to the type of transplant and according to specific recipient needs. The immunosuppressive

agents in use include antithymocyte globulin (ATG), OKT3, cyclosporine, tacrolimus (FK506), azathioprine, mycophenolate mofetil, and prednisone.

Treatment of Rejection High-dose steroids, usually methylprednisolone, are the first line of treatment for first rejection episodes. With the exception of HLA-identical transplant recipients, first rejection occurs in 40–50 percent of renal transplant recipients. When a rejection episode is resistant to high-dose steroids, which usually is evident after 1–2 days, OKT3 is effective in reversing 90 percent of these rejection episodes. Chronic rejection, which must be differentiated from other forms of late graft dysfunction, has no specific treatment. Prevention of acute rejection episodes and earlier treatment of acute rejection episodes with OKT3 may reduce the incidence of chronic rejection.

Long-Term Complications The three most common causes of death after renal transplantation are cardiovascular disease, infectious disease, and malignancy, which are known to be increased significantly in transplant recipients and reflect chronic long-term immunosuppression, particularly the infectious and malignancy-related deaths. The two most common causes of graft loss are death with a functioning graft and chronic rejection. Noncompliance, particularly in adolescent transplant recipients, may be responsible for 10–15 percent of late graft losses. Recurrent disease, especially recurrent glomerulonephritis, may result in late graft loss. After transplantation, bone and mineral metabolism can be adversely affected. Early manifestations include hypophosphatemia and hypercalcemia, which may be from persistent secondary hyperparathyroidism. Asymptomatic patients with serum calcium levels in the range of 10.5–12.5 mg/dL should not undergo subtotal parathyroidectomy within the first year because the majority of patients will have resolution of their hypercalcemia. Long-term bone disease usually is manifested as severe osteopenia or osteonecrosis. Osteonecrosis, particularly of the femoral head, is a significant long-term complication after renal transplantation related primarily to steroid therapy. Another common problem after renal transplantation is hyperglycemia, which requires treatment with oral hypoglycemic agents or insulin. Transplant-associated malignancies related to long-term immunosuppression, particularly lymphomas, are a long-term concern for renal transplant recipients. Skin cancer, particularly squamous cell carcinoma, has an incidence up to 20 times higher in immunosuppressed patients. Transplant recipients also have a higher incidence of Kaposi's sarcoma and genital neoplasms, such as vulvar, vaginal, and cervical carcinomas. Posttransplant

lymphoproliferative disease (PTLD) is a spectrum of B-cell abnormalities that are driven by EBV. The development of posttransplant lymphomas occurs more frequently in heavily immunosuppressed patients. Polyclonal lymphomas also may respond to antiviral treatment with acyclovir or ganciclovir, but monoclonal lymphomas respond less favorably.

Results Figure 10-8 illustrates the current 5-year survival rates of patients receiving living-related, living-unrelated, and cadaveric renal transplants.

ORGAN PRESERVATION

Because the majority of organs transplanted are from a cadaveric source, the organ inevitably must be stored for some time after removal from the organ donor until the recipient is prepared for the transplant procedure. The organ donor and the recipient often are not in the same location, and time is needed for transport of the donor organ to the hospital where the recipient is being prepared

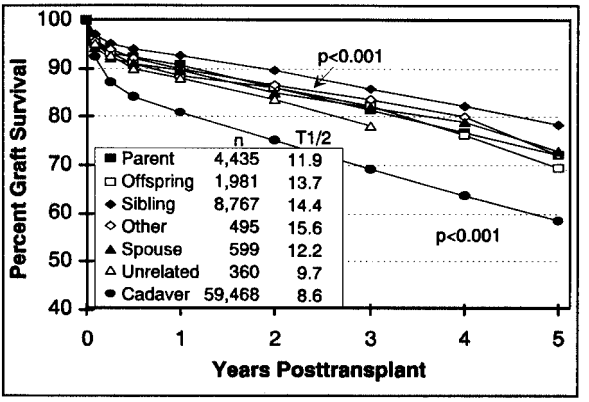


FIGURE 10-8 Five-year survival rates of patients receiving living-related, living-unrelated, and cadaveric renal transplants. (From: Cecka JM: Living donor transplants, in Cecka JM, Terasaki PI (eds): *Clinical Transplants 1995.* Los Angeles, UCLA Tissue Typing Laboratory, 1996, pp 363 – 377, with permission.)

for transplantation. This requires the use of effective, safe, and reliable methods to preserve the organ ex vivo until the transplant procedure can be performed. Acceptable preservation times vary with the organ. Most surgeons prefer to transplant the heart within 5 h after donor cardiectomy; the kidney can be stored safely for 40–50 h, but earlier transplantation is preferable. Most pancreas transplants are performed after 10–20 h of preservation time. Liver transplants usually are performed within 6–12 h after donor hepatectomy. Preservation of the organ begins at the time a donor is identified, and the donor must be adequately maintained hemodynamically so that the organ is not injured before procurement and preservation. Hypothermia and the composition of the organ preservation solution are key factors in successful organ preservation. In cold storage of organs, the organ is rapidly cooled to approximately 4°C by flushout of the vascular system with an appropriate organ preservation solution. Hypothermia is beneficial because it slows metabolism. Organs exposed to normothermic ischemia remain viable for relatively short periods (for most organs, 1 h or less). In warm ischemia, the absence of oxygen leads to a rapid decline in the energy content [adenosine triphosphate (ATP)] of the organ, a redistribution of electrolytes across the cell membrane, and a decrease in biosynthetic reactions. However, biodegradable reactions continue, including a decrease in intracellular pH, proteolysis, and lipolysis. These events contribute to changes in the concentration of intracellular metabolites, and structural alterations in cellular membranes contribute to loss of viability on restoration of blood reperfusion of the organ. Hypothermia alone is not sufficient for adequate preservation for the time necessary for optimal use of cadaveric organs; the organ also must be flushed with an appropriate preservation solution. Two requirements of any ideal preservation solution are (1) the presence of impermeant molecules that suppress hypothermically induced cell swelling and (2) an appropriate biochemical environment. The University of Wisconsin (UW) solution contains lactobionic acid as the primary impermeant. The UW solution also contains raffinose (a trisaccharide), hydroxyethyl starch as a colloid, and adenosine to stimulate ATP synthesis during reperfusion of the organ.

For a more detailed discussion, see Sollinger HW, D'Alessandro AM, Deierhoi MH, Kalayoglu M, Kirk AD, Knechtle SJ, Odorico JS, Reitz BA, Yuh DD: Transplantation, chap. 10 in *Principles of Surgery,* 7th ed.

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CHAPTER

11

SURGICAL COMPLICATIONS

OPERATIVE RISK

Cardiac Risk One means of estimating cardiac risk is to use Goldman's cardiac risk index (Table 11-1). The focus of the Goldman classification is the history of a previous myocardial infarction. If more than 6 months has elapsed between the cardiac infarction and the proposed operation, then there is a 6 percent risk. If a transmural infarct has occurred less than 3 months before operation, the risk of cardiac death is between 16 and 37 percent. Significant peripheral vascular disease should alert the surgeon to consider the cardiac risk. A cardiac stress test is indicated to identify those patients at coronary risk. The most sensitive examination of cardiac risk is the inability to perform a bicycle exercise for 2 min and achieve a heart rate higher than 100 beats/min.

For patients in congestive failure, the use of calcium channel blockers or beta blockers, digitalization with cardiac glycosides, and diuresis are part of the therapeutic armamentarium. Patients with rapid atrial fibrillation should have their heart rates controlled. If the cardiac rhythm cannot be returned to normal sinus rhythm, cardioversion should be considered.

Pulmonary Risk The patient at pulmonary risk can be identified by simple functional tests such as walking up a flight of steps or blowing out a match with unpursed lips from a distance of 8 to 10 in. If arterial blood gases are drawn while the patient is on room air, a PCO_2 greater than 45 mmHg suggests a diffusion defect. Other identifiable risk factors include a maximum breathing capacity of less than 50 percent of predicted or a 1-s forced expiratory volume (FEV_1) of less than 2 L. The most sensitive test for patients undergoing thoracotomy is the exercise oxygen consumption (VO_2).

Because most lung damage is a result of smoking or industrial pollution, cessation of smoking is essential for patients who are to undergo long elective procedures, and an 8-week preoperative cessation provides maximal benefit.

TABLE 11-1
COMPUTATION OF MULTIFACTORIAL INDEX SCORE TO ESTIMATE CARDIAC RISK IN NONCARDIAC SURGERY

	Points
S_3 gallop or jugular venous distention on preoperative physical examination	11
Transmural or subendocardial myocardial infarction in the previous 6 months	10
Premature ventricular beats, more than 5/min documented at any time	7
Rhythm other than sinus or presence of premature atrial contractions on last preoperative electrocardiogram	7
Age over 70 years	5
Emergency operation	4
Intrathoracic, intraperitoneal, or aortic site of surgery	3
Evidence for important valvular aortic stenosis[a]	3
Poor general medical condition[b]	3

Risk of cardiac complications based on index score: class I (0–5 points): 1%; class II (6–12 points): 5%; class III (13–25 points): 11%; class IV (>25 points): 22%.

[a]Findings of a cardiologist's examination, noninvasive testing, or cardiac catheterization.

[b]As evidenced by electrolyte abnormalities (potassium < 3.0 meq/L; $HCO_3 < 20$ meq/L), renal insufficiency (blood urea nitrogen > 50 mg/dL; creatinine > 3.0 mg/dL), abnormal blood gases ($P_{O_2} < 60$ mmHg; $P_{CO_2} > 50$ mmHg), abnormal liver status (elevated aspartate transaminase or signs at physical examination of chronic liver disease), or any condition that has caused the patient to be chronically bedridden.

SOURCE: Adapted from Goldman L: Cardiac risks and complications of noncardiac surgery. *Ann Surg* 198:780, 1983, with permission.

Renal Risk Renal abnormalities are reflected in the blood urea nitrogen (BUN) and creatinine levels. Reversible causes of renal insufficiency should be identified and corrected. Aminoglycosides should be avoided in these patients for bowel preparation. In the postoperative period, if severe hyperkalemia supervenes with electrocardiographic (ECG) changes, calcium should be administered intravenously, followed shortly thereafter by 50% dextrose,

10 units of insulin, and intravenous bicarbonate. Essential amino acids and hypertonic dextrose solution, given as total parenteral nutrition (TPN) may lower the potassium level.

Hepatic Risk Hepatic dysfunction is best estimated by the Child-Pugh criteria. In cirrhotic patients, the mortality accompanying noncardiac surgery is less than 5 percent for Class A patients, 5–10 percent for Class B patients, and between 25 and 50 percent or higher for Class C patients. When the blood ammonia concentration is higher than 150 ng/dL, an 80 percent mortality can be expected. The same pertains to albumin levels below 2.0 g/dL. In patients with ascites, the conversion of uncontrollable ascites to ascites that can be controlled with medication improves the operative risk. Spironolactone, furosemide, and restriction of salt may reduce the ascites.

Nutritional-Immunologic Defects Malnourished patients experience a higher complication rate. A weight loss of more than 15 percent over the previous 3–4 months, a serum albumin level of less than 3.0 g/dL, anergy to injected skin test antigens, and a serum transferrin level of less than 200 mg/dL are critical. Malnourished patients may require TPN preoperatively.

DIABETES MELLITUS

Pathophysiology Anesthesia may affect carbohydrate metabolism. Hyperglycemia may be increased by an accelerated breakdown of liver glycogen with the formation of lactic acid. The stress of an operation aggravates hyperglycemia because of increased levels of epinephrine, growth hormone, and glucocorticoids. These may require larger doses of insulin in patients undergoing operative procedures. Treatment is directed at preventing ketoacidosis, hyperosmolar nonketotic coma, decreased cardiac output, electrolyte imbalance, and decreased wound healing.

Management Diabetic patients should have preference on the operative schedule to minimize the effects of fasting and ketosis. Preoperative medication should be kept to a minimum because these patients are more sensitive to narcotics and sedatives. The choice of anesthesia should not be influenced by the presence of diabetes.

Patients with mild diabetes frequently do not require insulin or dietary control. The cornerstone of all diabetic management is the dietary or parenteral intake. The goal of a dietary or parenteral fluid

regimen is to keep the patient free of acetonuria without excessive hyperglycemia. Patients with well-controlled diabetes taking oral agents should continue the use of these drugs until the day before the operation. Patients who take tolbutamide usually require insulin during and immediately after a major operation.

Insulin Therapy Several protocols for the administration of insulin have been proposed. One popular method is shown in Table 11-2.

TABLE 11-2
INSULIN INFUSION PROTOCOL IN MAJOR SURGERY IN DIABETIC PATIENTS

1. Day before surgery
   a. Obtain 5:00 P.M. plasma glucose STAT.
   b. Start intravenous infusion of 5% dextrose in water at the rate of 50 mL/h and maintain this rate until the patient is taking solid foods without difficulty postoperatively.
   c. "Piggy-back" to dextrose infusion an infusion of regular insulin using IVAC or other infusion pump. Preparation of insulin solution: 50 units in 250 mL 0.9% *N* saline; flush 60 mL of infusion mixture through system and discard before attaching.
   d. Set infusion rate with this equation:

$$\text{Insulin (units/hour)} = \frac{\text{plasma glucose (mg/dL)}}{100}$$

   (Divide by 150 rather than 100 if the patient is thin or is not taking corticosteroids.)
   e. Repeat glucose determination every 3 h as needed with appropriate insulin adjustments to obtain a plasma glucose level between 100 and 200 mg/dL.
2. Day of surgery
   a. Continue dextrose solution as above.
   b. Manage fluid and electrolyte requirements in peri- and postoperative periods with non-glucose-containing solutions *only.*
   c. Obtain plasma glucose STAT every 2 h during surgery and every 6 h for the rest of that 24-h period; adjust insulin accordingly.

TABLE 11-2 *(continued)*

3. Days after surgery
   a. Continue dextrose and other fluid replacement as on the day of surgery.
   b. Obtain daily fasting and afternoon plasma glucose values to assess insulin treatment and adjust as necessary.
   c. Hypoglycemia contingencies (plasma glucose less than 50 mg/dL):
      (1) Obtain STAT plasma glucose; decrease insulin rate accordingly; treat orally.
      (2) Give 15 mL intravenous bolus of 50% dextrose in water if oral therapy is insufficient.
      (3) Repeat steps 1 or 2 at 15-min intervals if symptoms persist or recur.
      (4) Determine cause of hypoglycemia and treat promptly.
   d. Discontinue infusion when patient is tolerating solid food.
      (1) Reinstitute appropriate twice-a-day insulin dosage.
      (2) Do not stop infusion completely without switching to insulin injections.

SOURCE: From Meyer EJ, Lorenzi M, et al: Diabetic management by insulin infusion during major surgery. *Am J Surg* 137:323, 1979, with permission.

Severe hyperglycemia in patients undergoing major operations is best managed with intravenous regular insulin (Table 11-3).

GENERAL CONSIDERATIONS

The response to surgical procedures includes antidiuresis, an increase in extravascular volume, fever, and tachycardia. These are caused by the release of cytokines and other agents. Urine output falls, normally because of the release of antidiuretic hormone. A tendency to hyponatremia is present in the immediate postoperative period. Diuresis usually begins on the second or fourth postoperative day and coincides with the decreased secretion of aldosterone. Ileus of the colon and stomach persists for 2–5 days after an open abdominal procedure but for a considerably shorter period after

TABLE 11-3
CONTINUOUS INSULIN INFUSION GUIDELINES

1. Place 1 mL of U100 regular insulin in 100 mL of normal saline for a concentration of 1 U/mL
2. Preflush intravenous tubing to allow adherence of insulin to plastic
3. IVAC or IMED pump (or even pediatric)
4. Give 0.2 units/kg as IV bolus and give 0.1 unit/kg/h as continuous drip
5. Expect initial drop in blood glucose from rehydration and then approximately 10% drop from original blood glucose level each hour (e.g., 50–70 mg/dL/h)
6. Monitor blood glucose at 1 h and then every 2–4 h. Plasma electrolytes should be checked every 2–6 h until stable
7. Double rate of infusion or shift to alternative protocol if blood glucose does not fall in 2 h
8. Stop insulin infusion when blood glucose reaches ±250 mg/dL and change intravenous solution to contain 5% dextrose
9. Because of short half-life of intravenous insulin, insulin (regular or regular plus lente or NPH) must be given 20–30 min before discontinuing insulin infusion. Dosage adjusted according to duration of diabetes, degree of ketoacidosis, age of patient, body size, known sensitivity to insulin, amount of insulin given so far in treatment, or other factors affecting amount of insulin needed (pregnancy, renal failure, ongoing infection, etc.)

minimally invasive surgery. Wound pain can be severe for approximately 48–72 h, and postoperative fatigue may be prolonged.

FEVER

Pathophysiology Thermoregulation is controlled by the anterior hypothalamus. Various pathophysiologic mechanisms, such as pyrogens, are responsible for the generation of fever. These may arise from infectious agents, antigen-antibody complexes, steroids, and other inorganic substances. All pyrogens appear to evoke a com-

mon mediator, endogenous pyrogen or interleukin-1 (IL-1), a monokine produced by leukocytes. Fever per se usually is not a significant physiologic problem unless core temperature is elevated above 105°F (40.5°C).

Perioperative Fever Fever on the first postoperative night is usually ascribed to atelectasis, but other causes should not be disregarded. A delayed transfusion reaction can cause a fever.

Malignant Hyperthermia This is a rare anesthetic complication that occurs in about 1 in 100,000 general anesthetic procedures. It consists of a rapid rise in body temperature, usually during the initiation of a general anesthetic or the administration of succinylcholine. A family history of complications associated with anesthetics is a warning of this possibly lethal complication. Once the syndrome unfolds, dantrolene is administered intravenously. Support measures include positive-pressure ventilation with 100% oxygen and control of acidosis and electrolyte imbalance, cooling blankets, monitoring of urine output, and treatment of possible myoglobinuria.

Time Relationships of Fever Fever within 24 h is usually caused by atelectasis or failure to clear pulmonary secretions. High fevers with systemic symptoms such as rigors are associated with severe wound complications. Fever at 24–48 h is usually attributed to respiratory complications. Fever after 48–72 h is usually caused by thrombophlebitis or wound infection. Less common infectious complications include pneumonitis, acute cholecystitis, idiopathic postoperative pancreatitis, and drug allergy.

WOUND COMPLICATIONS

Wound Infection

Predisposing Factors Wound contamination occurs in the operating room, but not all wounds harboring bacteria become infected. *Staphylococcus aureus* is the most frequently involved offending organism. Enteric organisms frequently contaminate wounds when bowel operations are performed. Hemolytic streptococci are responsible for 3 percent of wound infections. Occasionally, "surgical scarlet fever" may complicate these infections. Other less common pathogens include enterococci, *Pseudomonas, Proteus,* and *Klebsiella.*

The incidence of wound infection developing in clean, atraumatic, and uninfected wounds is between 3 and 4 percent. The

figure rises to over 10 percent when the bronchus, gastrointestinal tract, or oropharynx has been entered during the procedure. With breaks in surgical technique, it rises to over 16 percent, and in operations involving perforated viscera, the rate is reported to be as high as 28 percent. In the latter situation, consideration should be given to delayed primary closure of the skin.

The rate of wound infection rises in patients over age 65. Diabetes is not an independent risk when adjusted to age. Obesity doubles the infection rate.

Prevention Wound infection rates can be minimized by (1) skin preparation, (2) bowel preparation, (3) prophylactic antibiotics, (4) meticulous technique, (5) temperature maintenance, and (6) appropriate drainage. Bowel preparation decreases wound infection. Mechanical preparation is a most effective modality, but a variety of antibiotic regimens should be included. Systemic antibiotics should be given immediately before the incision is made and serum levels maintained throughout the operative procedure. Wounds requiring drainage are more likely to become infected, but it cannot be concluded that the drains are responsible for the infection.

Management Management depends on the extent of destruction and the type of wound infection. A simple collection of purulent material is treated by opening the incision to provide adequate drainage. This is insufficient in severe clostridial myositis or necrotizing fascitis where radical debridement is necessary. Clostridial myositis is manifest by crepitus, which also may be present in necrotizing fascitis. The patient is more sick than expected than with a simple wound infection. A Gram stain may identify some of the offending organisms. In the absence of specific information, the wound should be cultured and the patient placed on a combination of antibiotics. Diabetic patients are prone to Fournier's gangrene, which is a form of necrotizing fascitis in the perineum or groin.

Wound Hematomas

Wound hematomas are caused by inadequate hemostasis. Anticoagulation, fibrinolysis, polycythemia vera, myeloproliferative disorders, and decreased or inadequate clotting factors all contribute to hematoma formation. Hematomas provide a good culture medium for bacteria and frequently become infected. When the hematomas are discovered early in the postoperative course, the patient should be returned to the operating room and, under sterile conditions, the wound opened and the hematoma evacuated. If discovered late, the patient can be managed expectantly if there is no

evidence of contamination. If drainage is required, a closed-suction drainage system is preferable.

Wound Seromas

These are lymph collections usually associated with large surgical areas such as axillary dissection and groin dissection. They are best managed with closed-suction drains if they are sterile and open drainage if they have become infected.

Wound Dehiscence

By definition, *dehiscence* is a separation within the fascial layer of the abdomen, whereas *evisceration* indicates extrusion of peritoneal contents through the fascial separation. Old age, malnutrition, hypoproteinemia, morbid obesity, malignancy, immunologic deficiency, uremia, diabetes, coughing with increased abdominal pressure, and remote infections are all contributory factors. Ascites also increases the incidence of wound disruption. Vitamin C is essential for collagen synthesis, and patients who are subclinically scorbutic have an eightfold increase in the incidence of wound dehiscence. Zinc is a cofactor for enzymatic processes, and zinc deficiencies also have been implicated in the formation of a dehiscence. Chemotherapeutic agents also inhibit wound healing.

Clinical Manifestations Dehiscence without evisceration is detected by the appearance of salmon-colored fluid draining from the wound. This usually occurs about the fourth or fifth day. Evisceration is evidenced by intestine on the abdominal wall.

Treatment In some instances, if there is no evisceration, the patient can be treated expectantly and a ventral hernia accepted. Patients with evisceration should be returned to the operating room for closure of the wound.

COMPLICATIONS OF THE GENITOURINARY SYSTEM

Urinary Retention

Postoperative urinary retention occurs more frequently in males than in females. The incidence after major abdominal surgery ranges from 4–5 percent but after anorectal surgery may be greater than 50 percent. Stress, pain, spinal anesthesia, and various anorectal reflexes conspire to cause increased alpha-adrenergic

stimulation that prevents release of the musculature around the bladder neck. Prazosin hydrochloride has been shown to significantly reduce postoperative urinary retention.

Patients experiencing urinary retention experience urgency, discomfort, and fullness, and an enlarged bladder can be percussed. Straight catheterization is undertaken initially and then usually repeated once. If the catheterization is required more than twice, a Foley catheter is placed and left to drain for 2–7 days.

Acute Renal Failure

Acute renal failure is frequently caused by inadequate resuscitation. It is also a consequence of transfusion reaction, in which case the patient should be treated with diuresis and alkalinization of the urine. A second important cause of acute renal failure is the use of nephrotoxic drugs such as aminoglycosides, vancomycin, amphotericin B, and occasionally high doses of penicillin.

Pathology Prerenal dysfunction is characterized by a BUN-to-creatinine ratio of 20:1 or greater. This is commonly observed with dehydration or under resuscitation. Another type of prerenal azotemia is a complication of liver disease known as the *hepatorenal syndrome.* This is due to hypovolemia and also maldistribution of blood flow. Recovery from hepatorenal syndrome depends on recovery from the intrinsic liver disease. Renal dysfunction also may be caused by the intrinsic damage of acute tubular necrosis, pigment nephropathy, and drug nephrotoxicity. There is a prolonged diminished renal perfusion in the face of sustained hypotension that results in ischemia of the renal parenchyma. The use of large amounts of radiocontrast medium causes reversible renal failure due to intrinsic damage. Another cause is the showering of atheromatous emboli during aortic surgery.

Postrenal failure is rare in the surgical setting but can result from ureteral clots or stones. It also can be caused by benign prostatic hypertrophy. Foley catheterization is the treatment of choice.

Prevention of Acute Renal Failure For patients with chronic urinary tract infection, specific antibiotics based on the culture should be used. Patients with benign prostatic hypertrophy should be treated with preemptive balloon dilatation or transurethral resection. A patient with inadequate urinary output should not be subjected to a general anesthesia unless the situation represents an emergency. In low-flow states, mannitol, bicarbonate, and diuresis induced by furosemide should be used. If there is any question regarding the volume status, central venous pressure monitoring is indicated.

Manifestations Acute renal failure presents in the postoperative period with oliguria and a urine output of 0.4–0.5 mL/kg/h in an adult. The diagnosis of acute tubular necrosis is made by measurement of the urinary sodium and potassium levels and osmolality. A fractional excretion of sodium (FENa) greater than 1 indicates intrinsic renal damage.

Management The management of renal failure is divided into two periods; the first is when the diagnosis is uncertain, and the second is when the diagnosis has been made. If the patient is oliguric and thought to be hypovolemic, a volume challenge is in order. Once adequate volume status has been established, furosemide or mannitol can be given to increase urinary output. "Renal dose dopamine" also may be used in conjunction with diuretics.

When the patient has been diagnosed with established renal failure, it is important to avoid overhydration, avoid toxic ionic damage such as hyperkalemia, provide nutritional support, and attempt to manage the patient without dialysis. Dialysis is undertaken in patients with acute renal failure for critical ionic excesses such as hyperkalemia and BUN concentrations that are higher than 100 mg/dL. Dialysis has an annual mortality of 5–10 percent.

RESPIRATORY COMPLICATIONS

Pathophysiology Respiratory complications are among the most common complications of surgery and the most lethal, responsible for 5–35 percent of postoperative deaths. Upper abdominal and thoracic incisions result in a significant decrease in vital capacity and functional residual capacity in the first 24 h after an operation. Postoperative pain also alters the mechanics of respiration.

A number of risk factors predispose the patient to the development of pulmonary complications. These include smoking, advanced age, obesity, chronic obstructive pulmonary disease, and cardiac disease.

Atelectasis

Atelectasis is the collapse of alveoli with ongoing perfusion of blood resulting in a perceptible increase in the shunt fraction. It may be due to a loss of surfactant allowing secretions to accumulate in the collapsed alveolus. Lung inflation in the postoperative period prevents and reverses atelectasis. This can be accomplished by coughing and deep breathing, chest percussion and postural drainage, incentive spirometry, intermittent positive-pressure breathing, and continuous positive airway pressure. Three groups

of medications have been applied: expectorants, detergents and mucolytics, and bronchodilators.

Pneumonitis

Pneumonitis is a nosocomial infection that is seen with increasing frequency on surgical services. The organisms involved include *Pseudomonas, Serratia, Klebsiella, Proteus, Enterobacter,* and *Streptococcus.* There is an emerging predominance of gram-negative organisms. Fungal pneumonia is uncommon, but with the increasing use of antibiotic regimens, it is likely to increase.

Clinical Manifestations These include fever, productive cough, dyspnea, pleuritic chest pain, and purulent sputum.

Management Management depends on indentifying the responsible organism and treating it with antibiotic therapy. Given the increasing incidence of gram-negative nosocomial infections in the intensive care setting, antibiotic therapy with an aminoglycocide and an antipseudomonal penicillin should be initiated when the diagnosis is made.

Aspiration

This occurs when large amounts of particulate-laden acid contents of the stomach enter the tracheobronchial tree. This should be removed as expeditiously as possible by suction. If untreated, the results resemble pulmonary edema. Chest radiographs demonstrate progression of local damage and infiltration. In over 50 percent of patients who suffer aspiration, a resulting pneumonia occurs.

Management The only effective treatment of aspiration is prevention by emptying the stomach and neutralization of gastric contents. Treatment of the early phase of aspiration includes removal of the debris and lavage of the upper airway. Endotracheal intubation is usually necessary to initiate treatment and to clear the tree. Bronchodilating agents may be helpful, and positive-pressure ventilation (PPV) is often necessary.

Pulmonary Edema

This is the transudation of fluid into the alveolus. The most common causes in surgical patients are fluid overload or myocardial insufficiency secondary to infarction or ischemia. Additional causes include sepsis, valvular dysfunction, neurogenic stimulation, and

hepatic failure. There are two time frames for the manifestation of pulmonary edema. The first occurs during resuscitation with overly aggressive fluid therapy. The second occurs in the postoperative period when fluid mobilization is taking place. The patient presents with dyspnea at rest, tachypnea, and air hunger. There may be changes in the mental status and disorientation. Wheezing and signs of bronchospasm may be audible. There may be distended neck veins, cyanosis, and peripheral pitting edema.

Management Management depends on addressing the inciting cause, oxygen therapy, positioning the patient in the upright position, and diuretics.

Fat Embolism Syndrome

This is a common pathologic finding after trauma, particularly trauma involving the long bones. The incidence of fat embolism ranges from 26 percent in patients with single fracture to 44 percent in patients with multiple fractures. This syndrome of pulmonary dysfunction, coagulopathy, and neurologic disturbances associated with increasing circulating fat globules is uncommon. It has been reported in approximately 9 percent of patients with femoral and tibial fractures.

Clinical Manifestations Over three-quarters of the patients manifest some degree of respiratory insufficiency, usually occurring soon after injury but occasionally as long as 48–72 h thereafter. Chest radiographs reveal bilateral alveolar infiltrates. Central nervous system manifestations may include disorientation and confusion. The skin demonstrates a characteristic petechial rash in the axilla, neck, and skin folds. Fever and tachycardia are common. The examination of urine for the presence of fat globules is not specific.

Management The patient is treated for the clinical manifestations. Treatment includes adequate fluid resuscitation, transfusion, oxygen, and other supportive measures. There is little support for the use of steroids, and the effects of heparin are debatable. Other modalities include low-molecular-weight dextran to reduce the blood viscosity and platelet adhesion.

Acute Respiratory Distress Syndrome (ARDS)

By definition, this is the clinical situation in which the patient is incapable of maintaining adequate oxygenation, adequate ventilation, adequate tissue delivery, or some combination of these defects. The

syndrome is characterized by atelectasis, reduced pulmonary compliance, and refractory hypoxemia. The most widely accepted definition of ARDS is a syndrome that includes (1) lung injury, acute in nature, (2) bilateral infiltrates on frontal chest radiograph, (3) PaO_2/FiO_2 less than 200, and (4) pulmonary capillary wedge pressure less than 19 mmHg with no evidence of congestive failure. The etiology is unknown, but abnormal cytokine response to injury has been invoked. There may be some activation of the complement cascade, activation of the thromboxane-leukotriene pathway, disorders in nitric oxide production, degranulation of neutrophils, and production of increased permeability factors by macrophages. This results in a ventilation-perfusion mismatch.

A newly described concept of ventilator lung injury is termed *volutrauma,* which is different from barotrauma and results in the maldistribution of inspired tidal volume secondary to positive high-pressure ventilation and a heterogeneous nature of lung injury in ARDS. Barotrauma, on the other hand, is simply extra-alveolar air.

Management Current mechanical ventilation strategies have emphasized the need to reduce volutrauma. These include (1) early use of positive end-expiratory pressure (PEEP), (2) pressure-limited ventilation with plateau pressures of less than 35 cmH_2O, (3) permissive hypercapnia, and (4) use of inhalational nitric oxide. Initial experience with the use of nitric oxide has suggested a response rate of 60–70 percent. Partial liquid ventilation or perfluorocarbon-assisted gas ventilation has been applied.

CARDIAC COMPLICATIONS

Myocardial Infarction

Perioperative myocardial infarction probably is the leading cause of death in the elderly after noncardiac surgery. The presence of coronary artery disease increases the incidence from a control level of 0.1–0.7 percent to 1 percent after operation. The most widely used criteria to estimate cardiac risk is that originally suggested by Goldman (see Table 11-1). The history is important in evaluating the risk of myocardial infarction. A history of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and angina should lead the surgeon to obtain a more detailed history on the cardiac evaluation. A preoperative ejection fraction of less than 0.35 is associated with a 75 percent incidence of perioperative myocardial infarction.

Clinical Manifestations Most cases occur during the first 3 postoperative days, and the most important precipitating factor is shock. Chest pain occurs in only 21 percent of patients. Dyspnea, cyanosis, tachycardia, and arrhythmia are all manifestations. The ECG may provide the diagnosis, but it is not an unequivocal finding. Determination of the CPK-MB isoenzyme is the most precise method for detection for myocardial necrosis after operation.

Management Preoperatively, patients with signs of cardiac insufficiency should be digitalized. Routine digitalization is not indicated, however. Treatment of a developed myocardial infarction consists of relief of pain and anxiety using morphine and sedation. Patients are treated with oxygen to relieve hypoxia. The patient should be managed in an intensive care setting. Cardiac shock is treated by vasopressor agents.

Arrhythmias

In cardiac procedures, the incidence of arrhythmias is approximately 50 percent, whereas thoracic surgical procedures have an incidence of about 20 percent and arrhythmias occur in about 2 percent of other operative procedures. Arrhythmias may be caused by hypokalemia or hyperkalemia, hypercalcemia, and hypomagnesemia. Digitalis may predispose surgical patients to serious dysrhythmias, and digitalis toxicity can result in supraventricular-atrial flutter with varying blocks. Hypercapnia and thyrotoxicosis are also precipitating causes.

Management of Preexisting Arrhythmias Cardiac glycosides can be used to control the ventricular rate in patients with supraventricular tachycardia. Reversal causes arrhythmia such as electrolyte disturbance, drug toxicity, and hypoxia should be controlled. Intravenous lidocaine may be used. For significant conduction defects, cardiac pacing should be considered.

Management of New-Onset Arrhythmias The patient's hemodynamic status should be assessed. Management depends on the ventricular rate, the site of origin of the arrhythmia (atrial or ventricular), the need for cardioversion, and identifying and correcting the underlying causes. In hypotensive patients with acute tachyrhythmia, cardioversion should be performed using an initial pulse of 100 J. If this is not successful, it should rapidly increase to 360 J. If bradycardia is present, the patient should be treated with atropine.

Paroxysmal Supraventricular Tachycardia This may be caused by hypoxia, myocardial ischemia or infarction, or congestive failure. The primary treatment is adenosine 6 mg intravenously, which may be repeated after 1–2 min with 12 mg. If the arrhythmia persists, verapamil intravenously is indicated but should be used with caution.

Atrial Fibrillation This is particularly common after pulmonary resection. Direct current cardioversion is indicated when the patient is hemodynamically unstable. Verapamil may be used to convert, and digitalis glycoside is also helpful once the heart rate is decreased. When atrial fibrillation supervenes in a patient on digitalis, quinidine or procainamide is usually successful.

Sustained Supraventricular Tachycardia This may be the result of digitalis toxicity, and the medication should be discontinued and potassium supplemented if the serum level is low.

Atrial Flutter This can be associated with mitral or tricuspid valve disease or sustained pulmonary hypertension. The heart rate is controlled with electric shock, and once the heart rate is controlled, digitalis maintenance therapy is indicated.

Ventricular Tachycardia This is the most dangerous arrhythmia and cannot be tolerated for an extended period of time. The underlying cause is usually intrinsic disease of the heart, including cardiomyopathy or coronary artery disease. Treatment is similar to that used for ventricular fibrillation and incorporates electric shock therapy and lidocaine. Refractory cases have been treated successfully with bretylium.

Ventricular Fibrillation This is usually fatal and due to ischemia. Direct current countershock is used initially. Epinephrine may be administered, and lidocaine therapy or bretylium also should be used. Arterial blood gases should be used to guide the resuscitation.

Hypertension

There is controversy about whether hypertension represents a dangerous preoperative situation. It is not clear that these patients are at increased risk for cardiac morbidity and mortality. Preoperative hypertension does increase the risk of perioperative blood pressure lability, which in turn may contribute to the incidence of stroke, arrhythmia, and myocardial ischemia. In patients with mild to moderate hypertension, several factors may call for delay of an opera-

tive procedure. These include ECG changes of myocardial ischemia, new-onset dysrhythmias, emergence of left ventricular hypertrophy on ECG, new onset of unstable angina pectoris, congestive heart failure, a recent neurologic deficit, and a new onset of high-grade hypertensive retinopathy.

In patients who are taking antihypertensive medications, they should be continued until the day of surgery. If hypertension develops during anesthetic induction or postoperatively, the adequacy of ventilation, hydration, and fluid status should be established. If the hypertension reaches alarming heights, sodium nitroprusside or nitroglycerin can be used. Diuretic therapy may be required to diminish the intravascular volume. Preoperative medication should be resumed as soon as possible.

HYPERCOAGULABLE STATES

Acquired Hypercoagulable States

Lupus anticoagulant factors interfere with heparin monitoring. The presence of these antibodies is associated with an increased risk of arterial and venous thrombosis. Patients with this factor should receive prophylactic anticoagulation before and immediately after surgery and also sequential compression boots against thromboembolism. Heparin-induced thrombocytopenia is a form of a consumptive platelet activation. It is idiosyncratic and not dose-dependent. Mild thrombocytopenia occurs 2–4 days after heparin exposure and may occur earlier if the patient had previously received heparin. A more severe syndrome includes profound hyperthrombocytopenia associated with multiple small-vessel thrombosis. In this circumstance, the mortality is significant. A diagnosis can be made based on measurement of antibody. Discontinuation of heparin results in lower morbidity and mortality if the syndrome is detected early.

Inherited Thrombotic Disorders

Antithrombin III deficiency is an autosomal dominant inherited trait associated with recurrent thrombosis in about 60 percent of patients and pulmonary embolism in up to 40 percent. Treatment is with heparin. These patients undergoing operation should be given fresh frozen plasma to raise the level of antithrombin III. Protein C deficiency also causes unexplained venous thrombosis as a result of a deficiency of a protein that is an inhibitor of the procoagulant system. Since the levels of this protein are affected by warfarin, anticoagulation therapy is usually sufficient. Protein S deficiency is

also associated with increased thrombosis, and patients may require treatment for acute thrombotic disease that is often widely disseminated.

POSTOPERATIVE PAROTITIS

This may be a serious complication that is associated with a high mortality related mainly to the primary disease. Seventy-five percent of patients with this disorder are over the age of 70 and have undergone major operative procedures. The causes include poor oral hygiene, dehydration, and the use of anticholinergic drugs. Most infections are from staphylococci.

The interval between operation and onset of symptoms varies from hours to weeks. The patient usually presents with pain in the parotid region, and the gland is slightly swollen and tender. There is often associated and overlying cellulitis. Eventually, abscess formation can occur, and a significant enlargement can result in airway obstruction. Prophylaxis includes adequate hydration and good oral hygiene aided by methods to stimulate salivary flow. Prophylactic antibiotics have no value.

When considering the diagnosis, pus should be expressed from Stensen's duct. While awaiting the results, a broad-spectrum antibiotic that acts against staphylococci is initiated. If the disease persists or progresses and there is a suggestion of fluctuance, incision and drainage, often of multiple sites, are indicated.

COMPLICATIONS OF SURGERY OF THE GASTROINTESTINAL TRACT

Ileus and Partial Small Bowel Obstruction

Ileus is defined as nonmechanical obstruction that prevents normal postoperative progression of the return of bowel function. It is thought to arise from a neuroinhibition that interferes with coordinated intrinsic bowel wall motor activity. The small bowel does not manifest ileus postoperatively and continues to function unless there is an inflammatory process. Gastric ileus can persist from 24–48 h, whereas colonic ileus may last 3–5 days. Ileus increases with manipulation, inflammation, peritonitis, and large amounts of blood left in the peritoneal cavity. Blood in the retroperitoneum also produces ileus, as does hypokalemia, hypocalcemia, hyponatremia, and hypomagnesmia. Opiates and phenothiazines contribute to the delay in resolution of ileus.

Failure to pass contrast medium beyond a fixed point is pathognomonic of intestinal obstruction. Ileus and mechanical obstruction may be difficult to distinguish. If ileus persists postoperatively, a long tube may be effective in reversing the process without operation. The long tube, however, is generally contraindicated in the face of mechanical obstruction.

Anastomotic Leaks and Fistulas

Factors that increase the likelihood of an anastomotic leak following an intestinal procedure include emergency procedures, poorly prepared patients, inadequately resuscitated patients, prolonged intraoperative hypotension, and hypothermia. The three major etiologic factors are poor surgical technique, distal obstruction, and inadequate proximal decompression.

Duodenal Stump Blowout The incidence of duodenal stump blowout following gastric resection has been reported to be approximately 1 percent with a mortality of 0.6 percent. Duodenal stump leakage occurs most commonly after operations for duodenal ulcer, particularly emergency procedures to stop hemorrhage. Specific measures can be taken to avoid this complication. When the duodenal closure is difficult, a catheter duodenostomy may be used to develop a controlled fistula. Duodenal blowout is more likely to occur between the second and seventh postoperative days, manifested by sudden pain, temperature elevation, and general deterioration. Adequate drainage must be instituted immediately and is best accomplished with at large sump catheter passed down to the duodenal stump region.

INTESTINAL LEAKS AND FISTULAS

Leakage of intestinal anastomoses is manifest by fever, leukocytosis, unexplained ileus, and a complicated postoperative course. Computed tomography (CT) is usually diagnostic. Percutaneous drainage often is effective in reversing sepsis.

If the leak is small, or if previous drains were placed in the region of the anastomosis, nasogastric suction, antibiotics, and TPN may contain the leakage without further need of operative intervention. If the patient is in jeopardy, reexploration is indicated, at which time the anastomosis should not be resutured. It must be completely resected and redone, or the two ends of the bowel should be separated and diversion performed.

A *fistula* is an anastomotic leak that has developed a pathway to the skin. Typical presentation includes fever, ileus, leukocytosis, and malaise. On the fourth or fifth postoperative day, there is

increased wound pain and redness leading to drainage of purulent material from the wound followed by leakage of intestinal contents. The treatment plan for patients with enterocutaneous fistulas is to allow the fistula to close spontaneously, if possible; operative intervention is reserved for patients in whom spontaneous healing does not occur.

Therapy of an Established Fistula The initial management of an established fistula is a period of stabilization of the patient, attempting to raise the albumin level to 3.0 mg/dL while giving the patient nothing by mouth. A sump-type drain is placed around the skin, and the skin and its edges are protected. Generally, TPN is administered, but enteral nutrition is also effective in some patients. After the patient is stabilized, the site of the fistula is identified by a fistulogram, and it is determined whether there is any distal obstruction. In the absence of distal obstruction, spontaneous closure usually occurs within 5 weeks of adequate nutritional support. Somatostatin has been used to promote closure, but there is no demonstration of speeding up of the process. A determination must be made as to whether an operation is indicated. If closure does not occur spontaneously, an operation is performed, at which time all adhesions are taken down and all abscesses drained. Resection and end-to-end anastomosis yield the lowest incidence of failure and the lowest incidence of complications. Ancillary procedures at the time of resection and operation include gastrostomy and feeding jejunostomy in some patients. After the procedure has been performed successfully, feeding is usually delayed for about a week.

Colocutaneous Fistulas These are generally the result of colonic anastomotic leaks, particularly in patients with acute diverticulitis. In contrast to enterocutaneous fistulas, fluid and electrolyte abnormalities are rare, and spontaneous closure occurs in about 75 percent of patients. The lack of spontaneous closure by 5 weeks is an indication for surgical repair, at which time the definitive operation involves resection of the fistula and affected segment with primary anastomosis and temporary diversion of the fecal stream by colostomy if necessary.

Postgastrectomy Syndromes

Dumping Dumping is the result of loss of the pyloric valve that allows hyperosmolar material to rapidly enter the small intestine. This results in physiologic changes including the release of vasoactive substances. There is also loss of plasma volume as the small intestine secretes actively to dilute the hyperosmolar con-

tents. Rapid absorption of glucose and secretion of insulin and the rapid entry of glucose and potassium into the cell result in hypokalemia.

The manifestations result in early postprandial bloating, borborygmus, cramps, light-headedness, palpitations, sweating, and hypotension. Carbohydrate-rich foods are more likely to provoke dumping and should be avoided. In severe cases, octreotide may relieve the symptoms. If the patient remains symptomatic, a Billroth II anastomosis should be converted to a Billroth I anastomosis. If this strategy fails, an interposed 6-cm reversed loop of jejunum may slow the transit of hypertonic solution into the small bowel.

Postvagotomy Diarrhea Most patients have increased bowel movements after truncal vagotomy. In about 5–20 percent of patients, diarrhea is troublesome, and in 1–2 percent, it is disabling. Treatment is difficult. In patients who are incapacitated, a 10-cm reversed jejunal loop 100 cm distal to the ligament of Treitz has been advocated.

Afferent Loop Syndrome This is a mechanical problem peculiar to gastroenterostomy reconstruction after gastrectomy. There is disturbance of flow from the afferent loop into the efferent loop. The afferent loop syndrome can be acute or chronic. In the chronic form, as the afferent loop becomes obstructed, bile, pancreatic juice, and duodenal secretions are suddenly regurgitated into the stomach. In the acute form, as the secretion increases, a perforation can occur.

The manifestations include sudden pain and cramps relieved by projectile vomiting of clear bile. The diagnosis can be made on the basis of an upper gastrointestinal series showing a massively distended afferent loop. Operation is required for relief of this symptom and in most instances consists of anastomosing the afferent loop into a Roux-en-Y efferent loop downstream. A vagotomy is carried out to reduce the propensity for marginal ulcer.

Alkaline Reflux Gastritis In patients in whom there is constant reflux of bile into the stomach, the symptoms consist of continual burning epigastric pain. Eating is associated with an increase in pain rather than relief, and vomiting may be present. Endoscopy reveals a great amount of bile emanating from the afferent loop, and there is a diffuse, beefy-red gastritis.

The most effective treatment is a combination of cholestyramine and sucralfate. If medication does not relieve the symptoms, a Roux-en-Y may be corrective.

Stomal Complications

An enteral stomal therapist is an essential member of the team. The stoma should be placed through the rectus muscle a sufficient distance from the umbilicus and the anterosuperior iliac spine. There should be no tension on the bowel as it is brought up through the fascia, and the bowel should be fixed to the fascia to prevent it from falling back into the abdomen. The fascial opening should be adequate. The stoma should not be placed in a skin crease or at the belt line.

Recurrence of Disease The incidence of complications for ileostomies is about 4 percent in patients with ulcerative colitis and up to 30 percent in patients with Crohn's disease. Crohn's disease may result in peristomal fistulas. Antibiotics should be administered, and there is little advantage to resiting the stoma because the Crohn's disease usually leads to recurrence.

Stomal Necrosis and Retraction Inadequate vascularization of the stoma can lead to ischemia or necrosis in the immediate postoperative period. The development of duskiness should prompt an evaluation to determine the extent of involvement. If necrosis is superficial to the fascia, no immediate action is required, but stricture usually results. If the necrosis extends below the fascia, immediate exploration and reconstruction are indicated.

Skin Complications Skin complications are usually a result of siting and the inability to obtain an appropriate seal around the stoma. The critical issue for healing of peristomal skin is the placement of a stomadhesive that can be left in place for 5–7 days. Bulk formers such as metamucil also thicken ileostomy contents so that they will be more manageable. When the breakdown is severe, the patient may require placement of a sump tube within the ileostomy.

Stomal Stricture This is usually a late complication. Primary maturation of the stoma has drastically reduced the development of serositis. A superficial stricture of the stoma can be dilated, and at times, an operation under local anesthesia can relax the skin. If the stricture is at the fascial level, the fascia must be enlarged and the bowel fixed to a newly enlarged opening.

Peristomal Hernias and Prolapse In occasional circumstances, a local procedure can reduce the hernia. In the majority of patients, the entire stoma must be repositioned. The fascial defect of the peristomal hernia should be closed to ensure that a ventral hernia does not occur.

METABOLIC COMPLICATIONS

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

This is perhaps the most common metabolic complication after surgery and is especially frequent in the elderly. If unrecognized, it may result in central nervous system damage, seizures, and even death. The development of this syndrome is augmented by the tendency to overhydrate patients postoperatively.

If the serum sodium concentration falls below 125 mEq/L, fluid restriction is all that is necessary because the syndrome generally corrects itself. If, however, the serum sodium level is significantly reduced, 3% saline solution is the treatment of choice. This is particularly true if the patients are confused and somnolent. Mannitol should be used in this situation to provoke a diuresis of excess water.

Disorders of Thyroid Metabolism

Thyroid Storm This is an infrequent occurrence seen in patients in whom thyrotoxicosis is unrecognized before the induction of anesthesia and surgery. Tachycardia, fever, and changing mental status are the predominant symptoms. Treatment consists of propranolol or other beta blockers to stabilize the cardiovascular system. Propylthiouracil and potassium iodide are given to decrease T_3 and T_4 release.

Myxedema Coma This is an extremely rare complication that occurs in patients who are chronically hypothyroid and are provoked by the stress of an operation. The manifestations include hypoventilation, hypothermia, bradycardia, and seizures or coma. The treatment consists of warming, hydration, assisted ventilation, and the administration of L-thyroxine intravenously.

Adrenal Insufficiency

This may occur as a result of previous administration of steroids or the destruction or exhaustion of the adrenal glands during an operative procedure. Adrenal insufficiency complicates other forms of severe illness such as sepsis, shock, or trauma and can result in unexplained hypotension that will end fatally unless treated. It is manifest by fever, abdominal pain, hypotension, light-headedness, palpitations, and changes in mental status. There is associated

hypoglycemia, hyponatremia, and occasionally hypokalemia. The cortisol level should be measured, and treatment consists of 200 mg hydrocortisone intravenously. The hydrocortisone should be continued in divided doses over 24 h and then tapered to a maintenance dose.

Liver Failure

Patients with cirrhosis, alcoholic hepatitis, or fatty infiltration are prone to develop liver failure postoperatively. Patients who develop shock are more at risk. The manifestations include somnolence, jaundice, diminished urine output, and ascites. Liver function tests reveal an elevated bilirubin level, a decreased albumin level, and a lengthening of the prothrombin time. Spontaneous bacterial peritonitis must be ruled out in these patients.

Treatment consists of correction of the electrolyte abnormalities; administration of neomycin, cathartics, or lactulose orally or by enema; and provision of nutritional support. A modified low-aromatic, high-branched-chain-amino-acid formulation is appropriate. A high cardiac output with low peripheral resistance usually complicates hepatic failure. Hemodynamic support should be initiated with dopamine and alpha-adrenergic agents to restore peripheral resistance.

PSYCHIATRIC COMPLICATIONS

There is an increased incidence of postoperative psychiatric complications in older patients. In some series, delirium has been diagnosed in up to 20 percent of elderly patients on the intensive care unit. "Postoperative psychosis" cannot be considered a distinct clinical entity, and no single factor has been shown to be responsible.

Clinical Manifestations The duration of the latent interval between surgical treatment and psychological disturbance may be days to weeks. In the recovery room, patients usually exhibit a lack of concern about the operation and an absence of affective response. After 24 h, the patient responds with concerns and emotions that have been conspicuously absent in the immediate postoperative period. The manifestations of this disorder are extremely variable. Fear can be accompanied by depression, elation, and overactivity. There may be acute delirium with confusion and disorientation or merely a vague change in perception or mood. Delirium may begin with an inappropriate remark or a dramatic outburst.

Depressive reactions are the second most important psychosis noted in several series. The patient is characteristically uncoopera-

tive in an active way or may be listless. It is not rare for a schizophrenic reaction to have its onset in the surgical patient. The incidence of postoperative psychosis is not related to the duration of preoperative hospital stay. By contrast, emergency operation often results in reactions marked by acute anxiety, nightmares, insomnia, and irritability.

Management There is a need to integrate psychological treatment with management of the surgical problem. Verbal communication between the surgeon and the patient is the best means of overcoming emotional or mental difficulty. Consultation with a psychiatrist is indicated in the case of any acute and severe emotional disturbance. This referral should be candidly discussed between the surgeon and the patient. A number of drugs including tranquilizers and S1 antagonists have been helpful in the treatment of postoperative psychological complaints.

Delirium Tremens and Other Forms of Delirium

A relatively normal-appearing patient may undergo withdrawal from alcohol or narcotics in the postoperative period. This is potentially fatal if not corrected. The patient is typically hyperactive with irritability, delusions, hallucinations, restlessness, and agitation. Prophylactic lorazepam should be administered in the perioperative period to patients with severe alcoholic histories who are candidates for delirium tremens.

Special Surgical Situations

Pediatric Surgery In children, severe anxiety states may be precipitated by the shock of operation. This occurs most frequently in the 1–2-year-old group. Postoperative reactions consist of disobedience, temper tantrums, defiance, and destructive behavior. Moderate and severe reactions may require medications.

Surgery in the Aged Elderly patients are more prone to becoming emotionally disturbed when confronted with new situations. Severe depression is not uncommon subsequent to an operation in older patients. These patients should be encouraged to maintain human contact and prevent withdrawal.

Gynecologic and Breast Surgery Removal of the breast and a variety of gynecologic procedures may be accompanied by severe depression. Routine counseling lowers the postoperative psychiatric morbidity significantly.

Cancer Surgery Cancer patients are exposed to two major threats, disease and extensive surgical treatment. They are concerned with death during the operation and the threat of disease throughout the postoperative years. Postoperative depression is related to anticipated interference with valued activities. A colostomy may suggest to patients that they will be rejected socially. Some patients suffer a sense of isolation, guilt, and abandonment.

Cardiac Surgery Severe psychiatric disturbances have been observed to occur with considerable frequency after open-heart surgery. They do resolve rapidly after the patient is transferred from the intensive care unit to the standard hospital ward. The incidence of psychosis is greater in males, older patients, and those expressing minimal preoperative anxiety. Children generally react well to open-heart surgery.

Dialysis and Transplantation Patients undergoing dialysis become extremely dependent and emotionally attached to the staff. A large number of psychological syndromes have been described in patients undergoing transplantation. This is particularly true of patients of who have had living donors provide the transplanted organ.

For a more detailed discussion, see Fischer JE, Fegelman E, and Johannigman J: Surgical Complications, chap. 11 in *Principles of Surgery,* 7th ed.

CHAPTER

12

PHYSIOLOGIC MONITORING OF THE SURGICAL PATIENT

HEMODYNAMIC MONITORING

The traditional clinical evaluation often is unreliable in critically ill patients because there may be major changes in cardiovascular function that are not accompanied by obvious clinical findings. Invasive hemodynamic monitoring at the bedside provides information about cardiorespiratory performance and guides therapy.

Arterial Catheterization

Arterial catheterization is indicated whenever there is a need for continuous monitoring of blood pressure and/or frequent sampling of arterial blood. States in which precise and continuous blood pressure data are necessary include shock of any etiology, acute hypertensive crisis, use of potent vasoactive or inotropic drugs, high levels of respiratory support, high-risk patients undergoing extensive operations, controlled hypotensive anesthesia, and any situation in which any of the factors affecting cardiac function is rapidly changing. This is particularly true in patients with shock, because indirect measurement of blood pressure by a cuff has been proved inaccurate. Inserting arterial lines is a relatively safe and inexpensive procedure. There are no absolute contraindications to arterial catheterization, although bleeding diathesis and anticoagulant therapy may increase the risk of hemorrhagic complications. Severe occlusive arterial disease with distal ischemia, the presence of a vascular prosthesis, and local infection are contraindications to specific sites of catheterization.

With an indwelling arterial catheter and monitoring system, the systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) can be displayed continuously. The pulse rate can be calculated from the arterial tracing when the electrocardiogram (ECG) is not available.

Many anatomic sites have been used to access the arterial circulation for continuous monitoring, i.e., the superficial temporal, axillary, brachial, radial, ulnar, femoral, and dorsalis pedis arteries.

The dual blood supply to the hand and the superficial location of the vessel make the radial artery the most commonly used site for arterial catheterization. Cannulation is technically easy, as is securing the catheter in place; there is a low incidence of complications. The mean and end-diastolic radial pressures usually are accurate estimates of the corresponding aortic pressures. Most authors recommend assessing the adequacy of the collateral circulation before cannulation of the radial artery. The axillary artery has been recommended as suitable for long-term direct arterial pressure monitoring, with relatively few complications and no reported permanent sequelae. The major advantages include its larger size, freedom for the patient's hand, and close proximity to the aorta so that there is better representation of the aortic pressure waveform and minimal systolic pressure overshoot. Because of the extensive collateral circulation that exists between the thyrocervical trunk of the subclavian artery and the subscapular artery (which is a branch of the distal axillary artery), thrombosis of the axillary artery will not lead to compromised flow in the distal arm. Major disadvantages are its deep location and mobility, which increase the technical difficulty for insertion, and its location within the neurovascular sheath, which may increase the possibility of neurologic compromise if hematoma occurs.

The femoral artery also has been used for continuous blood pressure monitoring. Major advantages are its superficial location and large size, allowing easier localization and cannulation when the pulses over more distal vessels are absent. The major disadvantages are the presence of atherosclerotic occlusive disease in older patients and the problems associated with maintaining a clean dressing in the presence of draining abdominal wounds and ostomies in surgical patients. Despite some disadvantages, studies have failed to demonstrate a higher complication rate in patients with femoral artery catheters. The dorsalis pedis artery has no significant cannulation hazards if collateral flow can be demonstrated to the remainder of the foot through the posterior tibial artery. Major disadvantages are its relatively small size and overestimation of systolic pressure at this level. The superficial temporal artery has been used extensively in infants and in some adults for continuous pressure monitoring. Because of its small size and tortuosity, however, surgical exposure is required for cannulation. A small incidence of neurologic complications as a result of cerebral embolization has been reported in infants. The brachial artery is not used often because of the high complication rate associated with its use for cardiac catheterization. This artery has been used successfully for short-term monitoring, but there are little data to support the use of prolonged brachial artery monitoring. If the collateral

circulation is inadequate, obstruction of the brachial artery may be catastrophic, leading to loss of the forearm and hand. Other problems include the difficulty in maintaining the site in awake, active patients and the possibility of hematoma formation in anticoagulated patients.

Central Venous Catheterization

The most common indications for central venous catheterization are to secure access for fluid therapy, drug infusions, or parenteral nutrition and for central venous pressure (CVP) monitoring. There are no absolute contraindications for CVP catheter placement, although bleeding diatheses may increase the risk of hemorrhagic complications. Vessel thrombosis, local infection or inflammation, and distortion by trauma or previous surgery are considered contraindications to specific sites of catheterization.

While central venous lines are placed primarily for venous access, useful information occasionally can be obtained by measuring the CVP. The CVP may be useful in a hypotensive trauma patient to differentiate a pericardial tamponade from hypovolemia. A properly placed catheter can be used to measure right atrial pressure, which, in the absence of tricuspid valve disease, will reflect the right ventricular end-diastolic pressure. CVP, which can give information about the relationship between intravascular volume and *right* ventricular function but cannot be used to assess either of these factors independently, cannot be used to assess left ventricular function in critically ill patients because ventricular disparity and independence of right and left atrial pressures have been confirmed repeatedly in these patients.

The most commonly chosen sites include the subclavian, internal jugular, external jugular, femoral, and brachiocephalic veins. The subclavian vein can be cannulated with a high rate of success and may be the easiest to cannulate in situations of profound volume depletion. Disadvantages include the higher risk of pneumothorax and the inability to compress the vessel if bleeding occurs. The internal jugular vein has been cannulated with success rates similar to those of the subclavian approach. The major advantages of internal jugular vein catheterization are the lower risk of pneumothorax and the ability to compress the insertion site if bleeding occurs.

Complications can be divided into technical or mechanical complications, usually occurring during catheter placement, and long-term complications related to the length of time the catheter remains in place. The list of technical or mechanical complications is as follows: catheter malposition, dysrhythmias, embolization (air

or catheter fragments), vascular injury (hematoma, vessel laceration, false aneurysm, or arteriovenous fistula), cardiac injury (atrial or ventricular perforation or cardiac tamponade), pleural injury (pneumothorax, hemothorax, or hydrothorax), mediastinal injury (hydromediastinum or hemomediastinum), neurologic injury (phrenic nerve, brachial plexus, or recurrent laryngeal nerve injury), and injury to other structures (trachea, thyroid, or thoracic duct). Pneumothorax is the most frequently reported immediate complication of subclavian vein catheterization, and arterial puncture is the most common immediate complication of internal jugular vein cannulation. Surface-modified central venous catheters have been developed to reduce catheter-related infection. Catheters impregnated with silver sulfadiazine and chlorhexidine resist bacterial adherence and biofilm formation. At least three types of thrombi can develop in patients with central venous catheters: mural thrombus, catheter thrombus, and "fibrin sleeve" or sleeve thrombus.

Pulmonary Artery Catheterization

Several studies in critically ill patients have shown that clinical assessment is inaccurate in predicting cardiac output, pulmonary artery occlusion pressure, and systemic vascular resistance and that the information obtained from pulmonary artery catheterization prompts a change in therapy in 40–60 percent of patients. A pulmonary artery catheter usually is indicated whenever the data obtained will improve therapeutic decision making without unnecessary risk.

The pulmonary artery catheter has provided a "quantum leap" in physiologic information available for the management of critically ill patients. The information that can be obtained includes CVP, pulmonary artery diastolic pressure (PADP), pulmonary arterial systolic pressure (PASP), mean pulmonary artery pressure (MPAP), pulmonary artery occlusion ("wedge") pressure (PAOP), cardiac output (CO) by thermodilution, mixed venous blood gases by intermittent sampling, and continuous mixed venous oximetry. On the basis of this information, a multitude of derived parameters also can be obtained.

The PAOP represents the left atrial pressure (LAP) as long as the column of blood distal to the pulmonary artery catheter tip is patent to the left atrium. This may not be so if the catheter is positioned in an area of the lung where the alveolar pressure exceeds pulmonary venous pressure (zone 2, as described by West) (Fig. 12-1) or both pulmonary artery and venous pressures (West's zone 1), causing intermittent or continuous collapse of the pul-

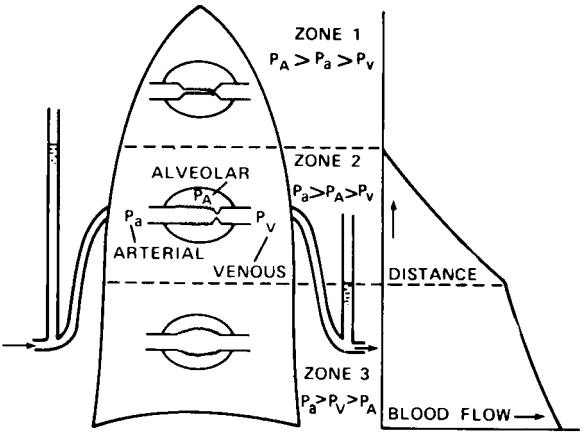

FIGURE 12-1 Model to explain the uneven distribution of blood flow in the lung based on the pressures affecting the capillaries. In zone 1, alveolar pressure (P_A) exceeds pulmonary artery (Pa) and venous (Pv) pressures so that the collapsible vessels are held closed and there is no flow. In zone 2, pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. Under these conditions, there is a constriction at the downstream end of each collapsible vessel. In zone 3, pulmonary arterial and venous pressures exceed alveolar pressure, and the collapsible vessels are held open. (From: West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: Relation to vascular and alveolar pressures. *J Appl Physiol* 19: 713, 1964, with permission.)

monary capillaries. The PAOP may then reflect alveolar pressure and not LAP. This is particularly important if patients have low pulmonary vascular pressures (i.e., hypovolemia) and/or are treated with high levels of positive end-expiratory pressure (PEEP). Because the pulmonary artery catheter is flow-directed, it is most likely to pass into dependent areas of the lung where blood flow is high and both pulmonary artery and venous pressures exceed alveolar pressure (West's zone 3). In this location, the continuous column of blood between the distal lumen of the catheter and the left atrium will remain patent, and the PAOP will reflect LAP. Raising intrathoracic pressure introduces an artifact that affects all intrathoracic vascular pressures to an extent that depends on the state of pulmonary compliance. In patients with acute respiratory insufficiency, compliance often is diminished, and the "stiff" lungs do

not transmit alveolar pressure as readily to the pulmonary circulation. In these patients, the PEEP artifact on the PAOP measurement usually should not exceed 1 mmHg for every 5 cmH_2O of PEEP applied.

Another method of evaluation is to observe the decrement in PAOP when PEEP is briefly removed. Because intravascular pressure measurements are affected by the intrathoracic pressure changes during respiration, they should be performed at end-expiration and obtained from a calibrated strip-chart recorder or oscilloscope rather than from a digital display.

The cardiac output is measured by the thermodilution technique, which correlates well with the Fick and the dye-dilution methods. Pitfalls in cardiac output measurement include injectate temperature different from the temperature used to determine the computer constant or that of the fluid being monitored by the reference probe, delivered volume less than the one entered in the computation constant, incorrect computer constant, rapid infusion of intravenous fluids during measurements, electrical noise created by electrocautery, faulty catheter lumens, improperly positioned catheter (e.g., if the catheter is in the wedge position or if the proximal lumen is above the atrium or within the introducer sheath), and presence of intracardiac shunts or tricuspid regurgitation. A continuous thermodilution technique is available for measuring CO. Pulmonary artery catheters are modified to locate a 10-cm thermal filament in the right ventricle during use.

Access to the central venous circulation for insertion of a pulmonary artery catheter is the same as for placement of a CVP catheter. Once an introducer sheath is in place, the pulmonary artery catheter is inserted and advanced until the tip reaches an intrathoracic vein (as evidenced by respiratory variations on the pressure tracing). The balloon is inflated with 1.5 mL of air and the catheter advanced while the operator observes the pressure waveform and the ECG tracing. After the right atrium is entered, the catheter is advanced through the right ventricle and into the pulmonary artery until a PAOP tracing is obtained (Fig. 12-2). Maneuvers often used to facilitate passage through the pulmonary valve include elevation of the head of the bed, turning the patient into the right lateral decubitus position, performance of the Valsalva maneuver, and increasing ventricular ejection in low-output states by the administration of inotropic drugs. To determine if the catheter is in the wedge position, the waveform needs to be inspected. The mean PAOP should be lower than the MPAP and lower than or equal to the PADP.

There are risks to pulmonary artery catheterization; they are infrequent and usually not life-threatening. In addition to the com-

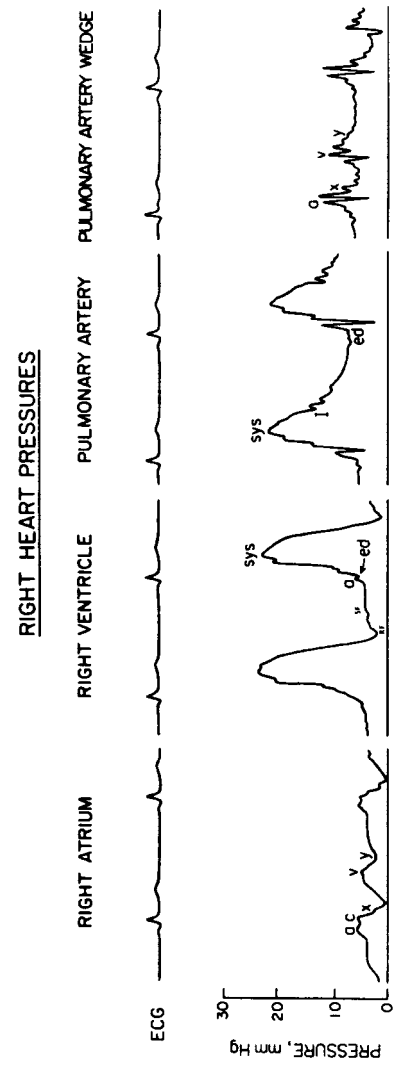

FIGURE 12-2 Normal pressure waveforms from the right side of the heart and pulmonary artery. sys = systolic; ed = end-diastolic. (From: Grossman W, Barry WH: Cardiac catheterization, in Braunwald E (ed): *Heart Disease: A Textbook of Cardiovascular Medicine.* Philadelphia, WB Saunders, 1988, p 250, with permission.)

plications attributed to central venous cannulation, complications can occur during passage or after the catheter is in place. The most common complication during passage of the pulmonary artery catheter is the development of dysrhythmias. They can occur in up to 50 percent of patients, but less than 1 percent of these are serious. Transient right bundle branch block (RBBB) has been reported in 3–6 percent of catheterizations. Complications that can occur after the catheter is in place include infections, thromboembolism, and rupture of the pulmonary artery. Infections from pulmonary artery catheters are directly related to the length and severity of illness. Pulmonary infarction can result from emboli, distal migration of the pulmonary artery catheter tip, or prolonged balloon inflation occluding distal blood flow in the pulmonary artery. Pulmonary artery rupture and hemorrhage are the most serious of all the pulmonary artery catheter complications and are more likely in patients with pulmonary hypertension and in the elderly. Complications related to peripheral migration of the catheter tip can be limited by continuous monitoring of the pulmonary artery tracing, avoiding prolonged balloon inflation, ensuring proximal catheter placement by review of daily x-rays, and the use of continuous heparin flush systems.

In addition to the information directly provided by arterial and pulmonary artery catheterization, many parameters can be calculated. The derived hemodynamic parameters (Table 12-1) aid the clinician by quantitating the relationships among heart rate, filling pressures, resistance, contractility, and cardiac output. Cardiac output (CO) is the sum of all stroke volumes ejected in a given time. It usually is represented as the product of average stroke volume and heart rate (beats per minute), where stroke volume is the amount of blood ejected by the heart with each contraction. The primary determinants of stroke volume are the ventricular preload, afterload, and contractility. If there is no change in ventricular compliance (the relationship between pressure and volume), left ventricular end-diastolic volume (LVEDV) is proportional to left ventricular end-diastolic pressure (LVEDP). The second determinant of stroke volume is afterload. Afterload is the sum of all the loads against which the myocardial fibers must shorten during systole, including aortic impedance, arterial wall resistance, peripheral vascular resistance, the mass of blood in the aorta and great arteries, the viscosity of the blood, and the end-diastolic volume of the ventricle. Contractility, the final determinant of stroke volume, may be estimated in the laboratory by the maximum velocity of contraction of the cardiac muscle fibers.

The level of PAOP that corresponds to optimal left ventricular preload can be determined only by sequentially assessing the effects of acute hemodynamic interventions on cardiac function and

may vary. Fluid can be administered rapidly in predetermined increments while changes in PAOP and in the indices of cardiac performance are monitored. A major increase in PAOP during infusion suggests poor ventricular compliance, exhausted preload reserve, and increased risk of pulmonary edema with further volume loading. If the PAOP rises modestly, if indices of cardiac performance improve, and if PAOP returns to within several millimeters of mercury of the original value within 10 min of stopping the infusion, additional fluid can be given without high risk of exacerbating pulmonary venous congestion.

RESPIRATORY MONITORING

Monitoring ventilation and gas exchange in critically ill surgical patients is of particular importance in deciding if mechanical ventilation is indicated, assessing response to therapy, optimizing ventilator management, and deciding if a weaning trial is indicated. In addition, gas monitoring permits an assessment of the adequacy of oxygen transport and calculation of derived parameters.

Ventilation Monitoring

Lung Volumes Several lung volume measurements are useful for monitoring ventilatory function in the operating room and intensive care unit. These include tidal volume, vital capacity, minute volume, and dead space. *Tidal volume* (V_T) is defined as the volume of air moved in or out of the lungs in any single breath. If the tidal volume is depressed, the patient may have difficulty in both oxygenation and ventilation. V_T can be measured at the bedside using a hand-held spirometer (Wright respirometer). *Vital capacity* (VC) is defined as the maximal expiration after a maximal inspiration. It can be measured at the bedside in a manner similar to the one used for V_T. VC is reduced in diseases involving the respiratory muscles or their neural pathways, in obstructive and restrictive ventilatory impairment, and in patients who fail to cooperate fully. VC is normally 65–75 mL/kg. *Minute volume* (or total ventilation) ($\dot{V}_E$) is the total volume of air leaving the lung each minute (product of V_T and f). Many ventilators display $\dot{V}_E$, or it can be measured with a Wright spirometer. An increase in the minute volume required to maintain a normal arterial blood carbon dioxide tension ($PaCO_2$) suggests an increased dead space relative to V_T or an abnormally high carbon dioxide (CO_2) production. A resting $\dot{V}_E$ of less than 10 L and the ability to double the resting $\dot{V}_E$ on command have been associated with successful weaning from mechanical ventilation.

TABLE 12-1
MEASURED AND DERIVED HEMODYNAMIC PARAMETERS

Parameter (Abbreviation)	Formula	Normal Range	Units
Systolic blood pressure (SBP)	Direct measurement	100–140	mmHg
Diastolic blood pressure (DBP)	Direct measurement	60–90	mmHg
Pulmonary artery systolic pressure (PASP)	Direct measurement	15–30	mmHg
Pulmonary artery diastolic pressure (PADP)	Direct measurement	4–12	mmHg
Mean pulmonary artery pressure (MPAP)	Direct measurement	9–16	mmHg
Right ventricular systolic pressure (RVSP)	Direct measurement	15–30	mmHg
Right ventricular end-diastolic pressure (RVEDP)	Direct measurement	0–8	mmHg
Central venous pressure (CVP)	Direct measurement	0–8	mmHg
Pulmonary artery occlusion pressure (PAOP)	Direct measurement	2–12	mmHg
Cardiac output (CO)	Direct measurement	*	L/min
Mean arterial blood pressure (MAP)†	$MAP = DBP + \frac{SBP - DBP}{3}$	70–105	mmHg
Cardiac index (CI)	$CI = \frac{CO}{BSA}$	2.8–4.2	$L/min/m^2$

Stroke volume (SV)	$SV = \frac{CO}{HR}$	*	mL/beat
Stroke index (SI)	$SI = \frac{SV}{BSA}$	30–65	mL/beat/m^2
Left ventricular stroke work index (LVSWI)	$LVSWI = \frac{SV \times (MAP - PAOP)}{BSA} \times 0.0136$	43–61	g × m/m^2
Right ventricular stroke work index (RVSWI)	$RVSWI = \frac{SV \times (MPAP - CVP)}{BSA} \times 0.0136$	7–12	g × m/m^2
Systemic vascular resistance (SVR)	$SVR = \frac{MAP - CVP}{CO} \times 80$	900–1400	dyne × s × cm^{-5}
Pulmonary vascular resistance (PVR)	$PVR = \frac{MPAP - PAOP}{CO} \times 80$	150–250	dyne × s × cm^{-5}
Coronary perfusion pressure (CPP)	$CPP = DBP - PAOP$	60–90	mmHg

BSA = body surface area; HR = heart rate.

*Varies with size.

†Can also be measured directly.

Pulmonary Mechanics Various respiratory mechanical parameters also can be monitored in the operating room and intensive care unit. These include maximal inspiratory pressure, static compliance, dynamic characteristic, and work of breathing. Inspiratory force is measured as the maximal pressure below atmospheric that a patient can exert against an occluded airway. The measurement requires a connector to an endotracheal or tracheostomy tube and a manometer capable of registering negative pressure. A maximal inspiratory pressure ($P_{I_{max}}$) value that is more negative than −20 to 25 cmH_2O is one of the clinical parameters used to confirm recovery from neuromuscular block after general anesthesia. $P_{I_{max}}$ values more negative than −30 cmH_2O have been used to predict successful weaning from mechanical ventilation. Compliance, a measure of the elastic properties of the lung and chest wall, is expressed as a change in volume divided by a change in pressure ($\Delta V/\Delta P$). In patients receiving mechanical ventilation, a rough measure of total thoracic compliance (both the lungs and chest wall) can be obtained by dividing the delivered V_T by the inflation pressure displayed on the ventilator gauge during conditions of zero gas flow. These can be achieved by using the "inspiratory hold" option on the ventilator, during which period the airway pressure falls to a plateau. If the patient is receiving PEEP, this must first be subtracted from the plateau pressure before calculating static thoracic compliance, that is,

$$\text{Static compliance} = \text{volume delivered}/(\text{plateau pressure} - \text{PEEP})$$

The usual range for adult patients receiving mechanical ventilation is 60–100 mL/cmH_2O. Decreased values are observed with disorders of the thoracic cage or a reduction in the number of functioning lung units (resection, bronchial intubation, pneumothorax, pneumonia, atelectasis, or pulmonary edema). When the static compliance is less than 25 mL/cmH_2O, as in severe respiratory failure, difficulties in weaning are common because of the increased work of breathing (see below).The dynamic characteristic is calculated by dividing the volume delivered by the peak (rather than the plateau) airway pressure minus PEEP. It is not correct to call this value *dynamic compliance* because it is actually an impedance measurement and includes compliance and resistance components. The dynamic characteristic is normally about 50–80 mL/cmH_2O. It may be decreased by disorders of the airways, lung parenchyma, or chest wall; if it decreases to a greater extent than the static compliance, it suggests an increase in airway resistance (e.g., bronchospasm, mucous plugging, kinking of the endotracheal tube) or an excessive flow rate. Work of breathing, which relates to the product of the change in pressure and volume, is a measure of the

process of overcoming the elastic and frictional forces of the lung and chest wall. The work of breathing in the critically ill patient who requires ventilatory support (WOB_{Pt}) can be divided into three components: normal physiologic work (WOB_{Phys}), work to overcome the pathophysiologic changes in the lung and chest wall (WOB_{Dis}), and work to overcome the imposed work of breathing (WOB_{Imp}) created by our methods of ventilatory support. Finally, the patient must do additional work to breathe spontaneously against a breathing apparatus that consists of the ventilator itself, demand valve, tubing, exhalation valves, and most important, the endotracheal tube. Poor demand system sensitivity, ventilator dyssynchrony, malfunctioning demand valves, and inadequate inspiratory flows also are contributing factors. The goal of ventilatory support is to carefully titrate the ventilator's contribution to minute ventilation so that the patient's effort remains a nonfatiguing work load. Failure to do so by supplying too much or too little ventilatory support can result in unsuccessful weaning trials and increase the duration of mechanical ventilation. Normal range for WOB_{Pt} is 0.3–0.6 J/L.

Gas Monitoring

Blood-Gas Analysis Blood-gas measurements provide information about the efficiency of gas exchange, the adequacy of alveolar ventilation, and the acid-base status. Blood gas values usually are reported in terms of directly measured partial pressures (PO_2 or PCO_2) and calculated hemoglobin oxygen saturations (SO_2). Calculated SO_2 values are derived from the measured partial pressure and a nomogram of the oxyhemoglobin dissociation curve usually corrected for blood temperature, pH, and perhaps other factors. Because these assumptions may not be accurate in critically ill patients, actual measurements of SO_2 by co-oximetry are preferred. SO_2 also can be measured continuously by using pulse oximeters or pulmonary artery catheters that incorporate oximetric fibers (see below). Alveolar gas tensions depend on the mixture of inspired gas, ventilation, and blood flow in the lungs, the matching of ventilation and perfusion, and the composition of mixed venous blood gases. Pathophysiologic causes of arterial hypoxemia include ventilation-perfusion inequality or venous admixture from regional alveolar hypoventilation, true intrapulmonary or intracardiac shunt, and decreased mixed venous oxygen content. A decreasing PaO_2 without a change in $PaCO_2$ suggests that blood oxygenation is deteriorating despite constant alveolar ventilation. In the acutely ill patient, this finding usually is attributable to ventilation-perfusion imbalance or intrapulmonary shunting. An important feature of

shunting is that as it increases, supplemental oxygen has progressively less effect on PaO_2 because shunted blood bypasses ventilated alveoli.

The $PaCO_2$ directly reflects the adequacy with which alveolar ventilation meets metabolic demands for CO_2 excretion. An increased $PaCO_2$ (hypercapnia) reflects the failure of the ventilatory system to eliminate the CO_2 produced during metabolism. This "ventilatory failure" traditionally is described as respiratory acidosis. Hypercapnia can occur because of hypoventilation (i.e., CNS depression), increased CO_2 production (e.g., hyperthermia, hyperthyroidism), or increased physiologic dead space resulting in inadequate alveolar ventilation. The mechanisms of hypocapnia are the reverse of those which produce hypercapnia, the most common being hyperventilation (respiratory alkalosis). In critically ill patients, sampling of mixed venous blood can be performed accurately only in the pulmonary artery.

The oxygen content of the blood is equal to the amount of oxygen bound to hemoglobin plus the amount dissolved in plasma. The amount of bound oxygen is directly related to the concentration of hemoglobin and to how saturated this hemoglobin is with oxygen (i.e., SaO_2 or $S\bar{v}O_2$). The amount of oxygen dissolved in plasma depends on the oxygen tension (i.e., PaO_2 or PvO_2). Oxygen delivery ($\dot{D}O_2$) is the volume of oxygen delivered from the heart each minute and is calculated as the product of cardiac output and arterial oxygen content (CaO_2). Oxygen consumption ($\dot{V}O_2$) is the amount of oxygen that diffuses from the capillaries into all tissues and can be calculated according to the Fick principle as the product of CO and arteriovenous oxygen content difference $[C(a - \bar{v})O_2]$. The oxygen use coefficient or extraction ratio (O_2UC), relates oxygen consumption and oxygen delivery ($\dot{V}O_2/\dot{D}O_2$). The adequacy of oxygen transport also must be assessed in relation to oxygen demand, which is the amount of oxygen *required* by the body tissues to use aerobic metabolism. Although oxygen demand cannot be measured clinically, the relative balance between consumption and demand is best indicated by the presence of excess lactate in the blood. Lactic acidosis means that demand exceeds consumption and anaerobic metabolism is present. If oxygen delivery or consumption is low, if use is high, or if lactic acidosis is present, arterial oxygen content might be augmented by increasing hemoglobin concentration or oxygen saturation, or cardiac output might be increased by manipulation of preload, afterload, or contractility. A response might be considered beneficial if oxygen consumption increases, if use returns to the normal range, or if lactic acidosis resolves.

Capnography *Capnography* is the graphic display of CO_2 concentration as a waveform. It should not be confused with *capnometry,* which refers to only the numerical presentation of concentration without a waveform. Currently available systems for CO_2 analysis include infrared spectroscopy, mass spectrometry, and Raman scattering. In addition, a disposable, noninvasive, and inexpensive colorimetric device is available. This device permits a semiquantitative measurement of the end-tidal CO_2 concentration when it is attached between an endotracheal tube and a resuscitation bag. In the majority of stand-alone capnographs, the CO_2 concentration is measured by infrared spectroscopy. A beam of infrared light is passed through the sampled gas. CO_2 molecules in the light path absorb some of the infrared energy. The capnograph compares the amount of infrared light absorbed by the patient gas in the sample cell with the amount absorbed either by gas in a reference cell or by the sample cell during a time of known zero-gas concentration. Normally, there is a fairly predictable relationship between the peak exhaled or end-tidal CO_2 ($P_{ET}CO_2$) and the $PaCO_2$. In healthy subjects with normal lungs, the $PaCO_2$ is 4–6 mmHg higher than the $P_{ET}CO_2$. Patients with chronic obstructive lung disease (and other derangements associated with increased dead space) have an increased arterial to end-tidal CO_2 gradient [$P(a-ET)CO_2$]. This difference occurs because the exhaled gas from the alveolar dead space, which contains little or no CO_2, dilutes the CO_2-containing gas from the normally ventilated and perfused alveoli. $P_{ET}CO_2$ measurement is at present perhaps one of the most reliable means of determining proper endotracheal tube placement. $P_{ET}CO_2$ monitoring is extremely useful as a diagnostic tool in several situations unique to the operating room. These include the detection of air emboli during neurosurgical procedures requiring the sitting position, the detection of increased CO_2 production in malignant hyperthermia, and the detection of disconnection or malfunction of the anesthesia breathing circuit.

Pulse Oximetry Pulse oximetry provides a reliable real-time estimation of arterial hemoglobin oxygen saturation. This noninvasive monitoring technique has gained clinical acceptance in the operating room, recovery room, and intensive care unit. Pulse oximeters estimate arterial hemoglobin saturation by measuring the absorbance of light transmitted through well-perfused tissue, such as the finger or ear. The light absorbance is measured at two wavelengths—660 (red) and 940 nm (infrared)—to distinguish between two species of hemoglobin—oxyhemoglobin and deoxyhemoglobin. Oxyhemoglobin absorbs less red light than deoxyhemoglobin,

accounting for its red color; at infrared wavelengths, the opposite is true. Light absorbances at both wavelengths have two components: the pulsatile (or ac) component, which is attributed to the pulsating arterial blood, and the baseline (or dc) component, which represents the absorbances of the tissue bed, including venous blood, capillary blood, and nonpulsatile arterial blood. The pulse oximeter first determines the ac components of absorbance at each wavelength and divides this by the corresponding dc component to obtain a pulse-added absorbance that is independent of the incident light intensity. It then calculates the ratio *(R)* of these pulse-added absorbances:

$$R = (ac_{660}/dc_{660})/(ac_{940}/dc_{940})$$

The ratio of the pulse-added absorbances at the two wavelengths is used to generate the oximeter's estimate of arterial saturation (SpO_2). The relationship between this ratio and SpO_2 is empirical. Although pulse oximetry may provide erroneous measurements when SaO_2 is less than 70 percent, these values rarely occur. SaO_2 values in the range of perhaps 70–95 percent will reflect changes in PaO_2; it is in this range that pulse oximetry finds great value in monitoring cardiorespiratory disease and directing therapy. Various physiologic and environmental factors interfere with the accuracy of pulse oximetry. These include decreased amplitude of peripheral pulses (hypovolemia, hypotension, hypothermia, vasoconstrictor infusions), motion artifact, electrosurgical interference, backscatter from ambient light, and dyshemoglobinemias. The pulse oximeter can only distinguish oxyhemoglobin and deoxyhemoglobin. If other hemoglobin species are present, an error is introduced. Laboratory co-oximeters, on the other hand, generally use more than two wavelengths and often can quantify other hemoglobin species directly. Intravenously administered dyes, particularly methylene blue and indocyanine green, can temporarily induce artifactually low saturation readings.

Continuous Mixed Venous Oximetry Measurement of the oxygen saturation of mixed venous hemoglobin ($S\bar{v}O_2$) is helpful in the assessment of the oxygen supply-demand relationship in critically ill patients. The use of improved fiberoptic oximetry systems in conventional pulmonary artery catheters has permitted continuous monitoring of SvO_2. The normal range for $S\bar{v}O_2$ in healthy subjects is 0.65–0.80, with an average value of 0.75 corresponding to a $P\bar{v}O_2$ of 40 mmHg at a normal pH of 7.4. A rapid or prolonged fall from the normal range is indicative of a significant deterioration in the patient's clinical condition. Values below the normal range may be associated with increased oxygen consumption due to fever,

shivering, seizures, exercise, and agitation or associated with decreased oxygen delivery because of low cardiac output, anemia, or arterial hemoglobin desaturation. Values above the normal range indicate an increase in oxygen delivery relative to consumption and are associated with the hyperdynamic phase of sepsis, cirrhosis, peripheral left-to-right shunting, general anesthesia, cellular poisoning such as cyanide toxicity, marked arterial hyperoxia, or a technical malfunction of the system (e.g., wedged catheter). Pulmonary artery catheter oximetry differs from pulse oximetry in several ways. First, the pulmonary artery catheter measures *reflected* rather than *transmitted* light. Second, being immersed in blood, the pulmonary artery catheter has no need for the pulse-added signal analysis used by the pulse oximeter. Continuous $S\bar{v}O_2$ monitoring serves three major functions. First, it serves as an indicator of the adequacy of the oxygen supply-demand balance of perfused tissues. In clinically stable patients, a normal and stable $S\bar{v}O_2$ may be considered an additional assurance of cardiopulmonary stability. Additional assessments of cardiac output and arterial and mixed venous blood gas analyses are not necessary. Second, continuously measured $S\bar{v}O_2$ may function as an early warning signal of untoward events. In this situation, the cause of the change in $S\bar{v}O_2$ is not necessarily clear because the change in $S\bar{v}O_2$ is sensitive but not specific. It may be necessary to measure cardiac output, SaO_2, and hemoglobin (Hb) in this setting to identify the etiology of the $S\bar{v}O_2$ change. Third, continuously monitored $S\bar{v}O_2$ may improve the efficiency of the delivery of critical care by providing immediate feedback as to the effectiveness of therapeutic interventions aimed at improving oxygen transport balance.

GASTRIC TONOMETRY

Hemodynamic and oxygen-transport variables document the severity of tissue hypoxia and oxygen debt. Gastric tonometry has been proposed as a relatively noninvasive monitor of the adequacy of aerobic metabolism in organs whose superficial mucosal lining is vulnerable to low flow and hypoxemia. The gastrointestinal (GI) tract will display metabolic changes before other indices of oxygen use. In the anoxic cell, uncompensated adenosine triphosphate (ATP) hydrolysis is associated with the intracellular accumulation of adenosine diphosphate (ADP), inorganic phosphate, and hydrogen ions with resulting intracellular acidosis. These hydrogen ions lead to tissue acidosis, with unbound hydrogen ions combining with interstitial bicarbonate to form the weak acid carbonic acid that dissociates to produce CO_2 and water.

A tonometer is comprised of a semipermeable balloon connected to a sampling tube. A tonometer in combination with a standard vented gastric sump is available. The annealed balloon allows CO_2 generated in the superficial layers of the mucosa to equilibrate within the saline instilled into the balloon.

Incomplete splanchnic cellular resuscitation has been associated with the development of multiple organ system failure, more frequent septic complications, and increased mortality in the critically ill patient. In critically ill patients, gastric tonometry has been used as a predictor of both organ dysfunction and mortality and has been shown to be a better predictor of mortality than base deficit, lactate, oxygen delivery, and oxygen consumption.

RENAL MONITORING

The primary reasons for monitoring renal function is that the kidney serves as an excellent monitor of the adequacy of perfusion and to prevent acute parenchymal failure. Renal function monitoring is helpful in predicting drug clearance and proper dose management. Urine output frequently is monitored but may be misleading. Although very low urine outputs, less than 0.5 mL/kg/h, are consistently associated with low glomerular filtration rate (GFR) values, levels greater than this also can be associated with low GFR values.

The value of plasma creatinine as a measure of renal function far exceeds the value of the blood urea nitrogen (BUN). The serum creatinine level is directly proportional to the level of creatinine production and inversely related to the GFR. In contrast to BUN concentration, plasma creatinine levels are not influenced by protein metabolism or the rate of fluid flow through the renal tubules. Acute reductions in the GFR are not immediately reflected because it takes 24–72 h for equilibration to occur. Creatinine production is directly proportional to muscle mass and its metabolism. Only with measurement of creatinine clearance can the severity of such renal function loss be determined. Serial determinations of creatinine clearance are the most reliable method for clinically assessing GFR and the most sensitive test for predicting the onset of perioperative renal dysfunction. Although measurements traditionally are performed using a 24-h urine collection, measurements using a 2-h collection are reasonably accurate and easier to perform.

Tests that measure the concentrating ability of the renal tubules are used primarily in the differential diagnosis of oliguria to differentiate a prerenal cause unresponsive to judicious fluid therapy from intrinsic renal failure as a result of tubular dysfunction. Tubular

function tests are useful in oliguric patients (urine output < 500 mL/day) because nonoliguric individuals typically have less severe tubular damage and their laboratory findings are likely to show more overlap with the values of patients with prerenal azotemia. The fractional excretion of sodium (FE_{Na}) is the most reliable of the laboratory tests for distinguishing prerenal azotemia from acute tubular necrosis. This test requires simultaneously collected "spot" urine and blood samples. FE_{Na} can be calculated as follows:

$$FE_{Na}\ (\%) = (U_{Na}/P_{Na})/(U_{cr}/P_{cr}) \times 100\%$$

where U_{Na} is the urinary sodium concentration (in mEq/L), and P_{Na} is the plasma sodium concentration (in mEq/L).The FE_{Na} value normally is less than 1–2 percent. In an oliguric patient, a value of less than 1 percent usually is because of a prerenal cause. A value greater than 2–3 percent in this setting suggests compromised tubular function. When the value ranges between 1 and 3 percent, the test is not discriminating.

NEUROLOGIC MONITORING

Monitoring the function of the central nervous system (CNS) can permit early recognition of cerebral dysfunction and facilitate prompt intervention in situations in which aggressive early treatment favorably influences outcome. In the perioperative and trauma settings, several methods have been used to evaluate brain function and the effects of therapy. These include intracranial pressure monitoring, electrophysiologic monitoring, transcranial Doppler ultrasound, and jugular venous oximetry.

Physical findings often are unreliable to ascertain the presence of increased intracranial pressure (ICP). The direct assessment of ICP is obtained by measurement. Measuring ICP permits calculation of *cerebral perfusion pressure* (CPP), which is defined as the difference between the MAP and ICP. Formerly, one of the end points of CNS monitoring was believed to be the control of ICP within safe levels; emphasis has shifted to following CPP itself. Maintaining cerebral blood flow requires using an elevated minimal CPP threshold when treating the injured brain. A CPP level of at least 70 mmHg is suggested. The most common indication for ICP monitoring is severe head injury. Patients with a Glasgow Coma Scale (GCS; see Table 40-1) score of 8 or less or a GCS motor score of 5 or less should be strongly considered for ICP monitoring. Other conditions for which ICP monitoring has been recommended include subarachnoid hemorrhage, hydrocephalus, postcraniotomy, and Reye's syndrome. Several methods of ICP

measurement are available (Fig. 12-3). A ventricular catheter connected to a standard strain-gauge transducer via fluid-filled lines offers excellent waveform characteristics and permits withdrawal of cerebrospinal fluid (CSF). This catheter can be difficult to insert when cerebral edema or hematoma causes shifting or collapse of the lateral ventricle system. A subarachnoid bolt is easily inserted, although at times it may give erroneous readings, depending on its placement relative to the site of injury. Epidural bolts have a lower risk of complications but are less accurate than ventricular catheters or subarachnoid bolts and do not permit withdrawal of CSF. Complications of ICP devices include infection, hemorrhage, malfunction, obstruction, and malposition. Bacterial colonization of ICP devices increases significantly after 5 days of implantation; significant intracranial infections are uncommon.

The electroencephalogram (EEG) reflects spontaneous and ongoing electrical activity recorded on the surface of the scalp. Intraoperative EEG recording has been used primarily for monitoring the adequacy of cerebral perfusion during carotid endarterectomy. The compressed spectral array (CSA) is the most commonly used method of visually displaying processed EEG information. Sensory-evoked potentials (SEPs) are minute electrophysiologic responses elicited by a stimulus and extracted from an ongoing EEG by signal averaging. They reflect the functional integrity of specific sensory pathways and serve to some extent as more general indi-

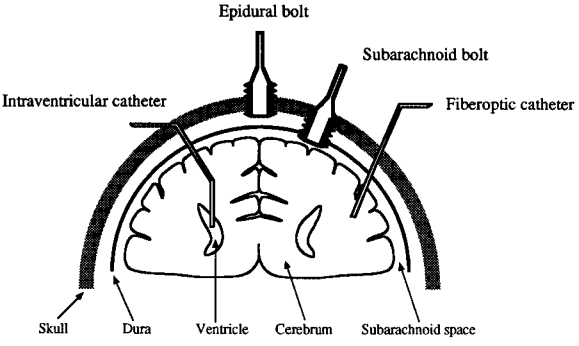

FIGURE 12-3 Diagram illustrating intraventricular catheters, epidural bolts, subarachnoid bolts, and fiberoptic catheters for ICP measurement. (Adapted from: Doyle DJ, Mark PWS: Analysis of intracranial pressure. *J Clin Monit* 8:81, 1992, with permission.)

cators of function in adjacent structures. Somatosensory evoked potentials (SSEPs) reflect the integrity of the dorsal spinal columns and the sensory cortex and can be useful for monitoring during resection of spinal cord tumors, spine instrumentation, carotid endarterectomy, and aortic surgery. Brain stem auditory-evoked potentials (BAEPs) reflect the integrity of the eighth cranial nerve and the auditory pathways above the pons and are used for monitoring of the posterior fossa during surgery. Visual evoked potentials (VEPs) may be used to monitor the optic nerve and upper brain stem during resections of large pituitary tumors.

Jugular venous oximetry is an invasive method of continuously monitoring jugular venous bulb oxyhemoglobin saturation ($SjvO_2$). Changes in $SjvO_2$ provide a measure of the relationship between total cerebral blood flow and total cerebral oxygen consumption. When arterial oxygenation remains constant, a decrease in $SjvO_2$ from control values reflects a decrease in cerebral blood flow or an increase in cerebral metabolic oxygen consumption unmatched by an increase in flow. The range of $SjvO_2$ in normal subjects is 55–71 percent. In head-injured patients, the range is considerably wider, but most investigators agree that a sustained desaturation of 50–55 percent warrants evaluation. $SjvO_2$ levels below 50 percent are indicative of cerebral ischemia.

METABOLIC MONITORING

Energy requirements depend on a number of factors including the body surface area, age, and sex. Basal energy expenditure (BEE) can be predicted with reasonable accuracy (± 5 percent) by the Harris-Benedict equation:

$$\text{Men:} \quad 66.47 + (13.75 \times W) + (5.00 \times H) - (6.76 \times A) = \text{BEE kcal/day}$$

$$\text{Women:} \quad 655.10 + (9.56 \times W) + (1.85 \times H) - (4.68 \times A) = \text{BEE kcal/day}$$

where W is body weight (in kilograms), H is height (in centimeters), and A is age (in years). Resting energy expenditure (REE) can be approximated from the BEE by increasing it by 10 percent. The stress of illness, the change in hormonal milieu relating to the stress state, alterations in substrate utilization, and fever all can be predicted to increase REE. While early studies emphasized increases of 25 percent for multiple-trauma patients and 50 percent for burn patients, even an increase of 60 percent above BEE would only result in a need for 40 kcal/kg/day, or less than 3000 kcal

in a 70-kg patient. Excessive caloric administration potentially is detrimental.

Oxygen delivery or cardiac output times arterial oxygen content and oxygen consumption (normally about 150 mL/min/m^2) assess oxidative metabolism. CO_2 production is a measure of a by-product of oxidative metabolism. The ratio of CO_2 production to oxygen consumption is termed the *respiratory quotient* (RQ). During normal oral dietary intake, carbohydrates, protein, and fat are ingested, giving an average RQ of approximately 0.8. During prolonged starvation, the body adapts to fat metabolism, and the RQ may fall to as low as 0.6–0.7. Conversely, during excessive carbohydrate administration, the transformation into fat releases additional CO_2, and the RQ rises above 1.0. Thus monitoring oxygen consumption and CO_2 production and calculating the RQ provide inferences into the adequacy of total calories as well as the mixture of substrates.

The classic Fick equation relates oxygen consumption to the product of cardiac output and arterial venous oxygen content difference. Repeated cardiac output determinations have an accuracy in the range of ± 5 percent but are not as important as variability in the patient's physiology, in which changes may exceed ± 10 percent in a short time. Pulse oximetry and mixed venous oximetry show that minute-to-minute variations in these values also occur. These factors result in a 10 percent variation between measurements and lower total values compared with validated spirometric techniques. This latter difference reflects the oxygen consumption of the lung, which is included in the spirometric method but not in the reverse Fick technique.

TEMPERATURE MONITORING

Temperature, along with heart rate, blood pressure, and respiratory rate, is one of the traditional four cardinal vital signs. Temperature usually is taken rectally in ill patients or orally when significant elevations are not expected. It is recommended that deeper core temperatures be taken in the critically ill. Core temperature can be measured by placing a thermistor probe into the esophagus or the rectum. Esophageal wires are uncomfortable and invasive and are used exclusively in patients under general anesthesia. Rectal probes are used commonly in the operating room and intensive care unit but may be extruded from the rectum and have a recognized risk of bowel wall perforation. Three devices are available for bedside measurement of core temperature in intensive care unit patients: pulmonary artery thermistor catheters, urinary bladder thermistor

catheters, and infrared auditory canal probes. Measurement of pulmonary artery blood temperature by the pulmonary artery thermistor catheter has been used increasingly as a reliable indicator of core temperature. The need for a catheter is an obvious disadvantage of this approach. Urinary bladder catheters have the advantage of giving both exact measurements of urine output and continuous urine temperature. Infrared probes noninvasively measure tissue temperature in the ear canal; their measurements have more variability than bladder readings.

For a more detailed discussion, see Varon AJ, Kirton OC, and Civetta JM: Physiologic Monitoring of the Surgical Patient, chap. 12 in *Principles of Surgery,* 7th ed.

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CHAPTER

13

SKIN AND SUBCUTANEOUS TISSUE

PHYSICAL PROPERTIES

Tension and elasticity are the primary physical properties of the skin. *Tension* is the characteristic that accounts for the fact that skin can resist stretching. Tension is most marked where the skin contains very dense elastic fibers, particularly if the skin is thin. Anatomic lines of tension are called *Langer's lines. Elasticity* refers to the skin's ability to resume its original shape after an external force has been applied. As with tension, elasticity decreases in the elderly.

Tensile strength is the resistance of skin to tearing under tension. The average strength is 1.8 kg/m^2. Abnormally low values of tensile strength are found in diseases such as Ehlers-Danlos syndrome, in which a defective form of collagen is produced. Also, tensile strength is reduced in patients taking high doses of cortisone for a prolonged period of time.

FUNCTIONS OF SKIN

Functions of skin include (1) percutaneous absorption, (2) circulatory vasoregulation, (3) serving as an organ of sense, (4) secretion of sweat, (5) providing an avenue for the insensible loss of water, and (6) contributing to thermal regulation.

Percutaneous Absorption This function of skin permits entry of substances into the bloodstream. The stratum corneum is the major barrier to diffusion. Water and lipid-soluble substances diffuse rapidly across the skin. Most electrolytes, including sodium and calcium, cannot penetrate the skin.

Percutaneous absorption of phenol and carbolic acid is rapid and may cause fatal poisoning. Estrogenic hormones and hydrocortisone also absorb rapidly and can be therapeutically effective with percutaneous application.

Substances in gas form, with the exception of carbon monoxide, penetrate the skin easily. This method has been employed pharmaceutically with the use of dimethylsulfoxide (DMSO) as a vehicle.

Circulation and Vascular Reactions The cutaneous vascular system is extremely complex. Changes in skin circulation contribute significantly to general vascular and circulatory physiology. Skin blood flow can be visualized directly through the beds of the nails. The color of skin depends on the quantity of blood in the subdermal plexus as much as on melanin and keratin pigments. In addition, skin temperature depends on the rate of blood flow.

Local vascular response may result from direct action on the vessel wall or its contractile elements. A red local reaction can develop after dilatation of small vessels. A *skin wheal* is a circumscribed area of skin edema secondary to dilated blood vessels and leakage of plasma into the extracellular space. Conversely, stimulation of sympathetic nerve fibers causes vasoconstriction of these cutaneous vessels. In addition, the cutaneous vessels respond to various chemical agents such as acetylcholine and nitrites, which cause vasodilatation, whereas norepinephrine, epinephrine, and vasopressin cause vasoconstriction. Although nitrites cause a sensation of flushing and increased blood flow, smoking paradoxically decreases blood flow through the skin.

Sensory Function Many specific sensory functions are facilitated by the skin. The Krause end bulbs mediate cold sensitivity. Ruffini's endings are the receptors for warmth. Meissner's corpuscles provide tactile sensation, and pacinian corpuscles are involved in the sensation of pressure. Pain is mediated by nonmyelinated nerve endings.

Causalgia is a syndrome of pain and vasodilatation that occurs after injury of major nerves. This syndrome also is called *reflex sympathetic dystrophy.* The most common cause is a prior operation with transection of minor nerve branches. Treatment of this condition is difficult and requires physical and occupational therapeutic resources. Active use of the involved extremity is important. For advanced cases, blockade of the contributing sympathetic ganglion with neurolytic agents is used. If ganglion blocks are transiently successful, a surgical sympathectomy may be curative.

Sweat Secretion Sweat glands in skin are eccrine glands or apocrine glands. The eccrine glands are distributed all over the body and are primarily responsible for heat regulation. The apocrine glands are similar to sebaceous glands and develop mostly during

puberty. Their activity is in response to autonomic nervous stimulation rather than thermal conditions.

Sweating is a response to local application of heat or to nervous impulses. Sympathetic nerve fibers liberate acetylcholine to stimulate sweat glands. Atropine and other anticholinergic drugs can block these receptors and interfere with sweat secretion. Hyperhidrosis results from an abnormal increase in nerve impulses or emotional states.

The content of sweat is primarily water with small amounts of sodium chloride. Potassium also is lost through sweat. Nitrogen compounds are secreted in sweat as well. The concentration of urea in sweat is twice as high as that in blood. Sweat also contains large amounts of lactic acid and ammonia.

Insensible Water Loss Besides sweat secretion, water is lost through the epidermis by continuous evaporation. In contrast to sweat, water lost through evaporation does not contain electrolytes or other solutes. Approximately 700 mL total water loss occurs through the skin each day. Hypothyroidism decreases the daily amount of water loss, whereas thyrotoxicosis greatly increases this amount.

Thermoregulation Regulation of body temperature is an important function of the skin. Heat escapes through skin under the processes of radiation, convection, conduction, and evaporation. Sweating is a primary process for heat evaporation. Increased humidity markedly decreases the efficiency of sweating for thermoregulation because of the impairment of evaporation.

Thermoregulation is accomplished in skin also by shifting blood flow from the interior to the skin. Cold stimuli result in pallor of the skin by relative vasoconstriction. After the stimulus has ceased, there is a reactive arterial vasodilatation. This results in a reddish discoloration of skin. In contrast, prolonged cold stimulus causes paresis of the venous limbs of capillaries. A reddish discoloration also may result from this condition, which is not associated with increased blood flow, and skin temperature does not rise. This condition leads to frostbite. Prolonged exposure of skin to cold temperature should be treated by immersion of the involved portion into water at a temperature of 40°C.

Heat exhaustion is a syndrome of excessive loss of salt and water during exposure to high temperatures. The clinical symptoms are exhaustion, headache, palpitation, dizziness, and confusion. Treatment is immediate cooling by evaporation or application of ice. Simultaneously, intravascular volume replacement of fluids is indicated.

PRESSURE SORES

Pressure on an area of skin for 2 h or more may result in ischemia sufficient to cause a pressure sore. Factors contributing to pressure sores include skin over bony prominence, anemia, malnutrition, and immobilization. Surgical therapy requires sharp debridement to excise the ulcer and underlying fascia and necrotic material. Frequently, a bony prominence must be modified to prevent subsequent pressure. The remaining wound often must be covered with a myocutaneous flap.

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa is a chronic infection of the cutaneous apocrine glands, subcutaneous tissue, and fascia. This disease occurs in the axilla, areola of the nipple, groin, or perineum. Commonly, there is slight induration and subsequent inflammation of the skin. Eventually, suppuration develops and cellulitis surrounds the abscess. Initial treatment is incision and drainage, but frequently this produces only a few drops of purulent material. Then the chronic stage develops, with multiple painful cutaneous nodules. Culture of these abscesses reveals a preponderance of staphylococci and streptococci.

Definitive treatment requires complete excision of the involved area and improved hygiene to prevent recurrence. Myocutaneous flaps or advancement flaps provide wound coverage.

CYSTS

Epidermal Inclusion Cysts An epidermal inclusion cyst results from epithelium of skin that is trapped subdermally because of trauma or other reasons and begins to grow and desquamate. The cyst is filled with keratin and desquamated cells. These cysts can occur anywhere on the body. They generally are cured by complete removal. If the cyst is infected secondarily, incision and drainage are indicated first.

Sebaceous Cysts Sebaceous glands are associated with hair follicles and are generally found on the midline of the trunk and on the face. A cyst is formed from a sebaceous gland when the exit of sebum is blocked. True sebaceous cysts are very rare and usually represent epidermal cysts that have been incorrectly diagnosed. The presence of glandular epithelium lining is necessary for the diagnosis.

Dermoid Cysts Dermoid cysts are congenital lesions that arise in early childhood. They generally occur in the midline of the body, on the lateral eyebrow, on the scalp, or in the abdominal and sacral regions. There have been no reports of malignant degeneration of these cysts. Dermoid cysts in the nasal region have a remote possibility of communication with the central nervous system. A computed tomographic (CT) scan should be obtained before excising nasal dermoids.

Pilonidal Cysts Pilonidal cysts are malformations of the neuroenteric canal that occur in the sacrococcygeal region. The ingrowth of hair in the coccygeal region sets the stage for cyst formation and repeated infections. This disease has been referred to as "jeep driver's disease" because long hours of sitting and bumpy driving aggravate the congenital condition. Chronic infection and drainage are the usual presentation. Treatment includes incision and drainage followed by secondary removal of the cyst or sinus when infection has subsided. Excision of the entire sinus is essential for successful treatment. This may be facilitated by injection of methylene blue to determine the extent of arborization of the sinus tract. A skin graft or muscle advancement flap may be necessary to close the defect. Some surgeons prefer to allow closure by secondary intention, particularly if there is residual infection.

Ganglia Ganglia are areas of mucoid degeneration in retinacular structures. They are cystic masses frequently found over the dorsum of the wrist and over tendon sheaths of hands or feet. These cysts contain clear fluid similar to joint fluid. Aspiration alone of the ganglion yields a 75 percent recurrence rate. Surgical excision of the entire ganglion is the recommended treatment. This may require excision of part of the joint capsule.

BENIGN TUMORS

Warts Verruca vulgaris, the common wart, is caused by a contagious virus. Warts usually occur on the hand or soles of the feet. They are quite tender and painful.

Treatment of verruca vulgaris can be accomplished with liquid nitrogen freezing or electrodesiccation under local anesthesia. Caustic agents also have been used but result in a higher recurrence rate.

Keratosis Keratosis is a precancerous lesion manifested by hypertrophy of the epidermis. Senile keratoses occur in older

individuals with a fair complexion. They should be treated by surgical excision if the lesion is large and the suspicion of malignancy is low. Topical treatment with 5-fluorouracil or liquid nitrogen may be done.

Seborrheic keratosis is a thickened area of skin that may appear brown, gray, or black. Occasionally these lesions are mistaken for melanoma. Electrocoagulation is adequate treatment.

Keloids Keloids are dense accumulations of fibrous tissue that extend above the surface of the skin from traumatic wounds or surgical incisions. They are the result of a failure of collagen breakdown and occur most commonly in blacks. Recurrence is common after simple excision.

First-line treatment of keloids is steroid injection. This method is effective in relieving the burning and itching, as well as in producing actual shrinkage of the lesion. Radiation therapy is not effective in treating keloids. Subcuticular sutures should be avoided in patients with a history of keloid formation.

Capillary Malformation Capillary malformations are commonly known as *port-wine stains* of the skin. They represent dilated abnormal capillaries in the subdermal plexus. They are smooth lesions with reddish or purplish patchy distribution. Excision of small lesions is appropriate. The larger lesions are now being treated with laser. This is reserved, however, for patients over 14 years of age.

Hemangioma Hemangiomas appear in infancy and may enlarge over the first year of life but usually regress thereafter. They are bright red, raised, and irregular skin lesions. Episodes of ulceration or superficial infection actually hasten spontaneous resolution of these lesions. Spontaneous resolution usually occurs by age 7 years.

Arteriovenous Malformation Arteriovenous malformations are also called *cavernous hemangiomas.* These lesions are evident at birth and do not change during growth of the child. Occasionally, they involve deep structures such as the central nervous system or muscles. Nonetheless, wide excision is the treatment of choice. Occasionally, preoperative embolization of feeding vessels can assist wide excision.

Glomus Tumor Glomus tumor is a rare benign neoplasm of the skin that usually occurs in the nail beds of the hands and feet. These lesions are extremely painful because they are derived from the glomic end organ, a nerve apparatus that normally functions to reg-

ulate blood flow in the extremity. These lesions are also called *angiomyoneuroma* and generally are benign. The malignant counterpart to this tumor is called *hemangiopericytoma.*

Neural Tumors Neurofibromas and Schwann cell tumors can occur in the skin. Their treatment is surgical excision. Neurofibromas are associated with von Recklinghausen's disease. Approximately 10 percent of patients with neurofibromatosis will have sarcomatous degeneration of these tumors.

MALIGNANT TUMORS

Skin cancer is associated with exposure. Ultraviolet light, ionizing radiation, and chemicals are causative factors. Skin cancer usually is manifested by a low-grade malignant tumor that metastasizes late. Therefore, cure rates of carcinoma of the skin are high.

Basal Cell Carcinoma Basal cell carcinoma is a skin malignancy that grows slowly and accounts for at least three-fourths of cancers in most clinical series. These lesions are waxy and grayish yellow and often have telangiectasia below the surface. Most basal cell cancers are located on the head and neck. They tend to invade and erode into deep structures including the skull, orbit, and brain if left untreated.

Squamous Cell Carcinoma Squamous cell carcinoma usually presents as an ulcerated skin lesion that tends to grow more rapidly than basal cell cancer. Biopsy is necessary to differentiate this lesion from other types of skin cancer. Again, most occur on the head and neck. The typical appearance is an ulcer with rolled margins resembling a small volcanic crater. Squamous cell carcinoma is more aggressive than basal cell carcinoma and will metastasize to regional nodes more rapidly.

Squamous cell cancers are found in areas of frequent irritation such as the vermilion border of the lip, areas of postirradiation dermatitis, or ulcerations in old burn scars. Bowen's disease is a slowly growing squamous cell carcinoma in situ for which excision is recommended.

Sweat Gland Carcinoma This rare tumor usually occurs in the sixth and seventh decades of life. Therapy consists of wide local excision and consideration of lymphadenectomy. Regional lymph nodes will be involved in approximately 50 percent of patients.

TREATMENT

Options for treatment of skin cancer include electrodesiccation, cryosurgery, chemosurgery, radiation therapy, and surgical therapy. Biopsy of the skin lesion and relevant history determine the choice of therapy. Electrodesiccation and curettage are applicable for superficial, nonrecurrent basal cell carcinomas. Chemosurgery is described as the Mohs technique. The lesion is excised under local anesthesia, and frozen sections are taken of the entire surface of the resection. Four or five resections may be necessary to completely excise the lesion. The advantage of this method is the possibility of eradicating small extensions of the central lesion with greater certainty than conventional excision provides. This technique is particularly useful in recurrent basal cell or squamous cell carcinomas. Radiation therapy can be used to cure basal or squamous cell carcinomas. In some instances, a good result with less effort can be accomplished. Surgical therapy is conventional treatment for most skin cancers. Controversy continues regarding an adequate margin of normal tissue. Most physicians recommend 0.5-cm margins around basal cell carcinomas and 1-cm margins around squamous cell carcinomas. In recurrent lesions, frozen-section or permanent-section determination of tumor-free margins should precede definitive reconstruction. Regional lymph node dissection is performed only for clinical evidence of node involvement.

Approximately one-third of patients with positive margins after resection of basal cell carcinoma will develop recurrence. If the patient is reliable, simple observation may be all that is indicated. Repeat surgical excision is the best treatment for recurrence.

Eighty percent of squamous cell carcinomas are cured by surgical excision. Mohs has reported about a 95 percent cure rate for recurrent basal cell carcinoma and a 75 percent cure rate for recurrent squamous cell carcinoma.

Fibrosarcoma This tumor occurs commonly in women in the thigh, buttock, or inguinal region. It usually is a relatively low-grade malignancy and is radioresistant. Wide surgical excision is the treatment of choice. Local recurrence is common.

Hemangiopericytoma This is a malignant tumor of angioblastic origin and is probably a variant of the glomus tumor. Prognosis is distinctly poor, with only 27 percent 5-year disease-free survival. Radiation therapy is considered the treatment of choice, especially for larger tumors.

Kaposi's Sarcoma This tumor has a markedly increased incidence in homosexuals. Acquired immune-deficiency syndrome

(AIDS) is commonly associated with Kaposi's sarcoma. Usually, the tumor begins in the hands or feet as multiple plaques that are reddish to purple and may be flat, ulcerated, or polypoid. Lymph node involvement is common. Radiation can retard the growth of Kaposi's sarcoma, but surgical excision is also helpful. Actinomycin D has produced some positive responses. Overall, the prognosis is poor.

Dermatofibrosarcoma Protuberans This tumor is a relatively low-grade malignancy that generally occurs on the trunk. It is radioresistant but responds to surgical excision with a 70 percent 5-year disease-free survival.

PIGMENTED LESIONS

Intradermal nevus, junctional nevus, and compound nevus are examples of benign pigmented lesions; however, they have variable degrees of malignant potential. The intradermal nevus is a nest of melanoblasts confined to the dermis. Frequently, these nevi contain hair. The junctional nevus is a proliferation of melanoblasts that originates in the basal layer of the epidermis and extends down into the dermis. These lesions occur around the genitalia, palms, nail beds, and mucous membranes. The compound nevus has both junctional and intradermal elements. These lesions are benign but have some malignant potential. Juvenile melanomas are nevi that occur before puberty. Most occur in the face and enlarge slowly.

The differential diagnosis between benign pigmented skin lesions and melanoma can be difficult. Changes in various characteristics of pigmented lesions are indications for excision. These include change in color or pigment distribution, development of erythema, change in size or consistency, and change in the surface characteristic, such as oozing, bleeding, or erosion.

The Hutchinson freckle (lentigo maligna) is a precancerous melanosis of the face that usually occurs in elderly people. Approximately one-third of these lesions will become malignant melanoma. Prognosis is excellent, however, especially when the lesion is excised from the face. Any suspicious lesions should be excised completely with a margin of normal skin.

Melanoma

Melanoma is a malignant lesion originating in the melanoblast of the skin. Mucous membranes and pigmented regions of the eye also can harbor primary melanoma. The lesion is usually darkly pig-

mented, smooth, firm, and nonhairy. At some phases of development the melanoma cells do not contain melanin and are referred to as *amelanotic melanoma.*

TNM Classification for Staging of Melanoma The T classification refers to primary tumor thickness. T1 includes lesions 0.75 mm or less in thickness. T2 lesions are 0.76–1.5 mm thick. T3 indicates tumors that are 1.5–4.0 mm thick. T4 tumors are greater than 4.0 mm thick or invade the subcutaneous tissue. N0 designates regional lymph nodes negative for metastasis. N1 indicates positive regional lymph nodes 3 cm or less in size. N2 indicates positive regional lymph nodes greater than 3 cm in size or the presence of intransit lesions.

The stage grouping is divided by involvement of nodes. Stage I is smaller tumors (T1 and T2) with negative lymph nodes, Stage II is larger tumors (T3 and T4) with negative lymph nodes, Stage III is any tumor size with positive lymph nodes, and Stage IV is any tumor with positive distant metastases.

The incidence of melanoma is increased by exposure to solar radiation in light-skinned people. The presence of melanin in the skin has a protective effect against ultraviolet light acting as a stimulus. Melanoma is much more common in patients with xeroderma pigmentosum, a genetic disorder associated with hypersensitivity to ultraviolet light.

Pathology Melanomas usually arise in nevi that have junctional activity. Nevi of the palms, soles, nail beds, genitalia, and mucous membranes have functional elements that make them more prone to be the source of melanoma than moles at other sites. Malignant melanoma rarely occurs in prepubertal children.

Four types of melanoma are described: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Superficial spreading melanoma is characterized by intradermal spreading and accounts for almost 70 percent of all cutaneous melanomas. Nodular melanoma is less common and is characterized by little radial growth but more invasive growth. The prognosis for nodular melanoma is significantly worse. Lentigo maligna melanoma is the most indolent of all and occurs mostly in older individuals. Acral lentiginous melanoma occurs in the palms, soles, and subungual regions; its histology is similar to that of lentigo maligna melanoma.

Surgical Treatment Surgical excision is the primary therapy for melanoma. For most pigmented lesions, an excisional biopsy with a margin of 2–5 mm is indicated. However, extremely large lesions

may require an incisional biopsy, which is appropriate prior to planning definitive therapy.

The acceptable margins for definitive excision of melanomas depend on the thickness of the lesion. A margin of 0.5 cm is adequate for lesions less than 0.75 mm thick. Lesions between 0.76 and 1.5 mm thick require a 2-cm margin. Thicker lesions require a 4-cm margin. Amputation of a digit is indicated for acral lentiginous melanomas.

Removal of regional lymph nodes should be performed when there is clinical evidence of adenopathy and no distant metastases. Prophylactic dissection of regional lymph nodes is more controversial. The choice between a prophylactic lymph node dissection versus waiting for clinical evidence of node involvement may be based on the probability of occult lymph node metastases with a given stage of primary tumor. Sentinel node biopsy and lymphoscintigraphy aid in planning regional lymph node dissection. Tumors less than 1.5 mm have about a 15 percent association with positive lymph nodes. Thicker lesions between 1.6 and 3.7 mm have a 35 percent association with positive lymph nodes. Tumors thicker than 3.7 mm have a 50 percent association with positive lymph nodes.

Some retrospective studies show a survival advantage for immediate lymph node dissection of clinical Stage I melanoma. A prospective, randomized study by the World Health Organization, however, showed no survival improvement for patients in this category. A prospective, multi-institutional trial is proceeding in North America to confirm or refute these results. Nonetheless, immediate lymph node dissection should be used when the melanoma originates in the skin covering a lymph node basin because the changes after excision of the primary tumor may complicate the clinical evaluation of lymph nodes.

Adjunctive Treatment *Regional Chemotherapy and Hyperthermia* Isolated regional perfusion has been tested for melanoma. The involved extremity is perfused with a solution at approximately 40°C. The chemotherapeutic agent most commonly used is melphalan. This therapy is probably beneficial only in those patients whose primary tumor is thicker than 3.7 mm. Also, patients with numerous satellite and transit metastases may benefit from isolated regional perfusion.

Immunotherapy A number of agents have temporarily controlled cutaneous metastases of melanoma. Local intralesional injections of bacille Calmette-Guérin provided remission in approximately 20 percent of patients in one study. Systemic treatment with biologic

response modifiers has begun to show some impact on disseminated melanoma. Interferon has proved to be effective in a small percentage of patients.

Prognosis Prognosis for patients with melanoma depends on the staging. The 5-year cure rate for Stage I lesions smaller than 0.76 mm is almost 95 percent. Lesions between 0.76 and 1.5 mm have an 85 percent 5-year cure rate. Stage II lesions are less favorable, with a 60 percent 5-year survival rate. Patients who are Stage III (positive lymph node involvement) have approximately 35 percent 5-year survival.

For a more detailed discussion, see Young DM, Mathes SJ: Skin and Subcutaneous Tissue, chap. 13 in *Principles of Surgery,* 7th ed.

CHAPTER

14

BREAST

EMBRYOLOGY

In the sixth week of gestation, a mammary ridge, or "milk line," appears in the embryo as an ectodermal thickening from each axilla to the groin. These ridges disappear except for a small area in the pectoral region. Anomalous persistence is often mistaken for nevi, and the aberrant breast tissue in the axilla or in the milk line may become prominent during pregnancy. The breast starts as an ingrowth of ectoderm as a primary "bud" with 15–20 secondary buds. These canalize in the last 2 months of gestation. In both newborn females and males, there is a transient breast enlargement secondary to increased levels of hormones crossed over from the maternal circulation. Several developmental abnormalities are noted, particularly in females, e.g., polymastia, polythelia, and accessory or ectopic mammary tissue.

ANATOMY

Except for mild hypertrophy during the neonatal period and puberty, the male breast undergoes little change throughout life. In females, the prepubertal "bud" develops from 11–15 years, and lobulation occurs after the first ovulation.

The adult female breast extends from the second to the sixth rib and from the sternal border to the anterior or midaxillary line. The glandular tissue base is circular in outline except for an extension to the axilla (tail of Spence). Cooper's ligaments help to suspend the glandular tissue from the deep layer of superficial fascia to the anterior superficial fascia immediately under the skin. The subareolar area and nipple contain smooth muscle that contracts with tactile or thermal stimulation.

Arterial Supply The breast is perfused by (1) perforating branches of the internal mammary artery (first through fourth interspaces) medially, (2) the lateral and highest thoracic arteries,

pectoral branches of the acromiothoracic artery, and (3) lateral branches of the posterior intercostal arteries.

Venous Drainage Superficial subcutaneous veins drain into the internal mammary or neck veins; deep veins correspond with the arterial supply. Mammary cancer may metastasize to vertebral bodies or the pelvis, bypassing the lungs because of intercostal drainage to vertebral veins (Batson's plexus).

Lymphatic Drainage Even though there is some variation, six anatomic groups are identified, i.e., the lateral (axillary vein), external mammary, scapular, central, subclavicular, and interpectoral (Rotter) groups. Assigned "levels" refer to their relation to the pectoralis minor. Level I (lateral to pectoralis minor) includes the external mammary axillary vein and subscapular groups. Level II (deep to pectoralis minor) includes the central group. Level III (medially or above) includes the subclavicular nodes. Collected lymph drains into the thoracic duct before entering the venous system. About 75 percent of lymph from the breast passes through the axillary nodes, whereas the rest of it passes through the parasternal nodes. The medial part of breast also drains into the internal mammary (intrathoracic) set of nodes. The average number of lymph nodes harvested surgically is about 20 in axillary dissection.

HISTOLOGY

The breast is composed of 15–20 tubuloalveolar glands. They terminate into lactiferous ducts lined by columnar epithelium. A milk sinus in the subareolar region is lined by squamous epithelium and opens into the ampulla of the nipple.

PHYSIOLOGY

Development and function of the breast are initiated by various hormones but predominantly by estrogen, progesterone, and prolactin. Estrogen is known to stimulate development of the breast ducts. Progesterone initiates development of breast lobules as well as differentiation of epithelial cells. Prolactin stimulates lactogenesis in late pregnancy and the postpartum period.

Cyclic Change Breast volume is greatest in the second half of the menstrual cycle. Vascular congestion and lobular proliferation regress with menses.

Pregnancy and Lactation Alveoli and lobules proliferate as the ducts branch. The nipple and areola darken, and Montgomery's glands (of the areola) become prominent. Oxytocin and a suckling-induced surge of prolactin promote production and ejection of milk.

Menopause With decline in ovarian estrogen and progesterone, the lobules and ducts involute, and the volume is replaced by fat. This change renders the breast more amenable for diagnostic mammography in older women.

GYNECOMASTIA

Gynecomastia implies enlargement of male mammary tissue. Physiologic gynecomastia may be seen in the neonatal period, in adolescence, or in old age and almost always as a result of excess estrogens in relation to circulating testosterone. Generally, at least 2 cm of subareolar breast tissue must be present for the diagnosis of gynecomastia. Glandular and ductal structures enlarge, along with enlargement of stromal elements. Androgen deficiency in, for example, orchitis or testicular failure or estrogen excess as a result of testicular or nontesticular tumors may be associated with gynecomastia. Rarely, thyroid dysfunction, alcoholism, or drugs may induce similar change. Pubertal gynecomastia is generally unilateral, whereas senescent gynecomastia is bilateral.

Treatment Medical treatment is rarely successful. Biopsy may be necessary to confirm the diagnosis. Large, progressive gynecomastia may require subcutaneous mastectomy through a circumareolar incision.

DIAGNOSIS OF BREAST DISEASE

Presentation A lump, nipple discharge, pain, a change in contour, skin ulceration, and asymmetry are the usual features that make the patient seek medical consultation. Clinical history is important.

Clinical Examination *Inspection* Asymmetry, skin retraction, edema (peau d'orange), nipple inversion, and erosion are more easily detected with the patient seated, hands on hips and then elevated overhead.

Palpation With patient seated erect, supraclavicular and axillary fossae are examined, including the tail of Spence and central breast tissue. The entire breast is reexamined with the patient supine and arms overhead. The lateral part of the breast is examined with slight elevation of the ipsilateral side by a pillow. Features of importance of a lump or lymph node are its size, shape, mobility, consistency, and location, and these should be recorded on an outline diagram.

Workup Subsequent to clinical examination, the workup proceeds in an orderly progression (Table 14-1).

TABLE 14-1
PATHOPHYSIOLOGIC MECHANISMS OF GYNECOMASTIA

I. Estrogen excess states
   A. Gonadal origin
      1. True hermaphroditism
      2. Gonadal stromal (nongerminal) neoplasms of the testis
         a. Leydig cell (interstitial)
         b. Sertoli cell
         c. Granulosa-theca
      3. Germ cell tumors
         a. Choriocarcinoma
         b. Seminoma, teratoma
         c. Embryonal carcinoma
   B. Nontesticular tumors
      1. Skin—nevus
      2. Adrenal cortical neoplasms
      3. Lung carcinoma
      4. Hepatocellular carcinoma
   C. Endocrine disorders
   D. Diseases of the liver—nonalcoholic and alcoholic cirrhosis
   E. Nutrition alteration states
II. Androgen deficiency states
   A. Senescent causes with aging
   B. Hypoandrogen states (hypogonadism)
      1. Primary testicular failure
         a. Klinefelter syndrome (XXY)
         b. Reifenstein syndrome (XY)
         c. Rosewater, Gwinup, Hamwi familial gynecomastia (XY)

d. Kallmann syndrome
e. Kennedy disease with associated gynecomastia
f. Eunuchoidal males (congenital anorchia)
g. Hereditary defects of androgen biosynthesis
h. ACTH deficiency

2. Secondary testicular failure
a. Trauma
b. Orchitis
c. Cryptorchidism
d. Irradiation
e. Hydrocele
f. Varicocele
g. Spermatocele

C. Renal failure

III. Drug-related conditions that initiate gynecomastia
IV. Systemic diseases with idiopathic mechanisms
A. Nonneoplastic diseases of the lung
B. Trauma (chest wall)
C. CNS-related causes from anxiety and stress
D. AIDS (acquired immune deficiency syndrome)

Imaging Studies

Mammography Used in North America since 1960, mammography has been refined in equipment and skilled interpretation. It delivers about 0.1 cGy of radiation per study. Mammography complements the clinical examination and history and enhances the diagnostic accuracy of breast diseases. It is generally indicated for screening in older women, for evaluation of a palpable mass, for follow-up examination after segmental mastectomy, or for evaluation of breasts that are difficult to examine clinically. It is therefore an important tool for early detection of (nonpalpable) occult cancer (<5 mm diameter) or multicentricity of disease. The presence of a clustered microcalcific, stellate density, a mass with irregular margins, skin thickening/retraction, or asymmetry may be suggestive of cancer. Screening mammography reduced the incidence of mortality by 33 percent in the Health Insurance Plan (HIP) study. Mammograms detected cancers early enough to be node negative in 80 percent of patients as compared with 50 percent detected only on clinical examination. The false-positive rate was 11 percent, and

the false-negative rate was 6 percent. Current guidelines of the American Cancer Society recommend a "baseline" mammogram at 35 years of age and annual mammograms after 50 years of age. Between 40 and 50 years of age the patient should consult her physician. In a woman whose mother has a positive history of cancer, the screening is recommended 10 years earlier than the age of mother at the time of her diagnosis. Stereotactically guided and needle localization techniques of biopsy are used to obtain a tissue diagnosis in nonpalpable lesions. Ultrasonography is helpful in distinguishing solid from cystic lesions. Cyst aspiration or biopsy can be performed under ultrasound guidance. Ultrasound is not recommended as a screening tool, however. Doppler flow studies, light scanning, and thermography lack diagnostic sensitivity. Magnetic resonance imaging (MRI) has proved questionable thus far in routine use. Isotope scans (sestamibi, mira luma) using technetium-99m has shown very limited promise. Ductography (galactography), i.e., injection of radiopaque contrast material into mammary ducts, is performed in patients with spontaneous, persistent nipple discharge to identify intraductal pathology (papillomas) and, rarely, communicating cysts.

Biopsy/Fine-Needle Aspiration Tissue diagnosis is mandatory prior to initiation of definitive treatment. Palpable lesions can be aspirated easily with a fine needle (FNA) for cytologic diagnosis. FNA is reliable in 80–90 percent of patients. Correlation of clinical examination, mammogram, and cytology ("triple diagnosis") enhances the accuracy to 95 percent. Core biopsy with a Tru-Cut needle, like the incisional/excisional biopsy, has higher diagnostic accuracy. Palpable cysts are treated by simple aspiration. *Nonpalpable* lesions generally suspected on mammography can be diagnosed with the help of stereotactic core biopsy or excised after a radiographically aided wire localization. Biopsy incisions should be made with cosmetic and subsequent surgical needs in view. Tissue is submitted for histology, hormone receptors, flow cytometry, and c-erbB-2 analysis if so desired. Staging workup is generally done before the definitive procedure.

INFLAMMATORY AND INFECTIOUS DISORDERS

Bacterial Infections *Staphylococcus* and *Streptococcus* are the most common organisms in breast abscesses. They are typically related to and seen in the first few weeks of lactation. Streptococcal

infections generally are diffuse and associated with cellulitis and lymphangitis, whereas staphylococcal infections are more localized, with formation of an abscess or abscesses. Treatment with antibiotics, drainage, and local care generally is adequate. Puerperal mastitis is more serious when it is hospital acquired in contrast to the sporadic type. It requires antibiotic therapy in addition to local care with a breast suction pump and usually a transient interruption of breast-feeding.

Recurrent Periareolar Abscess Recurrent periareolar abscess generally is due to obstruction of the milk sinus as a result of squamous metaplasia of a lactiferous duct (SMOLD). Resection of the involved duct is indicated to prevent recurrence.

Hydradenitis Suppurative Hydradenitis suppurativa of areolar or axillary sebaceous glands may present as chronic or recurrent cutaneous abscesses—requiring excision of the involved skin.

Mondor's Disease Mondor's disease is a cordlike tender area of skin with linear indentation due to thrombophlebitis of the thoracoepigastric or lateral thoracic vein ("string thrombosis"). Only symptomatic treatment is needed because the process resolves spontaneously in about 6 weeks.

BENIGN LESIONS

After years of nomenclature controversies, Page and associates recommend that benign breast lesions be assigned to one of the three categories: (1) nonproliferative, (2) proliferative without atypia, and (3) proliferative with atypia. However, there are other benign lesions, such as adenomas and fibroadenomas.

Nonproliferative Lesions Nonproliferative lesions include fibrocystic change and microcalcifications related to epithelial changes. About 70 percent of biopsy specimens show these changes.

Proliferative Lesions without Atypia This category includes sclerosing adenosis, moderate hyperplasia, and intraductal papillomas. About 25 percent of biopsy tissues show these changes.

Proliferative Lesions with Atypia This category includes lobular and ductal lesions showing evidence of atypia in their nuclear morphology. These are generally confused with carcinoma in situ.

The lesions have a higher risk of malignancy (4–5 times), especially in patients with a positive family history. Only 4 percent of biopsy specimens show these changes.

Fibrocystic Disease Better termed as *fibrocystic mastopathy* (or *fibrocystic disorder*), fibrocystic disease presents clinically as painful, irregular, and firm nodularities of the breast. It is generally more symptomatic in the second half of the menstrual cycle. Management includes restriction of caffeine and sometimes diuretics after basic clinical evaluation and, if necessary, mammography. Aspiration cytology and sometimes open biopsy may be required in suspicious lesions to rule out concomitant malignancy. Treatment with danazol (a synthetic androgen analogue) may become necessary in extremely symptomatic patients.

Cysts Cysts are areas of fluid accumulation varying in size from 1 mm to several centimeters. These are simply treated by aspiration. Excision or biopsy is indicated if the aspirate is bloody or a residual mass persists after aspiration.

Fibroadenoma Fibroadenoma presents as a firm, rubbery, painless, mobile, well-circumscribed mass, usually in younger women in the second or third decade of life. Fibroadenomas are slightly more common in African-Americans than in Caucasians. FNA is helpful in diagnosis. While excision is commonly recommended as the treatment of choice, some workers favor observing these lesions in patients under 25 years of age with benign cytology. Sclerosing adenosis is often an incidental finding but sometimes presents as a palpable mass. Occasionally, these lesions show calcifications on the mammogram.

Radial Scar Detected as a distorted fibrous density with microcalcifications on mammography, a radial scar often mimics malignancy. It usually requires biopsy to confirm the diagnosis.

Fat Necrosis Fat necrosis generally presents as a firm mass—sometimes with a preceding history of local trauma. In later stages of evolution, fat necrosis may present as an "oil cyst"—clearly distinguishable on mammography as a lucent area.

Papilloma Intraductal papilloma usually presents as spontaneous, unilateral, serosanguineus or bloody nipple discharge. Papillomas have tendency for development of carcinoma. About a third of patients with bloody nipple discharge have papilloma, and 20 percent have carcinoma. Sequential radial compression and ductography

generally help to identify the involved duct, and excision is easily accomplished with a circumareolar incision.

Phyllodes Tumor This tumor presents as a large, bulky mass, sometimes mistaken for a large fibroadenoma. It is important to distinguish the common benign phyllodes tumor from its malignant variant. Treatment is controversial and varies from wide local excision to simple mastectomy.

CARCINOMA OF THE BREAST

Incidence Carcinoma of the breast is the most common malignant neoplasm in women, with a steady increase in incidence since 1940. The risk of breast cancer quickly surges during the childbearing age (25–40 years) with a slower rise thereafter. In the 1970s, the probability of a woman developing breast cancer in the United States was 1 in 13; in 1980, 1 in 11; and in 1996, 1 in 8. Fortunately, however, in 1998, the trend seems to have plateaued. Even though the incidence in African-American women is lower, the 5-year survival rate is higher in white women—78 percent compared with 63 percent in blacks. This difference is generally attributed to earlier diagnosis in white women. Worldwide, England and Wales have the highest mortality from breast cancer (27 per 100,000 population) compared with the United States (22 per 100,000). South Korea has the lowest incidence of breast cancer (2.6 per 100,000).

Etiology Female gender itself is a predisposing factor, since only 1 percent of breast cancers occur in males.

Genetic Factors Henderson and Lynch have documented heredity and genetic predisposition for breast carcinoma and have suggested three categories: sporadic, familial, and hereditary breast cancers depending on the degree of familial association. Among these, 68 percent of cancers were sporadic, 23 percent were familial, and 9 percent were hereditary. Biomarkers such as BRCA1 and BRCA2, recently mapped to chromosomes 17 and 13, respectively, may indicate a woman's susceptibility to breast cancer.

Hormone Use While most studies indicate no increased incidence of breast cancer with the use of oral contraceptives, Lipnick and colleagues noted some adverse effect if oral contraceptives were taken at an early age or before the first full-term pregnancy. Also, hormone replacement therapy in perimenopausal and

postmenopausal women may slightly increase the risk of breast cancer. Obesity and a history of irradiation to the breast area also may increase the risk of breast cancer.

Breast-Feeding and Menopause The validity of the protective role of breast-feeding now is under question. Later menopause is associated with a higher risk of breast cancer, presumably due to more years of exposure to estrogens.

Infertility/Nulliparity Infertility and nulliparity are associated with a higher incidence of breast cancer, as is a first pregnancy later than 35 years of age. Physical exercise has a protective effect.

Natural History The natural history of breast cancer is cited in studies from the late 1800s at London's Middlesex Hospital, where median survival for 250 untreated patients was 2.7 years; survival was calculated from the description of onset of the first symptoms. Five-year survival was 18 percent, and 10-year survival 3.76 percent. Autopsies showed that 95 percent of the women died of breast carcinoma, and 75 percent had breast ulceration at death.

Biology of Breast Cancer A typical scirrhous adenocarcinoma begins in the upper outer quadrant (45 percent) of the left breast (60 percent) and takes 30 doublings from the one-cell stage over 5–8 years to reach a palpable size (1 cm in diameter). Metastasis may begin when the tumor is greater than 0.5 cm in diameter, and prognosis is adversely affected by the increasing number of axillary lymph nodes involved. As the tumor progresses, fibrosis shortens Cooper's ligament with characteristic skin dimpling. Systemic spread is most common to bone (49–60 percent), lung (15–20 percent), and liver (5–15 percent). In general, 10–30 percent of recurrences are local, 60–70 percent are distant, and 10–30 percent are both (local and distant). Sixty percent of patients who develop metastatic disease do so within 24 months of the initial definitive treatment.

Staging of Breast Cancer

Staging provides an overall perspective of the disease as it relates to prognosis. It includes data on the status of potential sites of regional metastases (lymph nodes) and distant sites (lungs, bones, liver, etc.). Besides tumor size and lymph node metastases, the absolute number of lymph nodes involved is extremely significant. Node-negative status is associated with only 20 percent treatment failure in 10 years, as compared with 71 percent failure in patients

with more than four positive nodes. Sentinel node biopsy following lymphatic mapping (with dye or radioisotope) as an alternative to axillary dissection is still under clinical investigation.

- Bone scan, computed tomography (CT), and magnetic resonance imaging (MRI) as staging tools are used commonly, even though they have poor specificity.
- Hormone receptors, flow cytometry, genetic information, c-erbB-2 oncogene evaluation, and other biologic parameters are profiled in clinical practice not only for prognostic and staging purposes but also for therapeutic planning.

Among the three staging systems available, the one modified by the American Joint Committee on Cancer (AJCC) based on TNM is followed (Table 14-2).

TABLE 14-2
MANUAL FOR STAGING OF CANCER*

HISTOPATHOLOGIC TYPE
The histologic types are as follows:
Carcinoma, NOS (not otherwise specified)
Ductal
  Intraductal (*in situ*)
  Invasive with predominant intraductal component
  Invasive, NOS
  Comedo
  Inflammatory
  Medullary with lymphocytic infiltrate
  Mucinous (colloid)
  Papillary
  Scirrhous
  Tubular
  Other
Lobular
  In situ
  Invasive with predominant *in situ* component
  Invasive
Nipple
  Paget's disease, NOS
  Paget's disease with intraductal carcinoma
  Paget's disease with invasive ductal carcinoma
  Other
  Undifferentiated carcinoma

TABLE 14-2 (continued)

HISTOPATHOLOGIC GRADE (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic, are used, the examiner can use the telescoped subsets of T1.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*: intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumor
T1 Tumor 2 cm or less in greatest dimension
  T1a 0.5 cm or less in greatest dimension
  T1b More than 0.5 cm but not more than 1 cm in greatest dimension
  T1c More than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to chest wall or skin
  T4a Extension to chest wall
  T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
  T4c Both (T4a and T4b)
  T4d Inflammatory carcinoma (See the definition of inflammatory carcinoma in the introduction.)

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary lymph node(s)
N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3 Metastasis to ipsilateral internal mammary lymph node(s)

Pathologic Classification (pN)

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0 No regional lymph node metastasis
pN1 Metastasis to movable ipsilateral axillary lymph node(s)
- pN1a Only micrometastasis (none larger than 0.2 cm)
- pN1b Metastasis to lymph node(s), any larger than 0.2 cm
  - pN1bi Metastasis in one to three lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
  - pN1bii Metastasis to four or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
  - pN1biii Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
  - pN1biv Metastasis to a lymph node 2 cm or more in greatest dimension

pN2 Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
pN3 Metastasis to ipsilateral internal mammary lymph node(s)

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node(s))

TABLE 14-2 (continued)

STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1*	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Note*: The prognosis of patients with N1a is similar to that of patients with pN0.

*SOURCE: Beahrs OH, Henson DE, et al: *Manual for Staging of Cancer,* 4th ed., American Joint Committee on Cancer. Philadelphia, JB Lippincott, pp 151–152, with permission.

Histopathology/Epidemiology

Carcinomas of ductal origin are most frequent and comprise about 80 percent of all breast cancers. The noninfiltrating (in situ) cancers do not invade beyond the investing basement membrane. The ductal or lobular in situ carcinoma (DCIS or LCIS), therefore, is unlikely to metastasize and carries a favorable prognosis. With progression, invasion beyond the basement membrane (as in infiltrating cancer) renders the lymphatics vulnerable, and thus nodal and distant metastases become a possibility. The original classification of breast malignancies proposed by Foote and Stevens is as follows:

I. Paget's disease
II. Carcinomas of ductal origin
    A. Noninfiltrating (DCIS)
    B. Infiltrating (scirrhous, medullary, colloid, papillary, etc.)

III. Carcinoma of mammary lobules
  A. Noninfiltrating (LCIS)
  B. Infiltrating (infiltrating lobular)
IV. Rare carcinomas
V. Sarcomas

Noninfiltrating Malignancies

Ductal Carcinoma in Situ (DCIS) Increased use of mammography has enabled early detection of cancer and a considerable rise in its percentage as noninvasive type. In the earlier literature, the incidence of DCIS was 1.4 percent among all biopsies, but recent series show an increase to 7 percent of all breast biopsies and nearly 30 percent of the nonpalpable malignancies. Histologically, four different patterns were identified: cribriform, solid, micropapillary, and comedo. The newer classification suggests division into three categories: (1) noncomedo without necrosis, (2) noncomedo with necrosis, and (3) comedo. Comedo is considered to be the most biologically aggressive, with a higher incidence of multicentricity and recurrence.

Lobular Carcinoma in Situ (LCIS) Ninety percent of LCIS lesions occur in premenopausal women, and these lesions are 12 times more common in white women than in African-American women. There is a significant rate of bilaterality. Both DCIS and LCIS can be multicentric, the latter having a higher incidence than DCIS. *Multifocality* refers to occult malignancy in the same quadrant as the index lesion, whereas *multicentricity* refers to the presence of disease in a different quadrant. About 10–30 percent of LCIS patients will develop subsequent invasive carcinoma 15–20 years later.

Infiltrating Malignancies

Infiltrating Ductal Carcinoma This is the most common form of breast cancer (78 percent), typically characterized by productive fibrosis (scirrhous) changes. It is usually seen in the perimenopausal age group as a firm, poorly defined, painless mass. Further progression and infiltration by the tumor cause Cooper's ligaments to shorten, resulting in dimpling of the overlying skin. A generic term used for this type of tumor is *invasive duct carcinoma not otherwise specified* (NOS). More specific duct carcinomas are medullary, papillary, tubular, colloid, and others that show specific histologic features with possible differences in their progress.

Medullary Carcinomas Medullary carcinomas represent 2–15 percent of invasive cancers. They are usually large, bulky, and hemorrhagic. There is lymphocytic infiltrate accompanied by active mitosis. About 40 percent have axillary lymph node metastases.

Mucinous Carcinoma (Colloid Carcinoma) This ductal cancer constitutes about 2 percent of breast cancers. The tumor is bulky and gelatinous. Five-year survival is 73 percent.

Tubular Carcinoma Tubular carcinoma is easily diagnosed mammographically and generally in the perimenopausal age. It has excellent survival.

Papillary Carcinoma Papillary carcinoma is generally seen in older women (seventh decade) and more commonly in non-Caucasians. The tumor is well circumscribed and has a lower incidence of axillary nodal involvement. It has the best 5-and 10-year survival rates.

Inflammatory Carcinoma Inflammatory carcinoma represents a type of aggressive, rapidly advancing ductal carcinoma with clinical features of inflammation. Erythema, peau d'orange, and skin ridging generally are mistaken for infection. Usually it lacks elements of pain and fever. This carcinoma generally involves the dermal lymphatics, and about 75 percent of patients have palpable axillary metastases. Five-year survival is dismal.

Paget's Disease of the Nipple Paget's disease of the nipple generally presents as a chronic nonhealing eczematoid excoriation of the nipple. It is almost always associated with underlying intraductal or invasive carcinoma. Microscopically, the tumor consists of large, pale, vacuolated cells (Paget's cells). Prognosis is better than that for the average ductal carcinoma.

Infiltrating Lobular Carcinoma This carcinoma originates in terminal ductules of the lobule and has features different from ductal cancers. Infiltrating lobular carcinoma constitutes about 10 percent of breast cancers. It has a high incidence of bilaterality, multicentricity, and multifocality.

Sarcomas Sarcomas of the breast are generally heterogeneous. These include fibrosarcoma, liposarcoma, and leiomyosarcoma and present as large, painless breast masses. Some sarcomas are well circumscribed, whereas others have infiltrative, ill-defined margins.

Angiosarcoma Angiosarcoma develops generally in an irradiated upper extremity or chest wall. Prognosis is extremely poor, and 5-year survival is rare.

Treatment

Surgical Treatment Halsted in 1882 performed his first radical mastectomy—even though he did not report it until 1890–1891. This refined the concept originally advanced by Jean Louis Petit (1674–1750). It entailed removal of the breast, both pectoralis major and minor, and the axillary lymph nodes to establish local-regional control. Patient selection is considered important, and not all patients are suitable for curative surgical intervention. The *criteria of inoperability* include patients with near certainty of developing distant metastases—e.g., tumor fixity to chest wall, fixity of axillary nodes, inflammatory breast carcinoma, satellite nodules, supraclavicular nodes, and arm edema. Halsted's criteria excluded 25 percent of patients from surgical therapy. At present, about 10 percent of patients exhibit these criteria, and most of them (80 percent) are reverted successfully ("downstaged") to operable status with chemotherapy and radiotherapy (neoadjuvant treatment).

Modifications of (Halsted's) radical mastectomy include preservation of the pectoralis major (Patey), preservation of both muscles (Madden), and extention of the Halsted mastectomy to include the internal mammary lymph nodes and adjacent chest wall (Urban).

Breast-conservation surgery implies limiting the amount of resected volume of breast tissue with the tumor and still trying to achieve as effective a local control as with mastectomy. Lumpectomy, segmental resection, and quadrantectomy (with or without axillary node dissection) in combination with radiation therapy are the options available. In 1980, Veronesi reported similar survival and recurrence rates in patients with tumors 2 cm in size or smaller with palpable axillary nodes whether they underwent radical mastectomy or quadrantectomy with axillary node dissection and radiation therapy (QU.A.R.T.). In 1985, the National Surgical Adjuvant Breast Project (NSABP) study was reported by Fisher. It compared modified radical mastectomy with segmental resection, axillary dissection, and radiation therapy in patients with tumors 4 cm in size or smaller. Survival and local recurrence rates were equal. In another group of patients in whom radiation was omitted, a high local recurrence rate was noted (24 percent in node-negative and 36 percent in node-positive patients). This clearly showed the benefit of radiation in breast conservation. Criteria for breast conservation generally include (1) small tumor size

(< 4 cm), (2) clinically negative axilla, (3) adequate breast volume, and (4) an experienced radiation therapist. It is important to achieve complete removal of cancer before the breast-conservation protocol is recommended.

PATIENT SELECTION

Multimodal therapy in the last 30 years has enhanced the local-regional control of advanced primary breast tumors. Surgical and radiation objectives are directed at local-regional pathology, while the medical oncologist aims to control systemic disease.

TREATMENT OF EARLY BREAST CANCER/IN SITU DISEASE

Ductal Carcinoma in Situ (DCIS) Even though total mastectomy offers almost 98 percent disease-free survival, less aggressive and limited resections and radiation in smaller tumors resulted in a 5-year recurrence rate of only 7.5 percent (NSABP, protocol 17). Combined data from 14 studies in 1098 women with DCIS treated with conservative surgery and radiation showed recurrence in 9.1 percent of patients—40 percent of these recurrent lesions were invasive. With controversial outcomes of conservative treatment, caution is warranted because safety and efficacy of limited surgery for DCIS are less certain. Postoperative radiation therapy is recommended, but the role of cytotoxic chemotherapy is questionable. Formal axillary node dissection is not warranted because the yield is less than 2 percent.

Lobular Carcinoma in Situ (LCIS) LCIS is a precursor of invasive cancer. Because the disease is usually diffuse and sometimes bilateral, local wide excision is not very beneficial. Since there is 5 percent risk of associated invasive cancer with multicentricity, operative therapy, e.g., total mastectomy, may be considered. Treatment of LCIS is still somewhat controversial.

TREATMENT OF STAGE I AND STAGE II BREAST CANCER

In the United States, partial mastectomy with radiation has gained popularity from 3.4 percent in 1972 to 25 percent in 1990. Modified radical mastectomy still is the most common procedure for breast cancer and more recently has been combined with immediate reconstruction. The recurrence rate at 5 years is similar in both groups, but 10-year disease-free survival is better with the more radical operation. Axillary dissection should be performed to adequately stage the disease. Mastectomy is preferred over segmental resection in patients with central (subareolar) lesions, extensive multicentric disease, large medial lesions (with potential for significant deformity after conservation), recurrent breast lesions who

had been irradiated previously, or a contraindication to radiation (e.g., pulmonary or cutaneous pathology). In patients with extensive DCIS and some degree of invasion, there is 10 percent increased risk of recurrence when treated with local excision and radiation. In this subgroup, mastectomy is therefore preferable. Operative mortality with either treatment is less than 1 percent. Morbidity includes seroma, lymphedema, and some degree of sensory deficit in the axillary region.

Breast Reconstruction Immediate reconstruction at the time of mastectomy with autogenous tissue, e.g., a transverse rectus abdominis mycoutaneous (TRAM) flap or a latissimus dorsi flap, is becoming increasingly popular and is showing better success in achieving satisfactory cosmetic results. Use of a prosthesis should be deferred when chest wall irradiation is planned. A major drawback to reconstruction is delay in recognition of local recurrence.

Future Trends International trends favor less radical procedures and refining patient selection suitable for breast conservation *without* radiation and liberal use of systemic adjuvant therapy. The role of axillary lymph node dissection is under review, and limiting it to sentinel node biopsy may evolve as an acceptable procedure with less morbidity.

TREATMENT OF ADVANCED LOCAL DISEASE (STAGE III AND INFLAMMATORY CARCINOMA)

Combination chemotherapy (CAF—cyclophosphamide, Adriamycin, and 5-fluorouracil) induces regression of breast lesions. Following two to six drug cycles, an extended simple mastectomy can be performed. Subsequent to this, radiation therapy is used. This regimen yields about 30 percent 5-year survival.

TREATMENT OF RECURRENT AND METASTATIC DISEASE (STAGE IV)

Local recurrence may be treated by excision. Regional recurrence or localized osseous metastases may benefit from radiation therapy. Treatment is palliative. Metastatic disease generally is treated with polychemotherapy, indicating an improved response rate from 25 to 50–60 percent, and the median duration of response ranges from 12–18 months. Stage IV patients who achieve complete remission have a median survival of 32 months. Ablation (oophorectomy or adrenalectomy), additive therapy (high-dose estrogen or progesterone), antiestrogens (Tamoxifen), and antiadrenal agents (aminoglutethimide) have the same response (60 percent). Tamoxifen has the fewest side effects (hot flashes and mild cytopenia) and is the

therapy of choice in patients with estrogen receptor (ER)–positive tumors.

ADJUVANT THERAPY

Node-Positive Breast Cancer The use of adjuvant therapy is predicated on the clinical data that cytotoxic therapy and hormonal therapy in patients with axillary metastases and no distant metastases prolong the disease-free interval and enhance survival rates. In patients with distant disease, polychemotherapy combinations of either cyclophosphamide (Cytoxan), methotrexate, and 5-fluorouracil (CMF) or that of cyclophosphamide, doxorubicin (Adriamycin), and 5-fluorouracil (CAF) are used most commonly. Prednisone or vincristine is sometimes added to the regimen. Variation in response is largely due to heterogeneity of the cell population of the tumor. Hormone receptors commonly studied are estrogen receptor (ER) and progesterone receptor (PR) proteins that bind and transfer steroid moiety into the cell nucleus. About 30 percent of premenopausal and 60 percent of postmenopausal women have ER-positive activity, and clinical response to antiestrogenic drugs correlates with the degree of ER/PR activity. Primary and metastatic tumors usually respond equally. Pre- and perimenopausal node-positive patients usually receive a 6-month course of CMF. Postmenopausal node-positive and ER-positive patients benefit from Tamoxifen, whereas ER-negative patients may receive chemotherapy (Table 14-3).

Node-Negative Breast Cancer Data suggest that (1) the majority of node-negative patients are cured by breast conservation or mastectomy and axillary node dissection and (2) recurrence is decreased by both chemotherapy and Tamoxifen. Poor response is usually expected in patients with lymphatic or vascular permeation, ER negativity, poor nuclear grade, high aneuploidy, and large tumor size.

Adjuvant radiation is used postoperatively in combination with breast-conserving surgery or in patients at high risk for local recurrence, e.g., chest wall fixity of tumor or with more than four positive nodes.

Prognosis

- Stage I breast cancer 5-year survival approaches more than 85 percent, and for Stage II, the figure is 66 percent.
- Stage III survival has improved with adjuvant therapy to about 40 percent.
- Stage IV crude 5-year survival approaches about 10 percent.

TABLE 14-3
PROPOSED THERAPEUTIC OPTIONS AND FREQUENCY OF STEROID RECEPTORS FOR PREMENOPAUSAL AND POSTMENOPAUSAL PATIENTS WITH BREAST CANCER

	Premenopausal		Postmenopausal	
Receptor Status	No. (%)	Proposed Therapy	No. (%)	Proposed Therapy
ER + /PR +	222 (45)	O,A,H,T T + CT Horm	520 (63)	T,A,H,CT Horm
ER + /PR −	58 (12)	O,A,H T⟶T + CT Horm	128 (15)	T,A,H T + CT Horm
ER − /PR −	136 (28)	CT	137 (17)	CT
ER − /PR +	72 (15)	O,A,H,T ?T + CT ?Horm	41 (5)	CT,T + CT Horm

O = oophorectomy; T = tamoxifen; A = adrenalectomy; H = hypophysectomy; ER = estrogen receptor; PR = progesterone receptor; Horm = hormonal (estrogen, progesterone, androgen); CT = cytotoxic chemotherapy; + = ≥ 10 fmol/mg cytosol protein; − = < 10 fmol/mg cytosol protein.

SOURCE: Adapted from Bland KI et al: Menopausal status as a factor in the distribution of estrogen and progestin receptors in breast cancer. *Surg Forum* 32:410, 1981, with permission.

NEWER TREATMENT MODALITIES

Trials of normal autologous bone marrow transplantation allowing high-dose chemotherapy has shown limited success. New biologic approaches targeted to inhibit angiogenesis (with angiostatin and endostatin) and growth factor receptor HER-2/neu (with herceptin) are being introduced at the present time with some promise. Recently introduced drugs, e.g., anastrozole (Arimidex), toremifene (Fareston), and Taxol, are being used more liberally as their clinical application becomes more defined.

Carcinoma of the Male Breast

About 1 percent of all breast cancer occurs in men. Incidence peaks between 60 and 69 years of age. Treatment is generally modified radical mastectomy. Adjuvant therapy is recommended for node-positive patients.

Breast Cancer during Pregnancy and Lactation

Incidence ranges from 0.4–3.8 percent of all reported breast cancers. The diagnosis is delayed because of difficulty in clinical examination and radiologic workup of the breast. Treatment is identical to that for nonpregnant patients. For Stage I and II disease, modified radical mastectomy is indicated. After mastectomy, normal pregnancy is allowed to continue. Chemotherapy, if indicated, is delayed until the second trimester. Breast conservation is generally to be discouraged except in the third trimester when radiation therapy can be delayed (for 2–6 weeks) until the delivery.

Rehabilitation

Once the wound is securely healed and the drainage tubes are removed, exercises are begun to restore the ipsilateral arm to full function and range of motion. Elevation and sequential compression help decrease the lymphedema. Support groups are available through the American Cancer Society and various hospital-sponsored breast centers to fulfill emotional and informational needs.

For a more detailed discussion, see Kirby I. Bland, Michael P. Vezeridis, and Edward M. Copeland III: Breast, chap. 14 in *Principles of Surgery,* 7th ed.

CHAPTER

15

TUMORS OF THE HEAD AND NECK

CONGENITAL LESIONS

Thyroglossal Duct Cysts

The thyroid gland originates from the pharyngeal floor at the foramen cecum during the fourth week of gestation. It descends in the midline of the neck close to the hyoid bone. The patent diverticulum that results from this descent is called the *thyroglossal duct.* When all or a portion of this duct persists, thyroglossal duct cysts or sinuses are formed.

These cysts present as midline masses in childhood. Eighty percent occur at or just below the hyoid bone. The level of the cyst is elevated by protrusion of the tongue, demonstrating its embryologic origin from the base of the tongue.

The differential diagnosis for any midline neck mass around the hyoid bone includes lingual thyroid tissue. Rarely, this may be the patient's only active thyroid gland. Therefore, the presence of thyroid tissue in the normal anatomic location must be confirmed by radioisotope scanning before a midline mass is excised.

Resection of thyroglossal duct cysts with the central portion of the hyoid bone is the recommended treatment. The dissection should follow the sinus superiorly to the foramen cecum so that it is excised entirely.

Branchial Cleft Anomalies

Branchial cleft cysts, sinuses, and cartilaginous remnants result from incomplete fusion of the branchial clefts. When a portion of a cleft persists, epithelium-lined cysts or sinuses with or without a cutaneous opening may develop. Branchial cleft carcinoma occurs rarely when there is a history of a branchial cleft cyst or the subsequent development of epidermoid carcinoma at that site. Branchial cleft cysts also contain lymphoid tissue and may enlarge in response to upper respiratory infections.

The most common type of branchial cleft anomalies are those of the second cleft. These are present at the middle and lower thirds of the sternocleidomastoid muscle and may be managed by simple excision. Excision of these cysts and sinuses is recommended to avoid the complications associated with recurrent infection. The dissection must be meticulous to avoid injury to the hypoglossal, vagus, and lingual nerves and to the carotid vessels.

Hemangiomas and Vascular Malformations

Congenital vascular lesions must be clearly classified as hemangiomas or vascular malformations in order to assess their prognosis and establish appropriate management plans. Hemangiomas have an increased mitotic activity and as such may be considered true neoplasms. They are typically absent at birth or may be present as a faint vascular blush. During the first several months of life, they undergo a rapid proliferative phase. Most hemangiomas undergo spontaneous involution by the age of 7 years. Systemic dexamethasone therapy for a short course has been found to arrest the growth of large lesions during their proliferative phase. Photodynamic laser therapy may be helpful in preventing the onset of the proliferative phase of hemangiomas.

Vascular malformations, unlike hemangiomas, have a normal rate of endothelial cell turnover. High-flow lesions result from gross abnormalities connecting the arterial and venous systems and may cause catastrophic problems of massive hemorrhage, high-output congestive heart failure, and hemolytic anemia.

Lymphatic malformations (cystic hygromas) classically occur in the neck or floor of the mouth. They normally grow proportionally to the child and do not regress spontaneously. Therefore, the management of such malformations is often surgical. Indications for early surgical resection include recurrent infections, obstructive symptoms, hemorrhage, and significant aesthetic deformities.

BENIGN LESIONS

Lips

The lower lip is subject to chronic irritants such as pipe smoking, lip biting, or actinic exposure. The basal layer of the epidermis develops dysplasia, creating thickening of the superficial mucosa. This thickening or hyperkeratosis becomes clinically visible and palpable. A proliferation and abnormal orientation of epithelial

cells, or dyskeratosis, may then follow, ultimately leading to carcinoma in situ. With penetration of the basement membrane, an invasive squamous cell carcinoma develops. When dyskeratosis or carcinoma in situ is present over a large extent of the lip surface, an excision of the entire vermilion border should be considered.

Mucous retention cysts are benign lesions of the oral lining that have no true epithelium. They are caused most often by rupture of the duct system with extravasation of mucus. The most common location of a mucous cyst is the labial mucosa of the lower lip. The treatment of choice is excision. A *ranula* is a type of mucous retention cyst that arises from the major salivary glands, most commonly the sublingual. This, too, is managed by excision.

Oral Cavity

An *epulis* is a granulomatous lesion of the gingiva. It represents an exaggerated inflammatory response to minor injury. Only symptomatic epulides need to be excised.

Peripheral giant cell reparative granulomas also occur commonly on the gingiva. The "giant" cell of origin appears to resemble an osteoclast. These granulomas are polypoid, submucosal, and fibrous. Radiographic examination may reveal erosion of the underlying bone. Excision must be complete to prevent recurrence.

The tongue and larynx are common locations for the development of papillomas. They are caused by the human papillomavirus, which induces squamous epithelial proliferation. Eradication may be accomplished by excision or cauterization.

Granular cell myoblastoma is a rare benign tumor of the tongue that originally was described as of embryonal muscle cell origin. These tumors are now believed to derive from Schwann cells and have been found to arise throughout the aerodigestive tract. In the tongue these tumors form firm submucosal swellings in the middle third and can mimic squamous cell carcinoma. Wedge excision is recommended.

Ulcers of the oral lining are common. The idiopathic aphthous ulcer is the most common type. The cycle of painful ulceration and spontaneous healing may occur several times a year. Viral infections, nutritional deficiencies, and emotional stress are common etiologic factors. These ulcers often respond to topical steroids.

Lichen planus is a degenerative mucocutaneous disease with a probable autoimmune basis. The oral lesions appear with or without cutaneous manifestations and may, at times, become erosive. Squamous cell carcinoma has been found in association with lichen planus infection. Systemic and topical retinoids are being evaluated in the treatment of this condition.

Nose

Polyps are the most common benign tumor of the nasal cavity and paranasal sinuses. They are often multiple, involving both sides of the nasal cavity. Polyps may present with nasal obstruction, mucoid nasal discharge, or anosmia. Those which arise in the region of the turbinates and ethmoid are mainly allergic in origin, whereas those of the posterior nasal cavity are most often infectious. Medical management should include an evaluation for allergies. Also, there is an association with aspirin use in the formation of nasal polyps. Steroid nasal sprays may be helpful. Surgical intervention occasionally may be necessary.

Juvenile nasopharyngeal angiofibromas are benign but highly expansible and destructive fibrovascular neoplasms that typically arise in adolescent males between 10 and 20 years of age. Originating in the superior nasal cavity, they can erode widely into the paranasal sinuses, orbit, pterygomaxillary fossa, and middle cranial fossa. Early symptoms include nasal obstruction and epistaxis, whereas more advanced lesions can produce anosmia, proptosis, or cranial nerve dysfunction. Management commonly requires preliminary angiography followed by surgical extirpation. Approximately 10 percent require a combined intracranial-extracranial approach. Radiation therapy generally is reserved for residual or recurrent disease, although its successful use as a primary modality also has been reported.

Paranasal Sinuses

Mucous retention cysts arise as a result of blockage of secretions from microscopic secretory ducts. The fluid mass is separate from the bony wall. Radiographically, these cysts appear as masses profiled by air. They most commonly occur in the maxillary sinus and are asymptomatic. Treatment rarely is necessary.

Mucoceles result from macroscopic blockage of a sinus ostium by an epithelial or osseous neoplasm or inflammation or trauma. Computed tomography (CT) or magnetic resonance imaging (MRI) shows the sinus to be filled and the bony wall thinned. Mucoceles occur most commonly in the frontal sinuses and cause frontal headaches. About 60 percent erode through the orbital roof and can cause proptosis, diplopia, and blindness. Treatment is evaluation of the sinus by an open approach. The entire mucosa should be removed and the sinus obliterated.

Larynx

The most common benign neoplasm of the larynx is the papilloma, accounting for more than 90 percent of such tumors. They arise

most commonly on the true vocal cords and, as such, present most often with hoarseness. They may be found in any site within the larynx. They are likely caused by human papillomavirus. In adults, masses are most often solitary and rarely recur after excision. In the juvenile group, the lesions tend to be multiple and may recur and spread rapidly after excision. Laryngeal papillomas today most often are treated with laser obliteration. Other less common benign tumors of the larynx include oncolytic tumors and granular cell myoblastomas. Chondromas of the larynx are rare, benign, cartilaginous neoplasms that usually occur on the cricoid cartilage. They cause hoarseness, respiratory obstruction, or dysphasia. All these benign neoplasms are managed by conservative excision.

Odontogenic Tumors

Odontogenic tumors are derived from tooth development. Ameloblastoma is a benign tumor that arises from the dental lamina and is often associated with impacted teeth in young patients. The usual presentation is that of a painless mass of the jaw with a multilocular radiolucent radiographic appearance. These tumors occur most frequently in the mandible. Treatment consists of resection of the entire lesion with a margin of bone to prevent local recurrence. Another group of odontogenic tumors includes calcifying odontogenic cysts, ameloblastic fibroma, cementomas, and keratocysts. These are generally less aggressive than ameloblastoma. They are treated effectively by enucleation and excision of the entire lining of the lesion.

Nonodontogenic Tumors

This group of tumors arises from bone that is not involved in tooth development. Torus is a benign, slow-growing projection from the surface of a bone. Torus palatinus occurs in the midline of the hard palate, and torus mandibularis usually develops on the lingual surface of the mandible opposite the premolar, often bilaterally. They are both common lesions. Tori often begin around puberty and are slow growing. They can induce ulceration of the overlying mucosa, thereby mimicking a mucosal neoplasm. No therapy is needed unless they interfere with speech, mastication, or the use of dentures. Exostoses are similar to tori and also commonly occur in the jaws. These are localized overgrowths of bone that may be nodular, pedunculated, or flat and often are multiple. Only symptomatic masses require excision. Osteomas are slow-growing tumors of mature bone that arise within the periphery of the involved bone. They arise most commonly on the mandible, on the lingual aspect of the ramus, or on the lower border of the angle of the mandible. Excision

is advised when continued growth encroaches on vital structures or becomes cosmetically unacceptable. Multiple osteomas are one of the manifestations of Gardner syndrome, with the others being multiple inclusion cysts of the skin, supernumerary teeth, and familial polyposis.

CARCINOMAS

General Considerations Invasive carcinomas of the head and neck disrupt normal function of alimentation and respiration. The derangements of feeding, breathing, and speaking may present as malnutrition, upper airway obstruction, and recurrent aspiration pneumonia. As many as 60 percent of patients dying with head and neck malignancy expire without clinical evidence of metastasis beyond the local-regional disease. Central nervous system invasion, rupture of the great vessels, airway obstruction, and invasive local obstruction are common causes of death in these patients. Because of the predominant local and locoregional natural history of this disease, significant attention must be paid to local diagnosis and therapy. Most malignant tumors that develop in the head and neck are squamous cell carcinomas (epidermoid carcinomas) originating from the respiratory and stratified squamous epithelium of the upper aerodigestive tract. Most squamous cell carcinomas of the head and neck behave similarly. Their unique clinical expression depends on the interruption of normal activity inherent in their epicenter and those areas to which they spread. Nasopharyngeal carcinoma may present with nasal stuffiness and progression to cranial nerve dysfunction. Carcinoma of the floor of the mouth may present with pain. Tethering of the tongue and dysphagia result in malnutrition and possible aspiration. Survival of the patient with head and neck cancer requires consideration of both tumor growth and residual local function in formulation of a plan for therapy. The appropriate selection of radiation therapy, extirpative surgery, chemotherapy, and reconstructive surgery is crucial in the attempt to prolong the patient's life and restore reasonable function and appearance. A multidisciplinary approach to this group of tumors is essential.

Epidemiology There are between 30,000 and 40,000 new cases of head and neck cancer and 10,000–15,000 deaths attributed to this disease each year. Approximately one-third of patients who develop a squamous cell carcinoma of the upper aerodigestive tract will die of it. In the United States, there seems to be a clear-cut relationship between squamous carcinoma and the chronic use of tobacco *and* alcohol *together*. The use of either tobacco or alcohol

alone increases the likelihood of squamous cell carcinoma, but the combined use of these drugs increases the risk greatly. Despite the differences in proposed causative agents of head and neck cancer throughout the world, it appears clear that an important factor in the origin of squamous cell carcinoma is a chemical carcinogen and that a linear dose-time risk ratio is likely. Therefore, prevention should be possible. The role of viral carcinogenesis via initiation or promotion is unclear but certainly suspicious. Patients with papillomatosis caused by human papillomavirus of the nasal cavity and larynx have been observed to be at higher risk for the development of squamous cell carcinoma. Elevated antibody to Epstein-Barr virus (EBV) is associated with the presence of nasopharyngeal carcinoma but is not specific enough to be of clinical use because viral infection is so common. That the virus plays either an initiating or promoting role in carcinogenesis is suggested not only by the presence of the EBV genome in cervical metastases, as well as by the primary tumor arising in the nasopharynx, but also by its absence in the lymph nodes of EBV antibody–seropositive patients who did not contain tumor and its absence in metastatic tumors of other histology. Squamous cell carcinoma of the upper aerodigestive tract appears to be disproportionately common and unusually aggressive in patients with acquired immune-deficiency syndrome (AIDS), as it is in other immune-deficient states such as chronic lymphocytic leukemia. Oral and pharyngeal presentations of Kaposi's sarcoma are common in human immunodeficiency virus (HIV)–positive patients and may require surgical or radiotherapeutic intervention.

Natural History Viral infection, chronic irritation by ill-fitting dentures, trauma, or infection from poor dental hygiene may elicit a response from the epithelium known as *hyperplasia* or *papillomatosis*, wherein cells with normal DNA configuration and organelle structure proliferate, resulting in more prominent intraluminal projection of the mucosa deep into the submucosa. Most of the clinical changes that reflect these histologic alterations include hyperplasia and hyperkeratosis. These changes have been grouped under the term *leukoplakia* (white patch). More recent evidence suggests that leukoplakia is not in itself premalignant but simply a manifestation of chronic irritation. Cellular manifestations of malignancy result in the diagnosis of epithelial dysplasia. Lack of a normal cellular progression to maturation characterizes dysplastic epithelium. Nuclei are larger and hyperchromatic and show mitotic activity. Cell layers become disorganized with loss of the gradual ascent to the epithelial surface and presence of immature cells at the basement membrane as well as the epithelial surface. The change from hyperplasia is thought to be irreversible and the initial

step in ultimate carcinogenesis. The clinical manifestation of these histologic changes has been termed *erythroplasia* or *erythroplakia*, or red patch. These lesions appear reddish, are frequently exudative, and may have associated leukoplakia. Biopsy or excision is mandatory because they are premalignant and also may indicate the presence of another adjacent malignancy.

The virulence of the primary tumor and its likelihood of metastasis or ability to cause the demise of the host have been estimated by a number of methods. Size of the primary tumor is the main parameter determining its clinical stage in the TNM staging system adopted by the American Joint Committee on Cancer (AJCC) and other worldwide organizations. Although a crude method, it is fairly reliable in suggesting the prognosis of the patient and the appropriate form of therapy. Histologic characteristics such as degree of differentiation, pattern of invasion, microvascular invasion, and perineural invasion and tumor thickness have been used to predict the likelihood of lymph node metastasis and overall prognosis. Other microbiologic techniques that help to predict prognosis include aneuploidy, thymidine labeling index, expression of histocompatibility antigens, and levels of epithelial growth factor receptor. The histologic, biochemical, and genetic characteristics of head and neck tumors also have been used in an attempt to predict response to radiation therapy and chemotherapy.

As with most solid tumors, the most cogent prognosticator of head and neck cancer is the presence or absence of lymph node metastases. Clinical and pathologic staging of the neck according to the AJCC system depends on the number of lymph nodes, size of the lymph nodes and fixation to the skin or subjacent neck muscles, and laterality with respect to the primary tumor. Although there are certainly many determinants of primary tumor behavior, size and differentiation are useful predictors of risk of metastasis. Increasing T stage is generally reflective of increasing N stage. Distant metastasis, however, is more closely related to N-stage than to T-stage disease. In a study of Stage III carcinoma of the oral cavity, the 2-year survival of patients with no lymph node metastases was 87 percent; with intracapsular lymph node metastases, 75 percent; and with cervical metastases with extracapsular spread, only 39 percent. Uncontrolled growth of squamous cell carcinoma of the neck results in carotid artery hemorrhage; invasion of the sympathetic ganglia resulting in Horner syndrome; erosion of the cervical vertebrae; invasion of cranial nerves IX, X, XI, and XII at the base of the skull; airway obstruction; and brachial plexus palsy. The site of the primary tumor also dictates the site of cervical metastases. Cancers of the tonsils and the base of the tongue have higher rates of metastasis to the neck, whereas buccal mucosa and palate lesions have low rates of

metastasis. The presence of distant metastases from squamous cell carcinoma ranges from 31 percent of patients with no evidence of cervical metastases to 59 percent of those with extensive neck disease. Despite this relatively high incidence, they are not uniformly the cause of death. Although metastasis to any site is possible, the lung, bone, skin, and liver are the most common sites. Systemic effects of both local and systemic disseminated tumors include hypercalcemia from bone metastases and elaboration of parathormone-like peptides, as well as the syndrome of inappropriate diuretic hormone (SIADH) from vasopressin-like substances. There is some evidence that the widespread use of chemotherapy has changed the natural history of metastatic squamous cell carcinoma, increasing the frequency of patients dying with disseminated disease (Fig. 15-1).

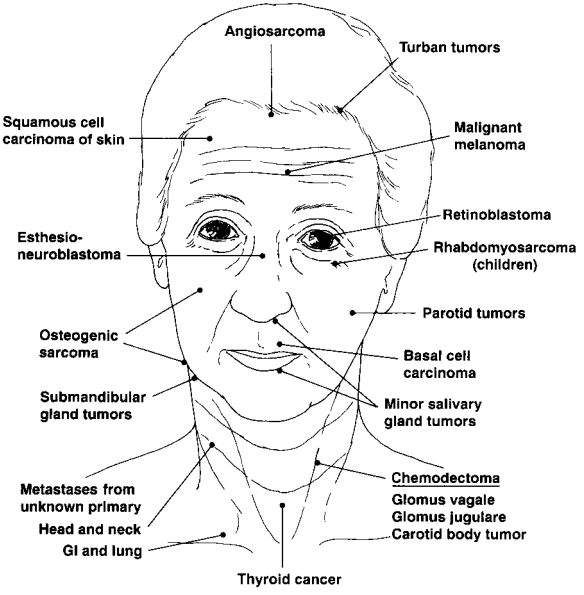

FIGURE 15-1 Malignant processes in the head and neck.

Diagnosis and Evaulation Important considerations of the history and physical examination for patients with potential head and neck cancer include a history of chronic tobacco and alcohol abuse. Men over age 40 with such a history comprise 80 percent of patients with head and neck cancer. In addition, a previous occurrence of lung cancer, esophageal cancer, or other head and neck malignancy places patients in a higher-risk category. Immunodeficiency states such as occur with transplant therapy for renal failure, malnutrition, and AIDS are also significant.

Physical findings relate to late tumor stage presentation, which is common. Pain in the ear of an adult is a relatively rare problem and usually indicates a malignancy of the oral cavity, oropharynx, or larynx. Formication, the feeling of ants crawling along the lip or cheek, may represent infraorbital nerve invasion by carcinoma. A change in speech is another physical indicator of oral carcinoma. Hoarseness is a sign of vocal cord impairment by local tumor growth. Airway compromise is usually a late symptom but can precipitate an emergency. Evaluation of the patient includes visualization of the entire upper aerodigestive tract. Careful intraoral examination and indirect mirror laryngoscopy are essential. A flexible nasopharyngoscope has added greatly to complete examination. Mobility of the tongue always should be noted. Position and movement of the vocal cords are also important. Limited motion of the mandible may come from direct tumor invasion or from invasion of tumor through the retromolar trigone. This may cause the uncomfortable symptom of trismus, an ominous clinical sign. Examination of the neck will reveal the presence or absence of metastatic lymph nodes. Careful examination will allow the examiner to assign an N stage to the patient, which is an important prognostic feature. A careful neurologic examination is also important to reveal evidence of more extensive disease. These findings would include extraocular movement disorders or Horner syndrome from invasion of cervical sympathetic nerves. Distant metastases are evaluated by laboratory procedures and radiologic examination, as well as by history and physical examination. Pleuritic pain or shortness of breath may indicate lung involvement, and distinct pain at specific sites may indicate bone involvement.

Definitive diagnosis depends on a biopsy. If the primary site is visible, a wedge biopsy should be taken at the edge of the tumor. Because of the significant incidence of synchronous primaries, however, evaluation of the entire upper aerodigestive tract is useful. Triple endoscopy, i.e., bronchoscopy, esophagoscopy, and direct laryngoscopy, is advisable for ideal workup of head and neck cancer. Radiologic evaluation of head and neck disease usually involves assessment of the mandible with dental films, mandibular

series, and panoramic films. Bone scans frequently are falsely positive; rather, CT scanning is a very sensitive method of diagnosing bone invasion. MRI is probably the most accurate and useful method of evaluating the mandible as well as other areas of head and neck.

Therapy Clinical therapy or palliative therapy for a given patient is based on the clinical stage (TNM) of the tumor at the time of presentation. Curative treatment methods are oriented toward total extirpation of locoregional disease. Palliative procedures are designed to produce relief of pain or airway obstruction or improvement in local function and hygiene. Palliative procedures are occasionally justifiable in the presence of distant metastases. Subtotal resection of local or locoregional disease is unlikely to be of benefit in any situation. For small tumors (< 2 cm), surgery and radiation therapy, well-planned and appropriately executed, will have equivalent local control and survival rates. The choice then depends on patient compliance, volition, associated disease, expense, interference with normal function, and available facilities. As the size of the tumor increases to T2 or greater, the likelihood of local control and ultimate cure with radiation therapy alone decreases. Therefore, surgery, or surgery with adjuvant radiation therapy, becomes preferable with larger lesions. The use of chemotherapy in a postoperative setting has been unsuccessful in most trials. Despite high response rates to preoperative administration of *cis*-plantinum and 5-fluorouracil (5-FU), there has not been a survival advantage with this novel form of treatment.

The basic principle of solid tumor therapy is en bloc treatment, either resection or radiation therapy of the primary tumor and the regional disease in the neck. When palpable lymph nodes are present in the neck, confirmation of metastatic disease may be obtained with fine-needle aspiration (FNA) and cytology, or the decision to proceed with therapy may be made on purely clincial grounds. Palpable or radiologically positive lymph node metastases require surgical therapy in the form of some type of neck dissection usually performed in continuity with resection of the primary tumor. Subclinical disease or micrometastases may be treated by a modification of neck dissection or radiation therapy depending on the modality chosen for treatment of the primary site.

Reconstruction Improved methods of reconstruction, better pathologic analysis at surgery, and a more comprehensive understanding of the natural history of head and neck cancer have made single-stage reconstruction at the time of the initial surgical therapy the present standard of care in most patients. Resection of the primary disease and regional metastatic disease, confirmation of

disease clearance by frozen section of the margin, and immediate reconstruction are usually possible for squamous cell carcinoma of the upper aerodigestive tract. In malignancies where frozen-section analysis may be inaccurate when bone is involved, in recurrent disease with previous radiation therapy, or when there is uncertainty about other aspects of the resection, secondary reconstruction may be more appropriate.

The basic needs presented by surgical resection are restoration of continuity of the alimentary tube with epithelial lining, provision of reliable external coverage for protection of the great vessels and bony structures, and separation of the central nervous system and upper aerodigestive tract. The fundamental improvements in reconstruction over the past decades have been the ability to transfer large volumes of well-vascularized tissue to the head and neck area. The realization came in the 1970s that the blood supply to the skin came not only from the randomly oriented subdermal plexus vessels and axial cutaneous vessels but also from perforating vessels from adjacent muscle. Large, flat muscles of the thorax can be rotated on their long vascular pedicles. This concept transformed reconstruction, in particular that of head and neck defects. The pectoralis major, latissimus dorsi, trapezius, sternocleidomastoid, and platysma muscles are all useful, either alone or with their overlying skin. Microvascular reconstruction or free-tissue transfer has made it possible for the surgeon to close any defect in the head and neck, no matter how large or complex. The large number of methods available allows the reconstructive surgeon to choose the method or methods most suitable to a specific site and analyze the results.

Complications Complications of treating head and neck cancers can be categorized as anatomic, physiologic, technical, or functional. The best approach to complications is prevention. Early restoration of positive nitrogen balance, good preoperative pulmonary hygiene, controlled diabetes mellitus, and weaning from alcohol dependence are important nonspecific measures. Use of preoperative antibiotics decreases the likelihood of wound infection and its sequelae. Preoperative radiation therapy given in therapeutic doses definitely increases the risk of complications. Patient education is crucial to ensure cooperation in what may be a difficult postoperative rehabilitation.

Nerve injury is a frequent complication of head and neck cancer surgery. Injuries due to traction, electrocautery, or other technical misadventures may occur. Careful technique and good knowledge of the normal anatomy are critical. Ischemia of tissues in the wound is another cause of complications. Preoperative irradiation

interferes with good blood supply to tissues. Hypoparathyroidism is another complication that can occur secondary to radical laryngopharyngectomy. Obstruction of one or both of the jugular veins, when combined with lymphedema of the face, may cause intracerebral edema. The breakdown of the skin wound or necrosis of a transferred flap may result in exposure of a previously irradiated carotid artery. Bacterial infection and subsequent rupture are not uncommon in this situation and must be treated as a surgical emergency. Other catastrophic complications that can occur are acute airway obstruction from a hematoma or a dislodged tracheostomy tube, tracheoinnominate fistulas, and massive hemorrhage. Pharyngocutaneous fistulas also may occur and must be treated by transfer of a musculocutaneous flap for provision of well-vascularized tissue.

Lip

Carcinoma of the lip is much more common in men than in women. The lower lip is by far the most common site, with squamous cell carcinoma as the most common histology. Pipe smoking and chronic thermal injury have been known for years to be the carcinogenic stimulus. Exposure of the protuberant lower lip to high doses of ultraviolet radiation in sunlight also results in malignancy.

Most lesions are well-differentiated Stage I carcinomas. Nodal metastases usually occur to the submental or submandibular nodes but are present in only 10–15 percent of patients. Standard treatment is local excision or radiation, with cure rates for either of approximately 90 percent.

Surgical therapy requires resection of the disease with a clear margin of normal tissue. If lymph nodes are palpable, ipsilateral or bilateral neck dissection is indicated. Reconstruction can be performed with the opposite lip used as a donor site.

Oral Cavity

The oral cavity includes the buccal mucosa, gums, retromolar trigone, floor of the mouth, and hard palate. Carcinogenesis in the oral cavity and the natural history of subsequent disease are generally similar independent of these anatomic areas.

BUCCAL MUCOSA

The buccal mucosa extends from the commissures of the lips to the pterygomandibular raphe and from the maxillary to the mandibular alveolus on both sides. Cancer of the buccal mucosa makes up about 5 percent of all oral cancers, and as in other sites, there is a

significant male predonminance. Most cases are advanced at the time of presentation, with a high incidence of nodal metastasis.

Verrucous carcinoma is a subset of buccal mucosa lesions that presents as an exophytic mass with a cellular histology characteristic of malignancy but lacking invasive aspects. This lesion is more common in females and may be related to papillomavirus. Forty percent of these patients may have other sites of invasive carcinoma in the oral cavity.

Infiltrative carcinoma of the buccal mucosa occurs commonly in tobacco chewers and snuff dippers in the United States. Standard therapy is surgical resection with or without adjuvant radiation therapy. Survival rates range from 60–75 percent for localized disease and from 25–45 percent for local-regional disease. Reconstruction of large buccal mucosa defects usually has included the combined use of the pectoralis major flap for internal lining and the deltopectoral skin flap for skin coverage.

HARD PALATE

The hard palate is not a common site of intraoral carcinoma. When neoplasia occurs here, it is usually benign or a malignant tumor of the minor salivary glands. Treatment is surgical resection with or without adjuvant radiation therapy. Because of the underlying bone, definitive radiation therapy is rarely useful. Cervical metastases are rare. The resulting defects are best treated with a dental prosthesis. Massive defects may require temporalis muscle flap.

FLOOR OF THE MOUTH

The floor of the mouth is a horseshoe-shaped area between the tongue and lingual surface of the mandible. The papillae that allow Wharton's ducts to empty into the oral cavity lie at the anterior border of this area. Fifteen percent of oral cancers arise in this area. Direct extension of tumor into the neck and bilateral cervical metastases are frequent. Medial growth of the primary tumor tends to invade the ventral surface of the tongue, whereas lateral growth invades the mandible. Most patients present with advanced disease.

Resection of floor of the mouth cancers with an adequate margin of normal tissue frequently requires removal of a segment of mandible. Therapeutic doses of radiation may result in ischemic necrosis of the mandible, which is difficult to treat. Surgical resection combined with modest doses of adjuvant radiation is appropriate for advanced disease. Survival rates are 70–80 percent for Stage I disease and 35–45 percent for Stage III disease. In reconstruction, a radial forearm free flap provides an excellent lining of this area that can drape over the mandible and allow free movement

of the tongue while providing a watertight seal. The choice of reconstruction depends on the amount of mandible to be removed.

Oral Tongue

Cancer of the oral tongue is second only to the lip as the most common primary site. Again, tobacco and alcohol are the most common associated conditions. Immunosuppressed patients of any age, however, may be at higher risk for tongue cancer.

The tongue is a complex muscular structure receiving motor intervention from the hypoglossal nerve. The tongue is connected to the hyoid bone by the hypoglossus muscle and superiorly to the mandible by the genioglossus muscle. The ventral surface of the tongue has openings of the sublingual ducts. On the dorsal surface are papillae with specialized sensory organs for taste.

Malignancy of the tongue occurs most frequently at the midportion of the lateral tongue and is often asymptomatic. Radial spread through the tongue may extend submucosally to the base of the tongue and across the midline or laterally to the floor of the mouth. Ipsilateral metastases are common to the submandibular and submental nodes. Clinical evidence of cervical mestastasis is present in 40–60 percent of patients. Survival rates are 70–90 percent for localized disease and 30–40 percent for regional metastases.

Definitive therapy for carcinoma of the tongue can be attempted with both external-beam radiation or interstitial radiation. External radiation in doses of 6500 cGy may be useful, but implantation of afterloading devices can deliver doses in the range of 10,000–15,000 cGy over a small area with greater effect.

The surgical therapy of carcinoma of the tongue consists of resection of the tumor with a margin of normal tissue and en bloc removal of the regional lymph nodes. Most surgeons are uneasy about the ability to obtain clear margins with such resections, which has led to common use of adjuvant radiation therapy. Resection at the base of the tongue may predispose the patient to aspiration and ultimate respiratory failure. Despite these problems, total glossectomy with or without laryngectomy has been shown to be a valuable procedure for both cure and palliation. A 3-year survival of 53 percent has been achieved in one series, with 80 percent of patients demonstrating intelligible speech if the larynx is preserved and 93 percent regaining the ability to maintain their nutritional status by oral alimentation.

There is no satisfactory way to reconstruct the tongue. Denervation of the tongue by resection or injury to both hypoglossal nerves usually renders the patient incapable of swallowing or effective speech. After surgical resection of a portion of the tongue,

the reconstructive goal is to allow free mobility of the remaining tongue while providing a watertight seal to the oral cavity. Advancing the posterior mobile tongue or setting back the excess anterior tongue may provide the optimal solution. The defect of total glossectomy involves the tongue, floor of the mouth, and sometimes the pharyngeal and laryngeal mucosa. Restoration of oral continence usually requires significant soft tissue. The pectoralis major flap serves well to replace the entire floor of the mouth, as does the jejunal free flap, which also can replace the pharynx and crevice esophagus. When a portion of the mandible must be resected for carcinoma of the oral tongue, the urgency of reconstruction depends on what part of the mandible has been resected. Resection of the symphysis or anterior segment of the mandible is a devastating problem that requires immediate reconstruction. Vascularized bone from the scapula, fibula, iliac crest, radius, or metatarsal is an excellent method of reconstruction. Other areas of the mandible are less demanding of reconstruction.

Pharynx

The pharynx is the continuation of the muscular tube that constitutes the alimentary tract. It is divided into three sections, each with a slightly different function: the nasopharynx, the oropharynx, and the hypopharynx. An important characteristic of the pharynx is its role in separating the respiratory and alimentary tracts, and its specialized structures reflect this function.

The oropharynx contains the base of the tongue from the circumvallate papillae back, the tonsils, the oral soft palate, the lateral pharyngeal walls, and the posterior pharyngeal wall. The boundaries of the hypopharynx are reflections of the anatomy of the larynx. The pharyngeal wall runs from the tip of the epiglottis to the inferior border of the cricoid cartilage. The anterior border of the hypopharynx is the postcricoid mucosa, and the lateral surfaces are the mucosal cavities on both sides of the larynx known as the *piriform sinuses.*

Carcinoma arising from the circumvallate papillae in the base of the tongue frequently remains asymptomatic and undiagnosed until late-stage disease is present. The disease is commonly overlooked because of reluctance of primary care physicians to perform indirect laryngoscopy or palpate the base of the tongue. The central location of these lesions gives rise to cervical lymphatic metastases in up to 70 percent of patients. In addition to epidermoid carcinoma, minor salivary lesion gland tumors are also seen. Exophytic lesions with cells resembling lymphocytes arise in the tissues of Waldeyer's ring, the tonsils, the lingual palatine, and the base of the

tongue. These lymphoepitheliomas behave like nasopharyngeal carcinoma and have been characterized as undifferentiated carcinomas with lymphocytic infiltration. Such lesions, both at primary lesions and at cervical metastases, are more radiosensitive than the garden variety infiltrative keratin-producing squamous cell carcinoma. Two-year local control rates are 75 percent for T1 lesions. Because of the proximity to and functional relationship of the base of the tongue to the larynx, interference with laryngeal elevation and closure of the epiglottis with the attendant aspiration pneumonitis is a hallmark of carcinoma of the base of the tongue.

Advanced disease at the primary site or disease with cervical metastases requires surgical therapy. If the lesion is lateral enough, partial glossectomy may be adequate. However, since resection of the base of the tongue usually removes the hypoglossal nerve to the tongue, subtotal or posterior glossectomy is unlikely to leave functional tissue. Radical resection may require total glossectomy with or without laryngectomy. Combined use of surgery with postoperative adjuvant radiation therapy results in 5-year survival of 50–60 percent for Stage III disease.

Reconstruction of defects arising from resection at the base of the tongue should attempt to close the pharynx and oral cavity with tissue that will heal to previously irradiated mucosa or withstand subsequent irradiation and still not interfere with the function of tissues left intact by the curative resection. The provision of sensate tissue to the area surrounding the larynx to prevent aspiration is also an important consideration. Occasionally, local tissue can be mobilized for closure without tension to avoid a fistula and provide sensate mucosa.

Tonsil

Squamous cell carcinoma may arise in the tonsil or the tonsillar pillars. As one of the Waldeyer's ring structures, the tonsil shows a higher incidence of lymphoepithelioma than other sites. Individuals with tumors of the tonsil present predominantly with late-stage disease. Cervical metastases at the time of presentation were seen in up to 67 percent of patients. Determination of the extent of local disease in advanced tumors is of considerable importance in decision making and execution of therapy. The site of local extension is particularly important because in treating patients with radiation therapy, geographic misses secondary to underestimation of local extent are a common reason for failure.

Carcinoma of the tonsil appears to be more radiosensitive than other primary-site squamous cell carcinomas. The usual approach to disease orginating at this site is to treat for curative intent with

radiation in doses ranging from 5500–7000 cGy to the primary site and bilateral cervical lymph node drainage areas. If there is bulky neck disease or extension of the primary tumor into adjacent bone or pterygoid muscles, surgical resection, reconstruction, and postoperative radiation therapy are safe and more effective.

The challenge of reconstruction in tonsillar carcinomas is a function of the dimensions of local growth and history of previous radiation. The soft tissue defect in the lateral wall of the pharynx created by a superficial lesion can be resurfaced easily with a skin graft, deltopectoral flap, or fasciocutaneous free flap. More extensive lesions may require transposing a pectoralis major musculocutaneous flap into the lateral pharynx.

Soft Palate

Isolated carcinoma of the soft palate is rare; the disease usually occurs in combination with other frank malignancies or premalignant entities such as erythroplakia. The oral side of the soft palate is by far the most common site for malignancy. Ipsilateral cervical lymph node metastases to the jugulodigastric nodes occur in 50 percent of patients, with bilateral metastases seen in 15 percent of patients.

Treatment of soft palate carcinoma follows the usual principle that small lesions are effectively eradicated by radiation therapy of approximately 6500 cGy and that combined therapy, i.e., surgery with adjuvant radiation therapy, is necessary for best results in larger tumors. The use of radiation therapy is particularly important because of the difficulty of reconstructing the soft palate after surgery.

Hypopharynx

Thy hypopharynx consists of the piriform sinuses, the lateral and posterior mucosal borders of the larynx, and the posterior pharynx. Tumor growth in this area is intimately related to the function of the larynx. Rather than size, the T stage of a piriform sinus lesion increases with extent into the medial wall or fixation of the vocal cord. Another consideration in hypopharyngeal carcinoma is the extent of disease in the cervical esophagus. Such advanced-stage local disease is common, with only 10–15 percent of cases confined to only one site in the hypopharynx. Even in small lesions there is a high likelihood of lymph node metastases. Between 50 and 60 percent of patients present with palpable lymphoadenopathy, and 40 percent of patients with clinically negative nodes demonstrate metastatic disease after elective neck dissection. Distant metastases at presentation and with treatment of disease appear to be more common than at other primary sites.

Since it is unusual for hypopharyngeal lesions to present at early stage, the treatment is usually combined, consisting of surgery followed by adjuvant radiation therapy. The extent of the surgery depends on the proximity to the larynx. Laryngopharyngectomy with bilateral modified neck dissection is the procedure that is most frequently necessary. With such an approach, survival rates of 20–40 percent have been achieved.

Primary closure of the pharyngeal mucosa after partial laryngopharyngectomy results in a high likelihood of fistula. A free autograft of bowel or skin is the preferred method for reconstruction. When a circumferential defect is present, the problem of bulk and gravity can be circumvented somewhat by skin grafting the prevertebral fascia as the posterior wall of the new pharynx and using the pectoralis major muscle and its overlying skin as a 270-degree reconstruction to complete the pharyngeal conduit.

When total esophagectomy is part of the treatment for carcinoma of the pharynx, transposition of the stomach or colon through the thorax can reconstitute the alimentary canal. Gastric pull-up with the stomach based on the right gastric and gastroepiploic vessels is a fairly reliable technique but has a mortality rate of 10–20 percent. Although colon, segments of stomach, and jejunum have all been used, the greatest experience has been with the jejunal free autograft. Successful reconstruction using the jejunum has been achieved in 90 percent of patients approached with this method. Eighty percent of the total group will achieve total per oral alimentation.

Squamous cell carcinoma of the cervical esophagus presents the same reconstructive demands as that of the hypopharynx. The mode of spread of the local disease, however, may involve submucosal skip areas and thus require total esophogectomy. The lymphatic drainage of the cervical esophagus is oriented more toward the mediastinum and parapharyngeal nodes than laterally into the neck and requires a different approach for lymphadenectomy.

Nasopharynx

Carcinoma of the nasopharynx makes up 0.25 percent of new cancers in the United States. It is, however, endemic in Southeast Asia, particularly in southern Chinese populations. The incidence is much lower in Orientals who have emigrated to North America.

The nasopharynx is a small, mucosal-lined, boxlike cavity at the base of the skull containing the pharyngeal tonsil and the openings of the eustachian tubes and the sphenoid sinus. Lesions may obstruct the eustachian orifices on the choanae, leading to hearing loss, nasal stuffiness, or obstruction and epistaxis. Infiltration and

bony erosion of the base of the skull into the cavernous sinus result in cranial nerve palsies, the most common being that of the abducens nerve, followed by the trigeminal nerve and the other oculomotor nerves. The most common presenting sign of nasopharyngeal carcinoma is a mass in the neck secondary to cervical metastasis.

CT scanning has helped delineate invasion of both paranasopharyngeal fascial planes and bony skull invasion in the absence of cranial nerve palsy. Prognosis depends on the histology. Keratinizing squamous cell carcinoma has the worst 5-year survival. Round cell carcinomas and mixed nonkeratinizing carcinomas are much less virulent.

Therapy with radiation in doses varying from 5000–8400 cGy to the primary site with 5000–7000 cGy to both sides of the neck results in a 5-year survival rate varying from 100 percent for Stage I disease to 30 percent for Stage IV disease. The total dose of radiation has an effect on survival, with those patients receiving lower total doses having a poorer survival. Sixty-two percent of cranial nerve defects can be reversed by radiation therapy, with an overall 30 percent survival in this subset of patients. Distant metastatic disease in nasopharyngeal carcinoma is common, particularly in patients who have bulky cervical metastases. Currently, however, adjuvant chemotherapy has not been particularly successful in improving survival.

Nasal Cavity

The nasal cavity and paranasal sinuses are exposed to many carcinogens in the air, and yet malignacies in these sites are rare. Nasal cavity carcinoma is endemic in areas of South Africa where inspired snuff has a high concentration of nickel. There also may be an increased risk of adenocarcinoma of the paranasal sinuses in woodworkers secondary to inspired wood dust. Squamous cell carcinoma is the most common histologic finding, although adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma make up about 20 percent. Lymph node metastases are uncommon.

Symptoms are usually rather diffuse, including nasal obstruction, local pain, epistaxis, and cheek swelling. Diagnosis is made by intranasal biopsy through a speculum or by antrostomy through the lateral nasal wall or labial buccal sulcus. The maxillary sinus is by far the most common site of origin of the disease.

Treatment of paranasal sinus tumors includes a combination of radiation therapy and surgery. Radiation therapy alone provides poor palliation and unacceptably low survival rates. Preoperative radiation therapy to 6000 cGy combined with radical surgery has

been the usual approach, resulting in 3-year survivals in the vicinity of 10–30 percent.

Surgical resection involves en bloc removal of the affected sinus and the surrounding involved structures. Total maxillectomy with or without orbital exenteration may be required for adequate clearance. Craniofacial techniques have improved the ability to safely remove tumors of the ethmoid and other paranasal sinuses and have increased 5-year survival rates to nearly 60 percent.

Reconstruction of the postoperative defect that has been irradiated previously is a difficult problem. Small defects can be obturated with nasal or dental prostheses. Larger defects, however, require three-dimensional reconstruction with free-tissue transfer.

Larynx

The larynx is divided into three anatomic areas: the supraglottic larynx from the epiglottis to the ventricle; the glottic larynx, including the true vocal cords and the anterior commissures; and the subglottic area, surrounded by the cricoid cartilage. Carcinoma of the larynx is the most common malignancy of the upper aerodigestive tract. Nearly 10,000 new cases per year present in the United States. The risk for laryngeal cancer is directly proportional to the amount of exposure to tobacco, with a lesser relationship to alcohol intake. Increasing age is also a risk factor. Black patients have an increased risk of developing laryngeal cancer at a younger age. Exposures to asbestos, nickel, and wood dust are also likely cofactors. The relationship of papillomas in the etiology of laryngeal cancer is unclear.

Individuals with carcinoma of the glottic larynx are most likely to present with early-stage disease. The symptoms include hoarseness, other voice changes, tickling in the throat, and coughing. Evaluation includes indirect laryngoscopy as well as physical examination of the neck. The geographic site and extent of the lesion, whether confined to the larynx or spreading beyond, are of importance. The mobility of the vocal cords is also crucial because it represents invasion of tumor into deeper structures of the larynx. CT scans and MRI are useful in documenting invasion of the thyroid cartilage. Biopsy can be performed with a rigid laryngoscope to clearly define the extent of disease.

Individuals with supraglottic carcinoma of the larynx are more likely to present with advanced-stage disease. Micrometastases are common despite a clinically negative neck. Patients with inadequate primary therapy for supraglottic carcinoma are more likely to fail from recurrence in the neck and distant metastases than from local recurrence alone.

The vocal cords are a small area that is in constant use and regularly exposed to carcinogenic stimuli. Tumors in this area usually behave indolently. When these tumors extend outside the glottis, a more aggressive pattern is noted. Early symptoms are noticeable with glottic cancer, making them more amendable to less radical therapy. The low likelihood of clinically evident or micrometastatic nodal disease also makes glottic cancer more suitable for less radical treatment.

Subglottic carcinomas are rare, making up only 1–2 percent of all laryngeal carcinomas. They tend to spread by submucosal extension down the trachea, and patients frequently present with advanced-stage local disease. Cervical metastases are not very common. Radical combined therapy, i.e., surgery and radiation therapy, is necessary. The significant factors for survival include presence of lymph node metastases, advanced local disease, vocal cord fixation, histologic grade, ulceration, and male gender.

In glottic cancer, radiation therapy has become the accepted treatment for most early squamous cell carcinomas. Conventional radiotherapeutic techniques deliver doses of 6000 cGy over 6 weeks. This results in a cure rate of 80–90 percent for T1 carcinoma and 70–90 percent for T2 lesions. More advanced lesions also have been approached with standard radiation therapy in doses of 6500–7700 cGy. Many of these patients will require surgical salvage. Such high-dose radiation therapy results in significant complications, including laryngeal edema and chrondronecrosis. Early lesions of the glottis that involve the mobile cord and do not extend to the anterior or posterior commissures may be treated with vocal cord stripping. T1 lesions of more bulk but confined to one cord may be removed by cordectomy, a procedure that is usually performed by opening the larynx rather than endoscopically.

The conventional therapy for cancers that cross the anatomic boundaries of the supraglottis and glottis, so-called transglottic lesions, is a total laryngectomy. Depending on the presence of palpable lymph nodes or suspicion of metastatic disease, radical or modified radical neck dissection may be indicated. Disease-free margin status is the most reliable predictor of local control. When total laryngectomy is used as definitive therapy for advanced-stage disease, 5-year survival rates of 60 percent for T3 and 50 percent for T4 lesions have been reported.

Voice preservation can be attempted in two ways: conservation surgery, i.e., removing only part of the larynx, and reconstruction of a voice-preserving mechanism after total laryngectomy. Lesions confined to one part of the larynx can be removed, leaving enough larynx behind to allow speech that is superior to mechanical speech. Conservation surgery is appropriate in patients in whom lesions are

less than 3 cm, the vocal cords are mobile, and a margin of 5 mm is possible. Also, there should be no cartilage or preepiglottic space invasion, and tongue mobility should be normal.

Mechanical voice restoration after surgery that removes the entire larynx is a difficult problem. Only 25–45 percent of alaryngeal patients acquire esophageal speech. Inability to expel air from the stomach and other physiologic reasons have been cited for this failure. Mechanical devices inserted into the airway have been largely unsuccessful. External vibrators do allow intelligible speech of low volume. Various attempts have been described to create a neolarynx. A simple tracheoesophageal puncture described by Singer and Blom can be maintained patent by a small tube that allows pulmonary air to enter the esophagus, and thus the pharynx, and be modulated by the tongue, lips, and buccal mucosa. This method has allowed fluent speech restoration in 75 percent of patients with little risk of aspiration. Transplantation of the larynx has not been successful, but research is continuing with this method.

Complications of total laryngectomy include pharyngocutaneous fistulas, acid and food regurgitation, and stenosis. These complications are particularly associated with previous radiation therapy, malnutrition, and cell-mediated immunodeficiency.

CONNECTIVE TISSUE NEOPLASMS

Connective tissue neoplasms are uncommon and make up less than 1 percent of head and neck tumors. Fibrosarcoma is the most common of these lesions. Others include malignant fibrous histiocytoma, angiosarcoma, and rhabdomyosarcoma. Ten percent of osteogenic sarcomas arise in the head and neck.

PARAGANGLIOMAS

Paragangliomas or chemodectomas are neoplasms in the head and neck that arise from neural crest cells and that histologically resemble their adrenal gland counterpart, the pheochromocytoma. They are classified by their location: carotid body, jugular, vagal body, orbital and laryngeal. Although these extraadrenal paraganglionic cells do contain a small amount of catecholamines, it is rare for them to produce a clinically significant excess of catecholamines. The carotid body tumor is the most common of the paragangliomas. It usually presents as an asymptomatic neck mass. Only 6 percent of these tumors are malignant. Paragangliomas are

highly vascular and have a characteristic appearance on angiography. Treatment should include complete resection, which in the carotid body requires subadventitial dissection.

AIDS-RELATED DISORDERS

HIV infection produces a large number of abnormalities in the head and neck, both neoplastic and nonneoplastic. Immunosuppression allows opportunistic organisms to cause serious disease. Oral candidiasis may be one of the earliest manifestations of AIDS. Herpes simplex virus infection can result in painful ulcerations of the lips, oral mucosa, and oropharynx. Varicella-zoster infection is a painful syndrome with distribution along cranial nerve V.

Oral hairy leukoplakia is similar to leukoplakia in chronic smokers but is more likely to be seen on the lateral border of the tongue. This lesion may be an early sign of ultimate HIV infection, again as an expression of decreased immunosurveillance.

Lymphoproliferative disorders are characteristic of AIDS and frequently manifest themselves in the head and neck area. Obstruction of the nasal pharynx secondary to overgrowth in Waldeyer's ring has been reported. Cervical lymphadenopathy is commonly a part of the AIDS-related complex. Malignant lymphomas, most commonly of the B-cell type, also have been reported and are second only to Kaposi's sarcoma in frequency. T-cell lymphomas also occur but are less common. For disease localized to one area, radiation therapy may be an effective form of treatment. Multidrug systemic chemotherapy is also effective but places the already immunosuppressed patient at a higher risk of disseminated infection.

Kaposi's sarcoma is the most common malignancy in AIDS. The oral form of Kaposi's sarcoma occurs most commonly in the palate. Usually the distribution is multifocal. Tumor may arise in or metastasize to the cervical lymph nodes or the salivary glands. The tumor initially presents as a flat, blue to purple patch and may appear to be a submucosal hematoma secondary to trauma. Later in the course of growth it becomes nodular. Single-drug treatment with vinblastine or VP16, as well as with interferon alpha, has been used systemically or as an intralesional injection to treat Kaposi's sarcoma of the oral cavity.

Squamous cell carcinoma appears in HIV-infected patients at an earlier age and without the usual risk factors of smoking and ethanol intake. This pattern is suggestive of a defect in immunosurveillance similar to that seen in patients having undergone organ transplantation. The median age of presentation of squamous cell carcinoma of the oral cavity is 32 years. The clinical course seems to be somewhat more aggressive.

SALIVARY GLANDS

Anatomy

The major salivary glands are the symmetrically paired parotid, submandibular, and sublingual glands that discharge saliva into the oral cavity via Stensen's duct, Wharton's ducts, and the numerous small orifices in the floor of the mouth, respectively. The normal volume of salivary secretion in the adult male ranges from 1000–1500 mL/day, mainly as serous fluid from the parotid and submandibular glands. Immunoglobulins A, G, and M, albumin, lysozyme, and other enzymes also are secreted. In addition to its lubricating properties, which allow food to be moved through the mouth, saliva has antibacterial and antiviral properties that protect the soft tissues of the oral cavity as well as the teeth.

The parotid gland is located behind the mandible adjacent to the pterygoid muscles and extends into the preauricular area down to the angle of the mandible. The medial extent of the gland usually reaches over the masseter muscle and vertical ramus of the mandible. The gland is divided into the deep and superficial lobes by the facial nerve that exits from the stylomastoid foramen. Seventy percent of the parotid gland lies superficial to the plane of the facial nerve. Stensen's duct, the parotid duct, condenses from the large intralobular ducts and passes adjacent to the buccal branch of the facial nerve. It enters the oral cavity adjacent to the second maxillary molar tooth.

The facial nerve supplies motor intervation to the muscles of facial animation. On passing through the parotid gland, the nerve divides into an upper and lower division. The upper division usually includes the temporal, zygomatic, and buccal branches. The lower division includes the marginal mandibular and cervical branches.

The submandibular gland lies beneath the platysma muscle surrounded by the anterior and posterior bellies of the digastric muscle and the mandible. Wharton's duct conveys the secretions of the submandibular gland into the oral cavity.

Sublingual salivary glands lie immediately beneath the mucosa in the floor of the mouth intimately related to the lingual artery and release their secretions into the oral cavity through numerous orifices.

Inflammatory Disorders Inflammation usually presents as a diffuse enlargement or firmness. Bacterial infection is the result of duct obstruction and retrograde infection with oral bacteria. Acute bacterial parotitis may be seen in the elderly postoperative patient who becomes dehydrated and is usually caused by *Staphylococcus aureus.* Rehydration and antibiotic therapy are usually successful.

Mumps, coxsackie virus, and echoviruses also may cause acute parotitis. Tuberculosis, actinomycosis, and cat scratch disease also may present with enlargement of either salivary glands or their adjacent lymph nodes. Systemic disorders such as sarcoidosis, Sjögren's syndrome, and cirrhosis with liver failure also result in salivary gland enlargement.

Tumors Of all salivary gland tumors, 70 percent are in the parotid gland. Of parotid gland tumors, 70 percent are benign, and of the benign tumors, 70 percent are pleomorphic adenomas. Pleomorphic adenoma is the proliferation of both epithelial and myoepithelial cells of the ducts as well as an increase in the stromal component. These tumors may grow to a large size without causing facial nerve symptoms. Pleomorphic adenoma usually presents as a solitary painless mass in the superficial lobe of the parotid. Malignant degeneration of pleomorphic adenomas occurs in 2–10 percent.

The second most frequent benign tumor of the parotid is the papillary cystadenoma lymphomatosum, or Wharthin's tumor. With a marked male predominance, this tumor usually occurs in the tail of the parotid gland and appears histologically as a lymphocytic infiltrate with cystic epithelial proliferation. There is a 10 percent incidence of bilaterality and multicentricity.

Malignant tumors of the salivary glands almost always present as a discrete mass. Pain is associated with malignancy in 20 percent of patients. Other symptoms include formication, facial nerve dysfunction, and complete paresis of the nerve. Facial nerve palsy is almost never seen with benign disease and must be considered a possible sign of malignancy. The risk of clinical or subclinical metastases to the cervical lymph nodes depends on the histology and grade of the primary tumor. High-grade mucoepidermoid carcinoma, adenocarcinoma, and squamous cell carcinoma have a high risk of metastatic disease, whereas adenoid cystic tumors and lower grades of mucoepidermoid and squamous cell carcinoma are at low risk of metastasis. In all, 20 percent of parotid gland neoplasms are malignant.

Diagnosis The discrete mass in the salivary gland must be considered a possible malignancy. History and physical examination provide important clues as to whether a salivary gland lesion is malignant. Complete resolution after a 10-day course of antibiotics is consistent with inflammation and constitutes an adequate therapeutic trial. FNA may be helpful for planning surgical excision. MRI gives the best anatomic information about tumor size and penetration. Sialography, or injection of contrast material into Stenson's or Wharton's ducts, is useful in demonstrating chronic stenotic changes of benign lymphoepithelial lesions versus occlusion from

stones. Eighty percent of parotid duct stones are radiolucent. Eighty percent of submandibular gland stones are radiopaque.

Treatment The surgical approach to a salivary gland mass is predicated on the assumption that it is malignant. The major problem is the presence of the facial nerve in the parotid gland. If there is no evidence of nerve involvement, the tumor should be excised by superficial lobectomy, preserving the nerve. If the tumor is malignant, total parotidectomy with preservation of the nerve is indicated, although it is a piecemeal procedure. Involvement of a branch of the nerve or the whole nerve requires removal. Replacement of the resected segment of nerve using a nerve graft can avoid the sequelae of facial nerve palsy.

When clinical examination with or without FNA does not clearly define the problem, biopsy should be obtained by superficial lobectomy. Benign tumors can be removed with a clear margin by superficial lobectomy. Involvement of the deep lobe requires total parotidectomy.

Treatment of the regional lymph nodes depends on the histologic type and grade of the tumor. Clinically node-positive necks are treated with an appropriate neck dissection. Elective or prophylactic neck dissections are not as frequently necessary as in other head and neck malignancies. High-grade mucoepidermoid or squamous cell carcinoma and high-grade adenocarcinoma are exceptions that warrant ipsilateral neck dissection.

Neoadjuvant or adjuvant chemotherapy has been effective in salivary gland malignancies. Postoperative radiation therapy, however, is effective. Radiation portals should include the site of surgery, the foramen ovale, the base of the skull, and the ipsilateral neck.

Adenoid cystic carcinoma is the most common malignant histologic finding in the submandibular gland, whereas pleomorphic adenoma is the most common benign tumor of this gland. Adjuvant postoperative radiation therapy appears to be helpful for these uncommon malignancies.

Tumors of the minor salivary glands, either benign or malignant, are most common in the hard and soft palate. Their presentation may be as submucosal or ulcerative masses. Pleomorphic adenoma is the most common benign tumor, and mucoepidermoid and adenoid cystic carcinoma are the most common malignancies. Treatment is wide local excision including the subjacent bone, with adjuvant radiation therapy reserved for malignant cases. Lymph node metastases are rare.

For a more detailed discussion, see Coleman JJ, Sultan MR: Tumors of the Head and Neck, chap. 15 in *Principles of Surgery,* 7th ed.

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CHAPTER

16

CHEST WALL, PLEURA, LUNG, AND MEDIASTINUM

ANATOMY

Framework The thoracic cage, which tapers sharply in the upper chest and is conical, consists of the sternum, 12 thoracic vertebrae, 10 pairs of ribs that end anteriorly in segments of cartilage, and 2 pairs of floating ribs. The cartilages of the first 6 ribs have separate articulations with the sternum; the cartilages of the seventh through the tenth ribs fuse to form the costal margin before attaching to the lower margin of the sternum. The extension of the pleural space above the clavicles and over upper abdominal viscera is critical in evaluating penetrating wounds.

Musculature The pectoralis major and minor muscles constitute the principal musculature of the anterior thorax. The latissimus dorsi, trapezius, rhomboid, and other shoulder girdle muscles form the muscular coat for the posterior thorax. The lower margin of the pectoralis major forms the anterior axillary fold, and the convergence of the latissimus dorsi and teres major muscles forms the posterior axillary fold.

Pleura The pleura is an active serous membrane with a vascular and lymphatic network. There is constant movement of fluid, phagocytosis of debris, and sealing of air and capillary leaks. The visceral pleura covers the lung and is insensitive. It is continuous over the hilum and mediastinum with the parietal pleura, which covers the inside of the chest wall and diaphragm. As opposed to the visceral pleura, the parietal pleura is well endowed with nerve endings; when altered by disease or injury, pain results. The parietal pleura has nerve endings for pain; only when disease extends to this pleura of the chest wall is pain produced. The pleura extends slightly beyond the lung border in each direction and is completely filled with normal lung expansion; only a potential space exists.

Intercostal Space The parietal pleura constitutes the innermost layer, followed by three layers of muscles, which elevate the ribs

during quiet respiration. The vein, artery, and nerve of each interspace are located behind the lower margin of the rib. Thus a thoracentesis needle or a clamp used to enter the pleura should be inserted across the top of the lower rib of the selected interspace.

Diaphragm The peripheral muscular portions of the diaphragm arise from the lower six ribs and costal cartilages, from the lumbar vertebrae, and from the lumbocostal arches; the muscular portion converges to form a central tendon. The phrenic nerve supplies the motor innervation, and the lower intercostals supply the sensory innervation. The diaphragm, which rises as high as the nipple, contributes 75 percent of pulmonary ventilation during quiet respiration.

THORACIC INCISIONS

Lateral Thoracotomy *Anterolateral* This incision extends from the sternal border at the fourth interspace to the midaxillary line. It requires division of the pectoralis major and minor muscles and the serratus anterior. The incision allows rapid entry into the chest with the patient in the semidecubitus position. Therefore, it is the preferred incision for trauma and hemodynamically unstable patients. Exposure is adequate for mediastinal operations, for some cardiac procedures, and for resection of the middle and upper lung lobes.

Posterolateral This incision is used for the majority of pulmonary resections, for esophageal operations, and for the approach to the posterior mediastinum and vertebral column. The skin incision starts at the anterior axillary line just below the infrapectoral fold, extends posteriorly below the tip of the scapula, and ascends between the scapula and the vertebral column. Parts of the serratus anterior, latissimus dorsi, and trapezius are divided, and the thoracic cavity is entered usually in the fifth interspace.

Midlateral No major muscle groups are divided, allowing for quick closure and less patient discomfort. Good exposure is attained with single-lung ventilation.

In general, with lateral thoracotomies, postoperative respiratory therapy is essential because patients experience significant pain and avoid using their chest muscles. Patients must be properly positioned with an axillary roll to prevent brachial plexus injury.

Median Sternotomy Median sternotomy is the optimal incision for anterior mediastinal and cardiac surgery. The pleural spaces can be entered or avoided as desired. The skin incision extends from

the sternal notch to the xyphoid, and the sternum is split to enter the chest. Since fewer muscles are divided, patients have less postoperative pain and impaired pulmonary function than with a lateral thoracotomy.

Bilateral anterior thoracotomy and thoracoabdominal incisions are used infrequently but have application in lung transplantation and retroperitoneal pathology.

Thoracoscopy Video-assisted thoracic surgery (VATS) has become an accepted approach to diagnosis and treatment of pleural effusions, recurrent pneumothoraces, lung biopsies, resection of mediastinal cysts, and esophagomyotomy. Major cancer resections are best performed with traditional open approaches.

PREOPERATIVE EVALUATION

All operations on the chest result in some short-term respiratory disability, and many cause permanent alterations in function of intrathoracic organs. Hence the following factors are examined to assess the ability of the patient to undergo surgery.

Pulmonary Function Pulmonary function must be adequate to tolerate the operation and the postoperative period. No single test is available that provides an adequate overall evaluation of lung function. Measurements of value include lung volumes, mechanics of breathing, regional lung function, diffusion capacity, and arterial blood gas determinations.

Spirometry Vital capacity (VC, normal 70 mL/kg), the amount of air that can be forcefully expelled from a maximally inflated lung position, is normal or near-normal in patients with moderately severe obstructive airway disease and is reduced in individuals with restrictive pulmonary or neuromuscular disease. The forced expiratory volume in 1 s (FEV_1) is reduced in obstructive airway disease, but the degree of reduction varies in the same individual. The FEV_1 may be the most useful test to monitor patients with marginal pulmonary function who are being prepared for operation by aggressive respiratory therapy. The FEV_1 is reported as an actual volume and as a percentage of the VC (FEV_1/VC). The values obtained with spirometry in patients are compared with those obtained from other normal individuals of the same sex, age, and height and are reported as a percentage of normal.

Blood-Gas Determination The $PaCO_2$ measurement provides an immediate indication of the patient's alveolar ventilation; any value

above 46 mmHg signifies hypoventilation. Elevation of the $PaCO_2$ suggests abnormalities in distribution of ventilation and perfusion; patients with chronic lung disease may be treated aggressively to improve pulmonary function and then be considered for operation. Normal PaO_2 is 85 mmHg at sea level. If it is below 70 mmHg, an attempt should be made to determine the cause and to improve the patient's respiratory exchange.

Specialized Tests Radionuclide perfusion scanning for regional lung function allows determination of the separate contributions of the right and left lungs to overall pulmonary function ("split-function" study) and is helpful for patients with compromised pulmonary reserve determined by spirometry. Postoperative VC and FEV_1 can be predicted for the patient who requires pulmonary resection (predicted postoperative FEV_1 = preoperative $FEV_1 \times$ percent perfusion in noninvolved lung segments). Perioperative mortality is increased significantly if the predicted postoperative FEV_1 is less than 800 mL.

Exercise Testing This is indicated for patients with reasonable exercise capability despite severe obstructive airway disease. These tests measure maximal oxygen consumption (MVO_2). Patients with an MVO_2 of less than 10 mL/kg/min have a prohibitive risk of postoperative complications.

Many patients are smokers, and every effort should be made to stop for 2 or more weeks before operation. Aggressive attention should be paid to reducing the amount and tenacity of secretions, as well as to identifying and treating any pulmonary infection.

Cardiac Status Electrocardiography is essential. If history, examination, or electrocardiogram (ECG) reveal any abnormalities, cardiology consultation is advisable. Exercise or pharmacologic stress tests and radionuclide angiograms provide excellent noninvasive evaluation of ischemia and ventricular function. Echocardiography and coronary angiography may be necessary (Fig. 16-1).

Nutrition Malnutrition increases the morbidity and mortality of any surgical procedure. Particularly important in thoracic surgery patients are the adverse effects of protein depletion on respiratory function. The muscle groups in the thorax, shoulder, and diaphragm that are involved in respiration and coughing share in the unselected loss of strength seen in all muscles. Coupled with the increased tendency for pulmonary edema and the relative immunosuppression of malnutrition, the risk of a thoracic operation rises.

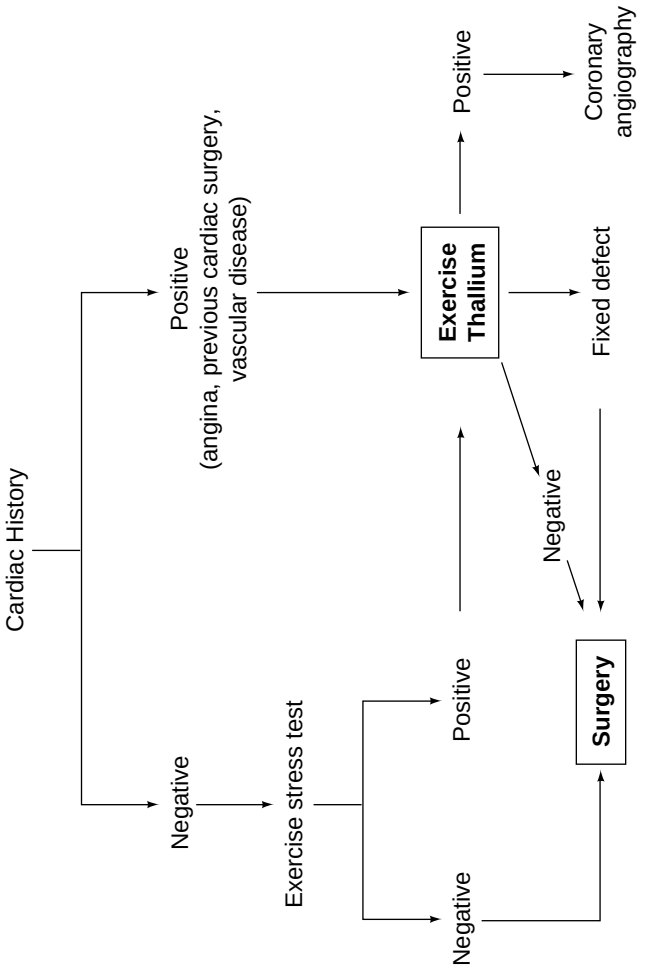


FIGURE 16-1 A suggested algorithm for investigating the cardiac status of all patients over age 45 or those with significant risk factors undergoing major thoracic surgery. (Adapted from Miller JI: Preoperative evaluation. *Chest Surg Clin North Am* 4:701, 1992, with permission.)

Nutritional status should be assessed by history, physical examination, and laboratory tests (i.e., hemoglobin, coagulation, liver enzymes, and total lymphocyte count).

POSTTHORACOTOMY CONSIDERATIONS

Pulmonary Function Changes Vital capacity is reduced 25–50 percent in addition to the amount of functioning lung that was removed. This is often accompanied by an increase in the closing volume, thus potentiating the development of atelectasis. The severe pain and the sedative effects of the postoperative analgesia produce reductions in tidal volume and elimination of normal sighs. Coughing is inhibited, as is ciliary function and alveolar macrophage activity; hence the protection against inhaled particulate matter and microbes is diminished.

Pain Incisional pain is severe, and unless it is well managed, it will cause diminished respiratory mechanics. It is a challenge to give patients enough pain medication so that they are able to cough without giving them so much that they lose their drive to do so. Analgesia is best administered intravenously or via an epidural catheter in a continuous fashion or with patient-controlled analgesia (PCA) and can be augmented in the early postoperative period with intraoperative intercostal blocks.

Complications Atelectasis involves closure of lung units, and it exists as microatelectasis (not visible on chest radiography) and macroatelectasis (the collapse of a segment, lobe, or entire lung). It is caused by retained bronchopulmonary secretions, decreased sighing, and decreased expiratory reserve volume and may lead to fever and ventilation-perfusion mismatch. Postoperative bronchopulmonary infectious complications consist of tracheobronchitis and pneumonitis. They are a consequence of diminished pulmonary function and can hinder postoperative recovery. The most common cardiovascular complication is supraventricular arrhythmia.

THORACIC INJURIES

The predominant types of injury include high-velocity penetrating wounds (usually military), knife or low-velocity gunshot wounds (civilian), and blunt injury from motor vehicle and industrial accidents.

Conditions Requiring Urgent Correction

Airway Obstruction The oropharynx should be cleared of debris and the neck positioned by an anterior chin-thrust motion while applying continuous cephalad traction to the head. Nasotracheal or orotracheal intubation or cricothyroidotomy should be performed as indicated.

Tension Pneumothorax When injury to the lung parenchyma allows air to enter (but not exit) the pleural space, the pressure increases, causing a shift of the mediastinum and compression of the contralateral lung as well as a decrease in venous return. Release of tension by a thoracostomy tube or large-bore needle is lifesaving.

Open Pneumothorax When a segment of chest wall is destroyed, air is sucked through the wound into the chest rather than through the trachea into the alveoli. A watertight seal (dressing) should be placed and a tube inserted into the pleural space, followed by early repair and closure.

Massive Flail Chest When severe blunt injury results in a two-point fracture of four or more ribs, the chest wall becomes flail. The patient is unable to develop sufficient negative pressure to maintain ventilation; intubation and positive-pressure ventilation are mandatory.

Massive Hemothorax If a patient has percussion dullness of a hemithorax after trauma, a chest tube should be inserted. If massive hemothorax is found ($>$ 1500 mL initially or $>$ 200 mL/h for 4 h), the patient should be explored.

Conditions Requiring Urgent Thoracotomy

1. *Massive air leak.* This signifies disruption of the trachea or a major bronchus. Greater than 80 percent of injuries are within 2.5 cm of the carina.
2. *Pericardial tamponade in the presence of trauma.*
3. *Esophageal perforation.*

Dangerous But Less Compelling Injuries

Diaphragm Rupture Rupture is caused most commonly by penetrating trauma or crush injuries. The left hemidiaphragm is more

prone to rupture (ratio of 9:1 compared with the right side). Repair is required to prevent herniation of abdominal contents, which can strangulate and perforate or prevent adequate ventilation by occupying the thoracic cavity. When the diagnosis is made early, repair should be performed via laparotomy.

Pneumothorax Pheumothorax is usually the result of injury to the lung or the tracheobronchial tree and can be associated with a hemothorax. In patients with more than 50 percent collapse, in those with hemopneumothorax, and in patients with penetrating chest trauma, an intercostal catheter should be inserted and attached to 10–25 cmH_2O of suction. If the pneumothorax is stable, it can be observed and will resorb at a rate of 1.25 percent per day.

Interstitial Emphysema This condition is caused by disruption of the respiratory tract or esophagus without air entering the pleural space; the air spreads into the mediastinum, the deep tissue planes, and the subcutaneous space. The patient's appearance is markedly distorted, but there is no reason to "treat" the condition, except to take steps to stop the air leak.

Rib Fractures and Lesser Flail Injuries The main concerns are pain control and for the patient to maintain adequate ventilation. Intubation and positive-pressure ventilation are required if there is any respiratory distress. Associated factors to beware of include delayed pneumothorax, hemothorax, pulmonary contusion, and subclavian injury from an anterior first rib fracture.

Sternal Fractures Sternal fractures are usually transverse, occurring at or near the manubrium, and are painful. It is essential to rule out injury to underlying structures, especially the heart (echocardiograms, continuous ECG monitoring for at least 24 h, determination of creatine phosphokinase levels).

Hemothorax Massive or continued intrathoracic bleeding requires a thoracotomy. If the costophrenic angle is merely blunted (implying < 300 mL), a hemothorax may be followed. Larger amounts of blood need to be evacuated with a thoracostomy catheter. If the hemothorax persists because of a poorly functioning tube, thoracotomy and removal of the clot are indicated to prevent fibrothorax and empyema.

Pulmonary Injury The lungs have a remarkable ability to tolerate penetrating and blunt trauma. Any penetrating object causes a degree of pneumothorax and bleeding. With insertion of an

intercostal catheter, the lung reexpands, tamponades the injury, and then eventually heals. Thoracotomy is rarely needed to control bleeding. Contusion is caused by blunt injury and is characterized by capillary disruption and a "fluffy" infiltrate on chest radiograph 24–48 h after the injury. If a significant area is involved, mechanical assistance may be required, but usually not for more than 48–72 h.

CHEST WALL

Congenital Deformities

PECTUS EXCAVATUM

Pectus excavatum is the most common congenital deformity of the chest wall and is attributed to overgrowth of the lower costal cartilages and ribs. The body of the sternum is displaced posteriorly to produce a funnel-shaped depression. Asymmetry is common, and the defect varies widely in expression. The anomaly is three times more common in males, and there is a familial tendency. Between 30 and 70 percent of patients report symptoms, including exercise intolerance, atypical chest pain, dyspnea, bronchospasm, and arrhythmias. However, there is little solid evidence to support functional cardiopulmonary impairment. Operative correction is recommended between 18 months and 5 years to prevent postural and psychological consequences of the defect, but correction in adolescence is also justifiable in order to allow evolution of the defect. The operative technique involves excising the deformed costal cartilage, separating the intercostal muscle bundles from the sternum, and then correcting the sternal concavity. This is done by combining a forward fracture of the sternum with an insertion of bone posteriorly, inserting a metal strut to elevate the sternum, or inverting the entire sternum.

PECTUS CARINATUM

The protrusion deformities of the sternum are much less common than pectus excavatum. Most patients are asymptomatic, and operative treatment consists of resection of the deformed cartilage and contouring of the sternum with transverse osteotomies.

STERNAL FISSURES

Fissures are caused by failure of the sternal primordia to fuse. The superior sternal cleft is broad and extends to the fourth costal cartilage. Osteotomies of each half and reapproximation usually can be performed. Distal sternal cleft is invariably part of Cantrell's pentology, which consists of other defects in the heart, diaphragm,

and ventral abdominal wall. Complete sternal cleft is the rarest form of fissure and should be repaired during infancy.

Chest Wall Tumors

Metastatic lesions and direct invasion from breast or lung primaries are the most common chest wall tumors. About half of primary tumors are malignant, and hence the initial biopsy should provide adequate tissue for proper diagnosis.

BENIGN TUMORS

Fibrous Dysplasia (Osteofibroma, Bone Cyst) This entity presents as a slowly enlarging, nonpainful mass.

Eosinophilic Granuloma This is a solitary destructive process associated with pain and tenderness that may heal spontaneously.

Osteochondroma This is a slowly growing tumor from the cortex of a rib.

Chondroma This occurs at the costochondral junction in children and young people. It can be confused pathologically with a chondrosarcoma, and therefore, initial wide local excision is recommended.

Desmoid Tumors These have a tendency to recur and should be resected with a wide margin.

MALIGNANT TUMORS

Although the sarcomas arising in the adult chest wall usually are classified by the cell type of origin, prognosis is related to histologic grade rather than cell classification. The currently recommended grading system groups these tumors as adult soft tissue sarcomas. These tumors include fibrosarcoma, chondrosarcoma, osteogenic sarcoma, Ewing's sarcoma, and myeloma. These tumors are potentially curable, usually by wide surgical resection. Factors that influence prognosis include age, tumor size, histologic grade, and stage.

Chest Wall Reconstruction

Radical excision of malignant chest wall tumors can be accomplished with respiratory support and adequate reconstruction to provide chest wall stability. Many techniques for reconstruction are used, including synthetic meshes, acrylic plates, and myocutaneous flaps.

DISEASES OF THE PLEURA AND PLEURAL SPACE

Pleural Effusion

A pleural effusion is an accumulation of fluid in the pleural space. A concave meniscus in the costophrenic angle suggests the presence of at least 250 mL of fluid. Lateral decubitus views can detect smaller amounts of fluid and can confirm that the fluid is free. A transudate is a protein-poor ultrafiltrate of plasma that is caused by alterations in systemic hydrostatic colloid osmotic pressure. Examples include chronic heart failure, cirrhosis, nephrotic syndrome, hypoproteinemia, and peritoneal dialysis. Changes in capillary permeability caused by inflammation or infiltration of the pleura produce a protein-rich effusion classified as an exudate. Examples include malignancy, infection, infarction, trauma, and sympathetic effusion. Characteristics of the fluid that distinguish exudate from transudate are pH < 7.2, high protein content, foul smell, red cell count $> 100{,}000/mm^3$, elevated amylase level, and Gram's stain positive for bacteria. Pleural effusions can produce dyspnea. Thoracentesis is the mainstay of diagnosis. Therapeutic drainage of transudative effusions is rarely indicated because they will reaccumulate unless the underlying condition is improved. Exudative effusions usually warrant a more aggressive approach (surgical drainage).

MALIGNANT PLEURAL EFFUSION

Malignant effusions are caused by interference of venous and lymphatic drainage by direct tumor invasion and frequently are massive and symptomatic. The fluid is exudative and often bloody. The presence of a malignant effusion is a poor prognostic sign, and treatment is palliative, consisting of tube thoracostomy or videothoracoscopy to evacuate all fluid, followed by chemical pleurodesis. Talc has become the most popular sclerosant, with reported success rates of 80–90 percent.

EMPYEMA

Empyema is a suppurative infection of the pleural space, most often associated with pneumonia (*Staphylococcus, Streptococcus,* and gram-negative organisms), trauma, pulmonary infarction, or extension from an intraabdominal source. Initially, the fluid is free, but the suppuration leads to a fibrinous "peel" that traps the lung and prevents reexpansion. Thoracentesis with Gram's stain confirms the diagnosis, and a computed tomographic (CT) scan is useful in delineating abscess, loculations, and lung parenchyma.

The first step of treatment is chest tube insertion and closed suction. If the lung reexpands and the cavity is obliterated, the tube simply can be removed. If the drainage persists and the lung is adherent to the chest wall, the closed drainage can be converted easily to open drainage. If the lung is trapped and does not reexpand with high suction, thoracotomy and decortication are indicated.

CHYLOTHORAX

Chylothorax is a milky, odorless effusion consisting of leaking lymphatic fluid from the thoracic duct. The most common cause is surgical trauma followed by noniatrogenic trauma and malignancy. Chylothorax is frequently massive (average loss > 750 mL/day) and can produce dehydration, malnutrition, and loss of circulating lymphocytes. Conservative treatment is usually successful and consists of keeping the lung expanded and decreasing chyle production by eliminating oral intake and starting parenteral nutrition. A 7–10-day trial of conservative management is justified. If this fails (persistent drainage after 7–10 days or > 500 mL/day in an adult), surgical treatment is indicated. If it is hard to find the actual site of injury, the thoracic duct is ligated in the right chest close to the diaphragm.

Tumors

Mesothelioma This neoplasm originates from the mesothelial lining of serosal cavities. Eighty percent of cases present in the pleura, with 20 percent in the peritoneum. It is associated with asbestos exposure, with smoking as an important cofactor. Mesothelioma exists in both benign (15 percent of the total) and malignant (85 percent of the total) forms. The benign form is usually asymptomatic and unifocal, and resection is the treatment of choice.

Malignant mesothelioma is locally aggressive, 2:1 male predominant, and multicentric, with multiple pleural-based nodules forming sheets separated by loculated, cystic spaces. Most patients die of the primary tumor, although hematogenous and lymphatic spread occurs in one-half of cases. Radical extrapleural pneumonectomy or complete pleurectomy combined with radiation can extend survival in selected patients with Stage I–II tumors, but long-term survivors are rare.

Metastatic Pleural Tumors Over 90 percent of pleural tumors are metastatic, with lung and breast primaries being the most common.

Spontaneous Pneumothorax

Spontaneous pneumothorax most commonly results from rupture of a pulmonary bleb or bullae and occurs in young males without significant pulmonary disease. The incidence of recurrence increases after each episode. An asymptomatic pneumothorax with less than 30 percent collapse that does not increase in size over 8 h can be observed; otherwise, a thoracostomy tube is inserted to allow lung reexpansion. Operation may be required for a persistent air leak ($>$ 1 week), for a massive air leak preventing lung expansion, or after the second episode. At thoracoscopy or thoracotomy, the site of leak is closed, and a pleural abrasion or parietal pleurectomy is performed.

LUNG

Anatomy

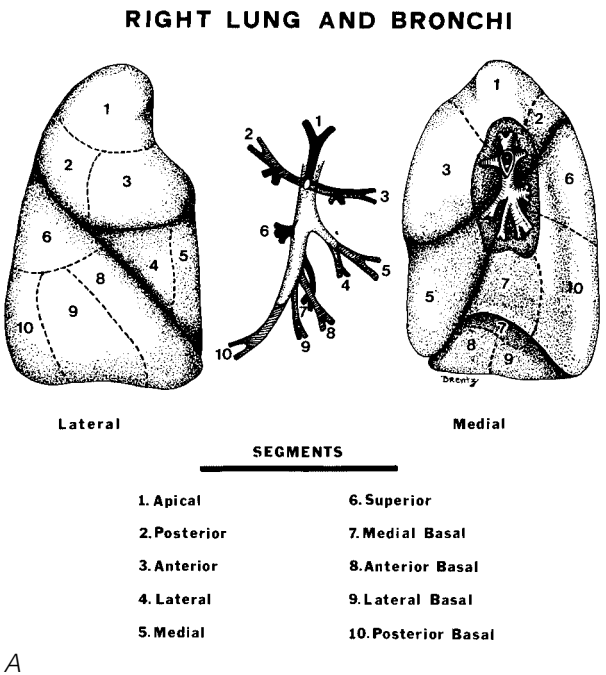
Segmental Anatomy The right lung has three lobes (upper, middle, lower), whereas the left lung has two lobes (upper and lower). Each lobe contains a segmental blood supply and bronchial network, with the right lung containing 10 segments and the left lung containing 9 segments. Separation of the bronchial and vascular stalks allows subsegmental and segmental resections when lung tissue needs to be preserved (Fig. 16-2).

Lymphatic Drainage Two groups of lymph nodes drain the lungs: the pulmonary, or N1, nodes and the mediastinal, or N2, nodes. In turn, the pulmonary nodes consist of intrapulmonary, lobar, interlobar (referred to as the *lymphatic sump of Borrie* because all lobes of the corresponding lung drain into this group of nodes), and hilar nodes. The mediastinal nodes consist of anterior mediastinal, posterior mediastinal, tracheobronchial, and paratracheal nodes. Lymphatic drainage of the right lung is usually ipsilateral, whereas drainage from the left lung is as frequently contralateral as ipsilateral.

Diagnostic Modalities

AIRWAY INVESTIGATION

Sputum Sputum is needed for culture and cytology and must be obtained past the level of the larynx. This is done by percutaneous transtracheal or orotracheal aspiration or by saline-induced coughing.

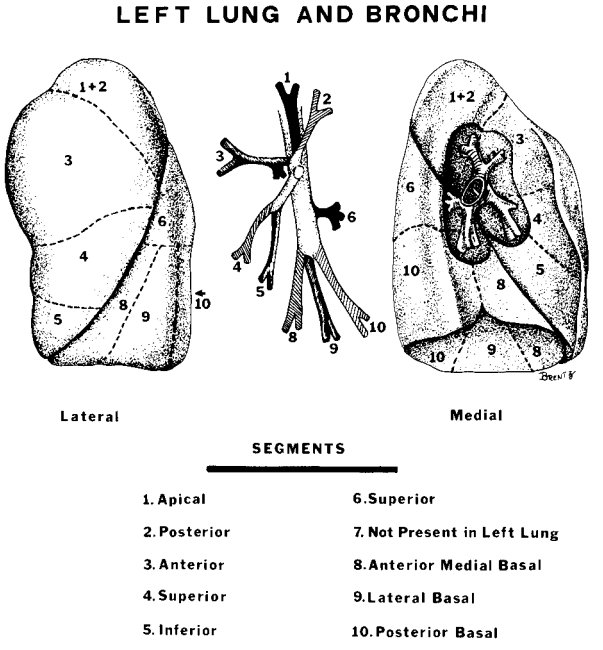


A

FIGURE 16-2 A and B. The segmental anatomy of the lungs. An appreciation of these anatomic divisions often makes it possible to preserve pulmonary tissue by performing segmental resections for localized disease.

Bronchoscopy Bronchoscopy allows direct visual examination of the tracheobronchial tree, direct biopsies of bronchial neoplasms, and the ability to assess mobility of surrounding structures, extent of endobronchial involvement, and on occasion, the source of bleeding. Therapeutic uses include removal of foreign bodies or inspissated secretions, ablation of endobronchial tumors, and management of hemoptysis.

Imaging The standard posteroanterior chest radiograph remains the most frequently used study and is an adequate screening tool. For better definition, the CT scan and magnetic resonance imaging (MRI) are used. Nuclear medicine imaging plays an important role



B

FIGURE 16-2 (*Continued*)

in ventilation-perfusion studies (for diagnosing pulmonary embolus and split function testing). Bronchography is used rarely. Pulmonary angiography is useful for embolization of intrapulmonary bleeding sources.

BIOPSIES

Needle Biopsies Percutaneous transthoracic needle biopsy (PTNB) is commonly performed to evaluate intrathoracic lesions. It is performed under local anesthesia and is associated with trivial pneumothoraces in up to 30 percent of patients. It can help identify malignancies, infections, sarcoidosis, and other pulmonary diseases. Contraindications include coagulopathy, pulmonary hypertension, bullous lung disease, and positive-pressure ventilation.

Mediastinoscopy Mediastinoscopy is used to evaluate and biopsy paratracheal masses or identify spread of pulmonary neoplasms. The paratracheal, tracheobronchial, and subcarinal nodes are accessible, whereas posterior nodes, nodes between the trachea and esophagus, and anterior mediastinal masses are not.

Parasternal Mediastinotomy The second and third costal cartilages are spread apart or removed, and the mediastinum visualized. This is particularly useful for evaluation of nodes left of the aortic arch and in the pulmonary hilum.

Thoracoscopy With improved equipment and single-lung ventilation, thoracoscopy has become an extremely versatile technique for evaluating the pleural space, inspecting the mediastinum, obtaining lung biopsies, and removing peripheral pulmonary nodules.

Open Lung Biopsy The chief indication for open lung biopsy is failure of other less invasive techniques to make a diagnosis. A formal operation under general anesthesia is required, and there is some morbidity associated with the procedure.

Congenital Lung Lesions

Agenesis Bilateral pulmonary agenesis is not compatible with life. Isolated unilateral agenesis (usually on the left) allows for normal life.

Hypoplasia Hypoplasia is seen most often in association with anomalies that compete with the lungs for space, such as diaphragmatic hernia.

Cystic Adenomatoid Malformation Neonates present with acute respiratory distress in the first few hours of life. Chest radiograph shows a multicystic "swiss cheese" region with overexpansion and mediastinal shift toward the normal lung. Lobectomy is the treatment of choice, and prognosis is excellent.

Pulmonary Sequestration A portion of lung may be isolated during development and receive its blood supply from the aorta instead of the pulmonary artery. Intralobar sequestrations rest within a lobe and do not have a visceral pleural envelope but rather communicate with the tracheobronchial tree. They occur in the posteriobasal segments and present as recurrent pneumonias; the treatment is lobectomy. Extralobar sequestration is less common, does

not have tracheobronchial communication, is enclosed by its own pleural sheath, and appears as an unexplained triangular mass in the posterior lung field. Treatment is resection.

Congenital Cysts These cysts can be single or multiple and are confined to a segment or lobe. They invariably present with infection, since the viscous fluid they contain becomes contaminated after communication with the airway. Resection, after preoperative bronchoscopy and arteriography, is indicated. These bronchogenic cysts also can present as mediastinal masses, and resection of these is controversial.

Arteriovenous Malformation Pulmonary arteriovenous malformation (AVM) is a fistula between pulmonary arteries and veins. Multiple small lesions associated with the Osler-Weber-Rendu syndrome account for half of all patients. The other half have lesions that are fewer in number and larger in size. When shunt fraction exceeds 25 percent of total blood flow, patients can present with cyanosis and polycythemia. Pulmonary angiography confirms the diagnosis. Invasive angiographic embolization is effective and has replaced pulmonary resection as primary therapy in most cases.

LOBAR EMPHYSEMA

Lobar emphysema presents with massive distention of a lobe or segment that shifts the mediastinum and compresses the contralateral lung. Involvement of the upper or middle lobe is the most frequent finding; lower lobe involvement is rare. Resection is straightforward and curative.

EMPHYSEMA

Emphysema is characterized by enlarged airspaces produced by coalescence of damaged alveoli, resulting in air trapping and hyperexpansion of the lung. Localized emphysema (blebs, bullae) may rupture and produce pneumothorax or enlarge massively and compress remaining normal lung. Patients with large, well-defined bullae with normal underlying lung are most likely to have symptomatic improvement after resection. Selected patients with diffuse emphysema involving predominantly the upper lobes may be candidates for lung volume-reduction surgery (LVRS). Improvement in dyspnea and pulmonary function last up to 2 years, but long-term results are unknown. Lung transplantation is reserved for patients with end-stage disease who are unsuitable for LVRS.

Pulmonary Infections

LUNG ABSCESS

Lung abscess is a focus of infection with parenchymal necrosis and cavitation. It is most commonly a complication of necrotizing pneumonia secondary to aspiration and is, therefore, located in segments that are dependent in the supine position (i.e., posterior segments of the upper lobes and superior segments of the lower lobes). Other causes are bronchial obstruction, seeding from systemic sepsis, pulmonary trauma, and direct extension from extraparenchymal infection. Patients present with fever, appear chronically ill, and describe recent onset of copious foul-smelling sputum production. Hemoptysis can occur and be massive; dyspnea is not common.

Treatment is primarily high-dose antibiotics and drainage. Spontaneous drainage by expectoration is adequate, but bronchoscopic aspiration may be needed. Conservative treatment is successful in 75 percent of patients. When internal drainage is inadequate, external drainage is established by tube pneumonostomy or pneumonotomy, which opens the cavity to the outside. Both procedures depend on pleural symphysis; spillage of the abscess material into the free pleural space can be catastrophic. Lobectomy is the definitive treatment. The indications are chronic symptoms, serious hemorrhage, and suspicion of carcinoma.

OPPORTUNISTIC INFECTIONS

Cancer chemotherapy, organ transplantation, major trauma, and the acquired immune-deficiency syndrome (AIDS) have created an increasing population of immunologically compromised patients. Pulmonary infections are the most common infections seen in this population. In the AIDS population, *Pneumocystis carinii* is the most common pathogen and is treated effectively with trimethoprim-sulfasoxisole. Transbronchial biopsy combined with bronchalveolar lavage can establish a specific infectious diagnosis and has reduced the need for direct lung biopsy. Surgical lung biopsy is reserved for confusing mixed infections not responding to empirical treatment. Surgical treatment of pulmonary complications in the AIDS population may be complex with poor prognosis. The spectrum of infections in non-AIDS patients is wider and should be approached aggressively using indications for surgery applied to normal hosts with similar infections.

BRONCHIECTASIS

Bronchiectasis is characterized by bronchial dilatation and variable involvement of surrounding parenchyma. The bronchial mucosa

usually remains intact, but the bronchi are filled with pus, mucus, and an occasional broncholith. Segmental bronchi of the lower lobes, the right middle lobes, and the lingula are involved most frequently. The disease is most commonly idiopathic; it can be associated with cystic fibrosis or obstruction by tumor, foreign body, or bronchostenosis.

The clinical picture is dominated by cough and mucopurulent sputum production (scant to 1000 mL/day), low-grade fever, weight loss, and hemoptysis. Complete bronchography is the definitive test. Postural drainage, chest physical therapy, and antibiotics will obviate operative treatment in most patients. If symptoms persist and the disease is localized, segmentectomy or lobectomy is indicated.

TUBERCULOSIS

Pulmonary infection with *Mycobacterium tuberculosis* behaves like a lung abscess: The smoldering central focus of infection communicates with the tracheobronchial tree, providing drainage for bacilli-loaded sputum and allowing ingress of air to cause cavitation. The intense inflammatory process promotes arterial hypertrophy, and erosion into these vessels can cause life-threatening hemoptysis. Chest radiograph showing upper lobe cavitary changes or a positive purified protein derivative test is suggestive of the diagnosis. Definitive diagnosis rests on growth of the organism in culture.

Treatment is primarily medical with a combination of drugs, including isoniazid and rifampin; oral pyrazinamide has largely replaced parenteral streptomycin. Pulmonary destruction with bronchopleural fistula and empyema, persistently active disease, hemorrhage, or inability to rule out cancer are indications for surgical resection. If limited pulmonary reserve precludes resection, thoracoplasty (resection of the ribs) can be used to collapse the pleural space and obviate infection.

CHRONIC GRANULOMATOUS INFECTIONS

Actinomycosis *Actinomyces israelii* is an anaerobic bacillus (not fungus) that inhabits the oral cavity and tonsilar crypts. Thoracic infection is thought to occur from aspiration and is characterized by suppuration, abscess, and sinus tract formation and relentless invasion. Diagnosis is suggested by sulfur granules (yellow-brown clusters of microorganisms) from sputum, sinus tracts, or biopsies and is proven by identifying the bacillus using special stains. The organism is sensitive to penicillin, and surgical resection is very rarely required.

Nocardia *Nocardia asteroides* is a rare pathogen except in immunocompromised hosts and begins as a pneumonic process grossly similar to tuberculosis and carcinoma. It is a bacillus (not fungus), is relatively easy to culture, and is usually treated successfully with sulfonamides.

FUNGAL INFECTIONS

Histoplasmosis *Histoplasma capsulatum* is the most common systemic fungal infection in the United States. The severity of infection is determined by the size of the inoculum and the immune competence of the host. The disease can take many forms and is distinguishable from tuberculosis only by culture. Amphotericin B is effective in the majority of patients and is the treatment of choice for serious illness. Asymptomatic patients with positive skin tests need not receive chemotherapy. The presence of large, thick-walled cavities that fail to improve after a course of amphotericin B is the most common indication for surgery. Lymphogenous dissemination leads to compression of mediastinal structures or sclerosing mediastinitis.

Aspergillosis *Aspergillus* infection presents in three forms: allergic bronchospasm, invasive (invariably fatal), and saprophytic. Saprophytic disease is caused by colonization of a preexisting pulmonary cavity ("fungus ball," or aspergilloma). Diagnosis can be made by skin tests and sputum cultures. Amphotericin B is the treatment for disseminated disease, but it does not enter into a cavity. Excellent results have been obtained with intracavitary instillation of amphotericin B. Operation is most often justified as prevention of hemoptysis, which occurs in more than half of patients, but morbidity is considerable.

TUMORS

Primary Carcinoma

Lung cancer is the main cancer killer for both sexes. The primary cause is tobacco addiction; long-term exposure or cocarcinogens are required, and the risk is reduced by cessation of smoking.

Pathologic Classification Most primary bronchogenic carcinomas arise from basal or mucous cells in the surface epithelium of the bronchial tree. Other sites of origin are the neurosecretory cells (Clara cells) and Kultchitsky cells (carcinoid tumors). The simplest division, based on approach and management, is between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

NSCLC *Squamous Cell Carcinomas* Though more common in the upper lobes, bronchogenic carcinomas develop in all parts of the lung. They are relatively slow growing, are late to metastasize, and may present as central bulky masses with bronchial obstruction or as peripheral lesions with cavitation. Peripheral tumors may present with extensive chest wall invasion before metastases occur. The Pancoast syndrome represents a specific example wherein a tumor in the superior sulcus may invade the brachial plexus, the upper two ribs, and the vascular structures at the thoracic apex. Squamous cell carcinoma was the leading pulmonary neoplasm in the United States, but adenocarcinoma is now the predominant cell type.

Adenocarcinomas These tumors arise in the subsegmental bronchi away from the hilum. Growth is more rapid than in squamous tumors, and early metastasis by the vascular route is common, particularly to the brain and adrenals.

Bronchoalveolar Carcinomas An uncommon form of adenocarcinoma develops in the very distal airways and lines the alveoli. It often presents as a peripheral nodule or multifocal carcinoma and is appropriately managed by resection. Less frequently, it presents as lobar consolidation and is rarely cured with surgery.

Small Cell Lung Cancer The small cell anaplastic carcinoma (oat cell carcinoma) is a highly malignant, rapidly growing neoplasm, often located centrally because of its origin from a proximal bronchus. It spreads by lymphatic and hematogenous dissemination and local invasion. The only variant considered for surgical resection is the rare solitary peripheral tumor without associated adenopathy.

Staging The most recent AJCC/UICC TNM classification is used.

Primary tumor = T:

T1: $\leq$3.0 cm, without invasion.
T2: $>$ 3.0 cm, invades the visceral pleura, or has associated obstructive pneumonitis. The proximal extent of the tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina.
T3: Any size with direct extension to the chest wall, diaphragm, pericardium, or mediastinal pleura or within 2.0 cm of the carina without involving the carina.
T4: Invasion of the heart, great vessels, trachea, esophagus, or carina or presence of a pleural effusion.

Nodal involvement = N:

N1: Metastasis to peribronchial or ipsilateral hilar nodes.
N2: Metastasis to ipsilateral mediastinal or subcarinal nodes.
N3: Metastasis to scalene, supraclavicular, or contralateral mediastinal or hilar nodes.

Distant metastasis = M:

M1: Distant metastasis present.

TNM Stage Groupings

Stage IA:	T1N0M0
Stage IB:	T2N0M0
Stage IIA:	T1N1M0
Stage IIB:	T2N1M0; T3N0M0
Stage IIIA:	T1–3 N2M0; T3N1M0
Stage IIIB:	T4 Any N M0; Any T N3 M0
Stage IV:	Any T Any N M1

Surgical therapy is directed at those tumors for which a complete excision can be accomplished. These generally include clinical Stages I–IIIA.

Clinical Manifestations Bronchogenic carcinoma is seen with increasing frequency in patients over age 50, with a peak incidence between the ages of 60 and 70 years. The incidence of carcinoma in now 1.5:1 in favor of men. Asymptomatic patients are most likely to have early-stage disease and be potentially cured. Clinical manifestations include those due to local airway growth (e.g., cough, hemoptysis, pneumonia) and symptoms due to growth into surrounding structures (e.g., hoarseness due to recurrent nerve invasion, localized or radicular chest pain, superior vena cava obstruction, dyspnea from pleural effusion). Loss of appetite and weight loss are ominous signs; such patients usually have an unresectable tumor or systemic metastases.

A small percentage of patients, not necessarily with systemic spread, present with extrapulmonary nonmetastatic manifestations, which may be relieved by resection of the primary tumor. These include pulmonary hypertrophic osteoarthropathy with clubbing of the digits, secretions of hormone-like substances (e.g., adrenocorticotropic hormone, antidiuretic hormone, serotonin, parathyroid hormone), or myasthenia-like syndrome.

Diagnosis and Workup At presentation, approximately two-thirds of patients have disease beyond that treatable by surgical excision. Diagnostic evaluation should determine whether the disease

is localized (Stage I–II), locally advanced (Stage IIIA–B), or metastatic (Stage IV). The key modalities are history and physical examination, imaging studies (e.g., chest x-ray and CT scan of chest and upper abdomen), and tissue diagnosis (e.g., sputum cytology, needle biopsy, bronchoscopy, mediastinoscopy, or thoracic exploration). Additional studies for metastatic disease include bone scan and brain CT scan or MRI. Any mediastinal nodes larger than 1 cm warrant investigation before pulmonary resection.

Treatment Patients with clinical Stages I and II non-small cell lung cancer should be considered for surgical treatment. Resection of the tumor generally requires lobectomy or pneumonectomy. The aim of surgical resection is to completely remove the primary tumor and all involved lymph nodes.

Stage I Disease In Stage IA disease, less than 20 percent of patients recur after surgical resection. Most frequently, a lobectomy is required. Lesser resections are reserved for patients with very poor pulmonary function who cannot tolerate a lobectomy and carry a higher rate of local recurrence.

Stage II Disease Involvement of hilar lymph nodes more frequently mandates pneumonectomy for complete resection. Most recurrences occur at distant sites, but to date, randomized trials have failed to demonstrate a survival benefit from adjuvant chemotherapy or radiation. Tumors that directly invade adjacent structures (T3) can be removed with en bloc resections of the lung and involved structure, including chest wall, superior sulcus, and central airways.

Stage IIIA Disease Management of tumors with ipsilateral mediastinal node involvement remains controversial. Multiple clinical trials of induction chemotherapy or chemoradiotherapy indicate that complete surgical resection is possible with up to 30 percent of patients cured. Similar results have been achieved with chemoradiation alone. Two large randomized trials are comparing these methods, and both approaches presently appear valid.

Stage IIIB Disease Surgical cure is very unlikely. Patients are offered chemotherapy and radiation to control disease with a small chance of cure.

Metastatic Disease (Stage IV) Occasionally, patients with a curable primary tumor and solitary brain metastasis realize a 10–15 percent cure with resection of both lesions.

SCLC Median survival without treatment is 2–4 months. Chemotherapy can prolong survival up to 2 years with a small percentage of cure. Stages I and II patients treated by resection and adjuvant therapy have a reported 5-year survival of 30 percent, but most patients present initially with diffuse disease.

Solitary Pulmonary Nodules

The solitary pulmonary nodule has been defined as an abnormal density up to 4 cm in diameter, rounded or ovoid, surrounded by lung tissue, and free of cavitation or lung infiltrates. Because of the relatively favorable outlook of the nodule if it is a cancer, and because of the possible benign lesions presenting this way, there is considerable interest in the differential diagnosis of these "coin lesions." The differential diagnosis includes hamartoma, granuloma, arteriovenous malformation, pulmonary infarction, and benign and malignant tumors. Approximately 80 percent of all coin lesions are malignant in patients over 50 years of age. Histologic diagnosis should be delayed only if the nodule has been present without growth for a long period of time with a benign pattern of calcification. With tuberculosis less frequent and rising lung cancer rates, current odds favor early resection. With the advent of VATS, resection of peripheral nodules is well tolerated. In patients over 50 years, smokers, those with inadequate proof of the nodule being present longer than 2 years, and failure to make a diagnosis by other means, resection is indicated (Fig. 16-3).

Other Lung Tumors

Carcinoid Tumors This group includes all neuroendocrine neoplasms arising from Kulchitsky cells. All are malignant and represent a spectrum from typical carcinoids to small cell lung cancer. Typical carcinoid tumors are slowly growing tumors and metastasize late. Since 80 percent arise in the proximal bronchi, bronchial obstruction with infection and atelectasis is the most common clinical presentation. The carcinoid syndrome is rare. Lobectomy is the most common method of resection, but parenchyma-sparing procedures (sleeve resections) are appropriate whenever feasible anatomically. The long-term survival rate is over 90 percent.

Tumors of Bronchial Gland Origin Cylindroma and mucoepidermoid tumors are the most common neoplasms arising from the bronchial glands. Their location is predominantly central, and they

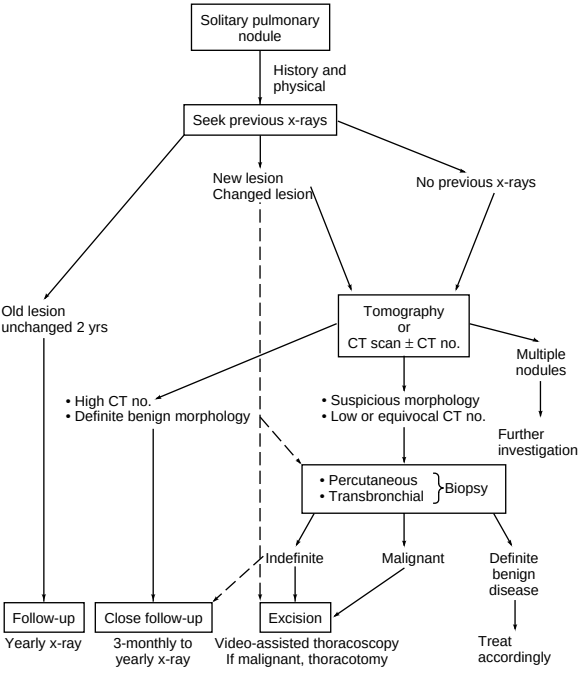


FIGURE 16-3 Algorithm for decision making in patients presenting with solitary pulmonary nodules.

may show a spectrum of behavior from benign to malignant, with distant metastases. Treatment is en bloc surgical resection, with cure rates higher than those for primary carcinoma.

Sarcomas A number of mesodermal sarcomas may occur in the lung (e.g., carcinosarcoma, leiomyosarcoma, lymphosarcoma, fibrosarcoma, and others) with the same symptoms as primary carcinoma. There is no increased incidence with cigarette smoking. Treatment is surgical resection, with prognosis depending on the stage of the neoplasm.

Benign Tumors Benign tumors comprise only 1 percent of pulmonary neoplasms. Hamartoma, which is composed of disorganized adipose, muscular, and fibrous tissue, is the most common. Hamartomas are usually asymptomatic and can be simply enucleated. Other tumors from epithelial, mesenchymal, or lymphoid origin can occur; their significance is related to the differential diagnosis from malignancy.

Metastatic Tumors Metastases to the lung are common during the clinical course of many extrathoracic primary neoplasms, and resection of these nodules can result in a significantly improved survival rate. Five factors important in selecting patients are (1) control of the primary tumor, (2) no extrathoracic metastases, (3) all lung metastases can be technically removed, (4) the patient can tolerate the operation, and (5) no better treatment exists. It is important to preserve as much lung tissue as possible; hence wedge resections or segmental resections are strongly preferred.

TRACHEA

Anatomy The trachea is a centrally located unpaired organ that has an average length in adults of 11 cm segmented by 18 to 22 cartilaginous rings. The rings are rigid for the anterior two-thirds, with a membranous portion posteriorly. This allows for flexibility without collapse. The blood supply is derived laterally from the inferior thyroid and bronchial arteries.

Congenital Lesions

The most common lesion is the tracheoesophageal fistula. Congenital stenosis, which is rare, presents in several variants: weblike diaphragms, tracheomalacia at sites of compression by a vascular ring, or absence of the membranous trachea with fusion of the rings posteriorly. Congenital stenosis should be suspected in infants with noisy breathing, wheezing, and retractions after birth. Operative treatment is indicated if repeated dilatation or tracheostomy fails to allow growth. When possible, the stenotic segment is resected and the trachea reconstructed with an end-to-end anastomosis. Diffuse involvement may require bone or cartilage splints.

Trauma

The most common injury requiring treatment is that occurring as a complication of tracheal intubation. Soft, low-pressure tubes have

reduced but not eliminated the problem. Ischemic necrosis at the tube cuff site can produce stricture, tracheomalacia, or erosion and fistula formation. Blunt and penetrating trauma produce a spectrum of injury ranging from laceration to complete transection.

Resection and end-to-end anastomosis constitute the preferred treatment. Fistulas are repaired by separating the two structures, closing the defects, and interposing muscle.

Neoplasms

Primary tracheal neoplasms are uncommon; more than 80 percent are malignant, and squamous cell and adenoid cystic carcinomas account for the majority of histologic types. Patients present with dyspnea, cough, wheezing, stridor, or hemoptysis. Bronchoscopy is an essential part of the evaluation. Airway stents and laser ablation are used for palliation, with excellent results in 60 percent of treated patients. Radiation therapy is used for long-term control. Operative resection is both a surgical and anesthesia challenge because obstructing lesions make ventilation difficult. Ventilation is delivered by placing an endotracheal tube through the distal trachea or bronchus or by "jet" ventilation. Up to one-half of the trachea can be resected and reconstructed with an end-to-end anastomosis. Upper tracheal lesions are approached through the neck, whereas distal lesions may require sternotomy or right thoracotomy. Prostheses and allografts for tracheal reconstruction generally have been unsuccessful.

MEDIASTINUM

The mediastinum is the central cavity of the thorax bounded laterally by the pleural cavities, inferiorly by the diaphragm, and superiorly by the thoracic inlet. It is divided into three compartments: (1) the anterior mediastinum, which lies above the heart and contains the thymus along with lymphoid and adipose tissue, (2) the posterior mediastinum, which lies behind the heart and contains the esophagus, thoracic duct, descending aorta, and the autonomic nerve trunks, and (3) the middle mediastinum, which contains the heart, pericardium, aorta, trachea, main stem bronchi, and related lymph nodes.

Tumors and Cysts

The most common mediastinal neoplasms are thymic tumors, lymphoma, neurogenic tumors, and germ cell tumors. Primary cystic

lesions account for 25 percent of all mediastinal masses. In children, almost half the tumors are lymphoma, followed by neurogenic tumors.

Manifestations and Diagnosis The most common symptoms are nonspecific (e.g., chest pain, cough, dyspnea) and are ascribed to compression of the trachea and esophagus. Other symptoms include superior vena cava syndrome, hoarseness from recurrent nerve palsy, and Horner syndrome. Nerve root compression through the intervertebral foramen ("dumbbell extension") can produce localized neurologic deficits. Ninety-five percent of mediastinal masses that are discovered as incidental radiographic findings are benign, whereas symptomatic lesions are about half benign and half malignant. CT scans and MRI provide great potential for imaging the mediastinum. Tissue for pathologic examination may be obtained by endoscopy, percutaneous needle biopsy, mediastinoscopy, or mediastinotomy. Small, anatomically discrete, encapsulated mediastinal masses are best managed with resection without preoperative biopsy. Large masses should be biopsied first because most will be treated nonoperatively (e.g., lymphoma) or with a combined-modality approach using preoperative chemotherapy (e.g., germ cell tumors or thymomas).

NEUROGENIC TUMORS

Neurilemmoma Neurilemmomas account for 40–60 percent of all neurogenic tumors. They arise from mature Schwann cells in intercostal nerves and are usually benign.

Neurofibromas Neurofibromas contain elements of both nerve sheath and nerve cells and account for 10 percent of all neurogenic tumors. Advanced age or presence of neurofibromatosis increases the risk of malignancy to 30 percent, which carries a poor prognosis.

Neuroblastomas These are poorly differentiated tumors arising from the sympathetic nervous system that can be hormonally active. More than 75 percent occur in children under 4 years of age. Bone, liver, and lymph node metastases are not infrequent and may make the lesion unresectable. Neuroblastomas are radiosensitive, and debulking followed by radiation can have favorable results.

PHEOCHROMOCYTOMAS

Intrathoracic primary pheochromocytomas are rare and are usually nonsecreting. Thirty percent are malignant.

THYMOMA

Thymoma is the most common anterior mediastinal mass in adults, is rare in children, and has a peak age incidence between 40 and 50 years. Symptomatic patients present either with mass effects on adjacent organs or with paraneoplastic syndromes such as myasthenia gravis or, rarely, hypogammaglobulinemia and red cell aplasia. Histology contributes nothing to the distinction between malignant and benign, which is based entirely on invasive gross characteristics. Benign thymomas can be resected for cure, but malignant thymomas have a poor prognosis. Postoperative radiation is of unknown benefit and does not compensate for an incomplete surgical resection.

LYMPHOMAS

Mediastinal lymphoma is most frequently located in the anterior compartment and is present in 50 percent of patients with Hodgkin's and non-Hodgkin's lymphoma. Chemotherapy and radiation are the standard treatment for lymphomas, and resection is almost never indicated. Surgery is performed as a diagnostic procedure.

TERATODERMOID TUMORS

Teratomas are found in the anterior mediastinum, are often partially cystic, and consist of ectodermal elements, including hair, teeth, and sebaceous glands. Surgical excision through a median sternotomy is the preferred treatment. Eighty percent are benign, and resection is curative. The prognosis for malignant tumors is poor because of local recurrence and distant metastases.

GERM CELL TUMORS

Five cell types of extragonadal germ cell tumors are present. Seminoma and embryonal cell carcinoma are the most common, followed by choriocarcinoma, malignant teratoma, and endodermal sinus carcinoma. The tumors are highly malignant, and 90 percent of patients present with symptoms of compression of adjacent structures. Because of improved chemotherapy during the past decade, most patients are now managed with chemotherapy initially. Residual mediastinal masses are resected to determine if active tumor remains, which determines subsequent therapy. Seminoma is very radiosensitive, and 5-year survival approaches 75 percent.

MESENCHYMAL TUMORS

Lipomas are the most common, followed by fibromas. The malignant forms are rare. Other tumors include hamartoma, leiomyoma, and others. Surgical resection is the treatment of choice.

MEDIASTINAL CYSTS

Congenital cysts constitute 20 percent of mediastinal masses and account for a majority of middle mediastinal lesions. A CT scan demonstrating a mass with near water density occurring in a characteristic location is diagnostic.

PERICARDIAL CYSTS

These are the most common cysts occurring in the mediastinum. They appear at the right cardiophrenic angle as a smooth-walled cystic mass and can communicate with the pericardium. If diagnosis is certain, they may be observed.

BRONCHOGENIC CYSTS

Bronchogenic cysts are most frequently located posterior to the carina or main stem bronchi. They can communicate with the tracheobronchial tree, producing an air-fluid level and allowing for confusion with lung or mediastinal abscess. All bronchogenic cysts should be resected to remove a site for potential chronic inflammation.

ENTERIC CYSTS

Enteric cysts are located in the posterior mediastinum adjacent to the esophagus. When lined with aberrant gastric mucosa, peptic ulceration can lead to perforation and abscess formation. Resection is always indicated.

Mediastinitis

ACUTE MEDIASTINITIS

Acute mediastinitis is a fulminant infectious process with high morbidity and mortality. It is initiated most frequently by esophageal perforation and less often by tracheal rupture and direct spread from oropharyngeal infections. Substernal and interscapular pain, dysphagia, respiratory distress, and crepitus are the chief findings, with florid sepsis and hemodynamic instability supervening rapidly in untreated patients.

Antibiotics and fluid resuscitation are begun immediately. The primary problem, such as esophageal rupture, is treated according to accepted principles. Drainage through the chest and neck is created as required.

CHRONIC MEDIASTINITIS

Chronic inflammation and fibrosis in the mediastinum are thought to result from granulomatous infections, although identification of

an organism is rare. The process remains silent until it progresses to produce obstruction. Operative exploration is frequently required to establish a diagnosis and to relieve obstruction.

Superior Vena Caval Obstruction

Superior vena caval obstruction is caused by bronchogenic carcinoma in 85 percent of cases. Presenting signs include venous distention, facial edema, plethora, headache, and respiratory symptoms. The dismal prognosis in these patients often relates as much to the underlying malignancy as to the venous obstruction. Contrary to traditional teaching, a tissue diagnosis should be obtained prior to treatment. Palliative radiation with or without chemotherapy is the most common treatment. Rare benign cases may warrant venous bypass.

For a more detailed discussion, see Rusch VW, Ginsberg RJ: Chest Wall, Pleura, Lung, and Mediastinum, chap. 16 in *Principles of Surgery,* 7th ed.

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CHAPTER

17

CONGENITAL HEART DISEASE

The incidence of congenital heart disease (CHD) is 8 per 1000 live births and is 10 times more frequent within family members. Etiology usually cannot be established, although rubella in the first trimester is known to cause patent ductus arteriosus (PDA). The genetic abnormality trisomy is associated with a high incidence of CHD.

The fetal heart develops between weeks 3 and 8 of gestation. Incomplete septal formation leads to the varieties of atrial septal defects (ASDs) and ventricular septal defects (VSDs). Abnormalities in septation of the primitive bulbus cordis lead to truncus arteriosus and other anomalies. Of the six branchial aortic arches, only the left fourth and sixth remain. They become the aortic arch and ductus arteriosus, respectively. Remnants of the remaining branchial arches lead to vascular ring malformations.

Fetal circulation is characterized by elevated vascular resistance and little pulmonary blood flow. Most of the blood entering the right atrium is shunted to the left atrium via the foramen ovale, whereas blood reaching the pulmonary artery is shunted into the aorta via the ductus arteriosus. With expansion of the lungs and decreased pulmonary vascular resistance, the flap valve of the foramen ovale is closed [since left atrial (LA) pressure exceeds right atrial (RA) pressure], and then within the first few days of life the ductus closes.

The seven most prominent CHDs are VSD (20 percent), (the following occur in 10–15 percent of patients) ASD, PDA, coarctation of the aorta, aortic stenosis, pulmonic stenosis, and transposition of the great arteries (TGA).

Classification

Congenital heart disease may be classified in five groups by the type of anatomic abnormality present: left-sided obstructive lesions, lesions producing increased pulmonary blood flow, lesions producing cyanosis, complex malformations with mixed physiology, and anomalous origin of vessels and vascular rings.

Pathophysiology

Physiologic abnormalities, such as pressure gradients across stenotic valves, shunts through septal defects, and elevated pulmonary artery pressure, can be diagnosed by echocardiography or cardiac catheterization. Untreated, patients may develop congestive heart failure or severe hypoxemia. Cardiac hypertrophy, irreversible ventricular function, or pulmonary vascular disease can occur.

Obstructive Left-Sided Lesions The most common disorders are aortic valvular stenosis and coarctation of the aorta. These lesions restrict systemic blood flow, resulting in systolic pressure overload and ventricular hypertrophy. Electrocardiogram (ECG) and magnetic resonance imaging (MRI, especially suited for older children) can identify ventricular hypertrophy.

With progressive disease, patients are susceptible to ventricular arrhythmias, and with aortic stenosis there is a risk of sudden death. Surgical intervention should be timed to prevent development of severe hypertrophy and ventricular dysfunction.

Left-to-Right Shunts A defect in the ventricular septum or a connection between the aorta and the pulmonary artery results in a shunt of oxygenated blood from the left-sided circulation to the right side. Shunting through an uncomplicated ASD is also left to right. A left-to-right shunt produces an increase in pulmonary blood flow. The most common defects producing left-to-right shunts are VSD, ASD, PDA, and atrioventricular septal defects.

Pulmonary Congestion Left-to-right shunt is significant when pulmonary blood flow is greater than systemic flow. Increased pulmonary vascular resistance is the late result of increased pulmonary blood flow resulting in an enlarged left ventricle.

Medical management includes vasodilator and diuretic therapy, often with digoxin. Operative intervention is indicated if an infant fails to grow despite medical therapy or if there are complications.

Increased Pulmonary Vascular Resistance Elevated pulmonary blood flow and pressure produce changes in the pulmonary vasculature resulting in a progressive increase in vascular resistance. Pulmonary hypertension subsides as soon as the cardiac defect is corrected. Elevated pulmonary vascular resistance can take longer to resolve, but if halted early, vascular changes may regress. Untreated, children and adolescents with large left-to-right shunts can have irreversible pulmonary vascular disease.

In evaluating pulmonary hypertension, if the pulmonary resistance is elevated, it is helpful to determine whether the vessels are

reactive to oxygen, nitric oxide, or other pulmonary dilators. If the pulmonary vasculature bed is active and is capable of dilating in response to stimuli, a child may be a good candidate for operation.

Rarely do permanent pulmonary vascular changes occur before 1–2 years in uncomplicated VSD or PDA, but there is significant individual genetic variation in susceptibility. Infants with trisomy 21 and VSD or atrioventricular septal defect are at increased risk for fixed pulmonary vascular disease; repair at 2–3 months is advised. Most lesions that result in increased pulmonary vascular resistance should be corrected at 3–12 months. Transposition or truncus arteriosus requires operation in the first few weeks of life. Simple ASD rarely requires repair in infancy.

Cyanotic Lesions Right-to-left shunting of systemic venous blood back into the systemic circulation results in arterial hypoxemia and cyanosis. Cyanosis occurs because of the combination of an anatomic obstruction that results in decreased pulmonary blood flow and an intracardiac defect that allows right-to-left shunting of unoxygenated blood (e.g., tetralogy of Fallot, TGA, truncus arteriosus, or tricuspid atresia).

Most physiologic disturbances result from deficient oxygen transport to tissues. Cardiac failure and cyanosis can occur with complex lesions that produce mixing of blood with bidirectional shunting despite normal pulmonary blood flow.

The degree of cyanosis depends on the degree of anoxia and level of reduced hemoglobin (more easily seen in polycythemic states). About 5 g of reduced hemoglobin is required for visible cyanosis. Cyanosis in newborns may be difficult to detect because of higher levels of fetal hemoglobin.

Cyanosis from a pulmonary abnormality results in respiratory distress. Oxygen saturation of blood in the pulmonary veins of less than 95 percent suggests pulmonary disease. Cyanosis from an intracardiac shunt permits direct entry of venous blood into systemic circulation, which is only minimally responsive to inspired oxygen. An increase in pulmonary blood flow, even with a large shunt, can reduce cyanosis and improve oxygen transport.

Clinical features of chronic cyanosis include clubbing of digits or hypertrophic osteoarthropathy, which usually occurs after 2 years of age and slowly resolves after correction of anoxia. Polycythemia is a physiologic response of bone marrow and results in increased viscosity of blood with thrombotic complications (hematocrit $>$ 80 percent associated with cerebral venous thrombosis in infants). Decreased exercise tolerance with dyspnea on exertion (DOE) is another sign. Hypercyanotic spells are a sign of cerebral anoxia and require emergent treatment. Treatment consists of placing the infant in the knee-chest position and administering

oxygen, morphine, and phenylephrine. Urgent surgical placement of a systemic-to-pulmonary shunt or early total correction of the defect is indicated if the hypercyanotic spells develop. Brain abscesses may result because of the direct access of bacteria in venous-to-arterial circulation through a right-to-left-sided shunt when there is polycythemia and sluggish capillary flow. Cerebral injury can occur because of paradoxical venous thromboembolism; thrombus can migrate through the venous circulation, transverse the intracardiac defect, and reach the cerebral circulation.

In older children with chronic cyanosis, there is increase in bronchial circulation through the development of aortopulmonary collateral vessels. These may be of significance because of the risk of bleeding during operation and overperfusion of the lungs. Coordinating operative intervention with the occlusion of aortopulmonary collateral vessels is helpful.

Examination

History A maternal history of prenatal exposures, medications, or infections, as well a family history to eliminate hereditary disorders, should be taken. Note the age of the infant when the murmur or symptoms appeared (e.g., cyanosis, poor feeding, increased fatigue).

Physical Examination Assess the infant for growth and development (vital signs, height, weight, head circumference) and particularly for signs of cyanosis (clubbing), respiratory difficulty, or diaphoresis. Note any deformity of the left hemithorax. The chest is palpated for thrill, which indicates significant cardiac disease. Pulses in all four extremities should be felt with simultaneous palpation of the upper and lower extremity pulses to detect PDA or aortic regurgitation. During auscultation, a single second sound may be found in pulmonary valve atresia and tetralogy of Fallot. An excessively loud second sound signifies pulmonary hypertension or TGA. Murmurs should be characterized as to type, intensity, location, and transmission. The presence of rales suggests impaired left ventricular function with elevated pulmonary venous and capillary pressures. The hallmark of congestive failure is hepatic enlargement, which can regress rapidly in response to treatment.

Diagnostic Tests Heart size and contour, lung vascularity, rib notching, and changes in cardiac contour can be noted on chest radiographs. Electrocardiography (ECG) best determines ventricular hypertrophy, axis deviation, and conduction defects. Echo-

cardiogram is noninvasive but precise and sensitive. It is the diagnostic method of choice. Transthoracic echocardiography during pediatric surgery can confirm preoperative diagnosis, monitor ventricular function, and assess adequacy of repair. Transesophageal echocardiography can be applied to infants weighing more than 3 kg. Doppler studies can detect and quantify intracardiac or great vessel shunts and the presence and severity of atrioventricular and semilunar valve regurgitation or stenosis.

Cardiac catheterization is an interventional procedure. It is used for the diagnosis and treatment of simple and complex arrhythmias. The advantages are precise pressure measurements, detection of abnormal shunts, visualization of ventricular or vascular morphology, and calculation of vascular resistance.

PRINCIPLES OF CARE

Preoperative Management Preoperative therapy is determined with attention to oxygenation, acid-base status, fluids, body temperature, and respiratory mechanics. Metabolic acidosis should be corrected immediately. Patients depending on a PDA should be started on intravenous infusion of prostaglandin E_1 (0.05 μg/kg/min). Treatment with digitalis, diuretics, or inotropic agents may be necessary. It is not advisable to rush an unstable infant to the operating room before correction of underlying heart failure, correcting metabolic defects by improving perfusion, correcting acidosis, and stabilizing hemodynamics.

Intraoperative Management General anesthesia is induced with central venous access and arterial pressure monitoring. A percutaneous double-lumen internal jugular central venous catheter usually is inserted. A percutaneous radial artery line is inserted. A small Foley catheter is placed, and rectal and tympanic membrane temperatures are monitored.

The use of profound systemic hypothermia during cardiopulmonary bypass allows lower temperatures that give some end-organ protection and allow perfusion with lower flow rates. In patients with complicated anatomy, small infants, or neonates, deep hypothermia and total circulatory arrest may be used to allow safer, more precise intracardiac correction with a better visual field. After repair, the infant is rewarmed.

Hemodilution and systemic inflammatory effects can result in significant postoperative total body volume overload and may lead to transient dysfunction of the heart, lungs, and kidneys. Some suggest aggressive early postoperative ultrafiltration to improve

cardiac performance, improve pulmonary compliance and alveolar oxygen transport, and diminish the risk of multiorgan injury.

Postoperative Management Four key areas are hemodynamics; fluids, electrolytes, and renal function; arrhythmias; and mechanical ventilation and respiratory therapy.

OBSTRUCTIVE LEFT-SIDED LESIONS

Coarctation of the Aorta

This occurs in 10–15 percent of patients; it is more common in males than females (3:1). It can represent a spectrum of disease including an isolated obstruction to diffuse hypoplasia, but preductal or "infantile" type represents a diffuse narrowing of the aorta between the subclavian artery and the ductus arteriosus, usually with ductus-dependent blood flow distally. Newborns present with acute heart failure. The condition is associated with other cardiac defects such as VSD, bicuspid aortic valve, and mitral valve anomalies. Coarctation of the aorta, subaortic stenosis, parachute mitral valve, and supravalvular left atrial ring are known as *Shone's complex*.

Pathophysiology and Clinical Manifestations Neonates present with congestive heart failure, which may include extreme acidosis, renal shutdown, and pulmonary congestion. Diagnosis can be confirmed by echocardiography.

Congestive heart failure after age 1 rarely occurs before age 20. Hypertension is a significant concern. Chest x-ray may establish the diagnosis by demonstrating bilateral notching of the ribs posteriorly; ECG will show signs of left ventricular hypertrophy and left ventricular strain. MRI or enhanced magnetic resonance angiography can establish the diagnosis. Without operative repair, patients die of rupture of the aorta, cardiac failure, rupture of an intracranial aneurysm, or bacterial endocarditis.

Adult type involves more localized narrowing at the site of insertion of the ligamentum arteriosus, and patients may be asymptomatic, presenting with hypertension later in childhood. Headaches, epistaxis, and leg fatigue are the most common symptoms. A combination of hypertension in the upper extremities and absent or decreased pulses in the lower extremities suggests coarctation. Before surgery, patients should be treated with beta-adrenergic blockers.

Operative Technique A left posterolateral thoracotomy in the fourth intercostal space is used. Coarctation usually is readily seen.

The mediastinal pleura is incised, and the vagus nerve is retracted medially. The aortic arch proximal to the left subclavian artery, the left subclavian artery, the ligamentum arteriosum, and the distal aorta are serially mobilized. The intercostal arteries are isolated and preserved.

The proximal aorta, left subclavian artery, and distal aorta are occluded, and the coarctation is repaired by one of three techniques: subclavian flap arterioplasty, resection and end-to-end anastomosis, or wide resection with beveled hemiarch anastomosis.

In older children, the distal aortic pressure should be measured to determine the adequacy of flow through the collateral channels. Pressure should be more than 50–55 mmHg. Pressure of less than 45–50 mmHg increases the risk of spinal cord ischemia if the cross-clamp time exceeds 20 min.

After anastomosis, blood pressure should be measured proximal and distal to the site. For neonatal coarctation with VSD, pulmonary artery pressure is measured; if it remains elevated, immediate pulmonary artery banding is performed.

Interrupted Aortic Arch

This is a rare defect. Neonates with interrupted aortic arch (IAA) present 2–3 days after birth with congestive heart failure, acidosis, and hypoperfusion of the lower half of the body. Almost 30 percent of patients with Type B IAA have DiGeorge's syndrome, which is manifest by absence of thymic tissue, hypocalcemia, and immunologic abnormalities.

Anatomy and Physiology In Type A IAA, the interruption is distal to the left subclavian artery (40 percent of patients). Type B IAA results in total interruption of the arch between the left carotid and left subclavian arteries (55 percent of patients). In Type C IAA, the interruption occurs proximally between the innominate artery and the left carotid artery (5 percent of patients).

Most patients also have a large VSD, and some are associated with other left-sided obstructive lesions as well as varying degrees of hypoplasia of the left ventricular outflow tract (LVOT). The aortic valve is bicuspid in 40–50 percent of patients, the aortic annulus may be moderately to severely hypoplastic, and many patients with Type B IAA have subaortic obstruction.

Children with IAA depend on ductal flow for perfusion to the lower extremity; as the patent ductus begins to close, the child develops poor perfusion to the lower body with rapidly progressive metabolic acidosis and renal insufficiency. Severe pulmonary congestion and heart failure develop rapidly.

Diagnosis Diagnosis is made with echocardiography and MRI to determine the site of arch interruption.

Treatment After diagnosis, immediate infusion with prostaglandin E_1 is begun. Acidosis is corrected, and inotropic agents are begun to lessen the degree of heart failure and enhance renal perfusion. Intubation and mechanical ventilation may be required. On correction, urgent operation is required.

Type A lesions are repaired through a left-sided incision in the fourth intercostal space. Resection and beveled hemiarch repair are performed. If VSD is present, a pulmonary artery band may be considered. Complete repair through a midline approach can be performed if the VSD is large.

IAA Types B and C should undergo early complete repair through a midline sternotomy with deep hypothermia and circulatory arrest. The coarcted segment is repaired, and a primary end-to-end anastomosis is performed. Associated VSDs are repaired through a right atriotomy incision. When severe LVOT obstruction also is present, the subvalvular obstruction can be corrected with septal myotomy and myectomy. Augmentation of the ascending aorta and arch can be considered for those with multiple levels of obstruction.

Aortic Stenosis (Valvular/ Subvalvular/Supravalvular)

Categories *Congenital Aortic Stenosis* This represents 8–10 percent of patients with CHD. Stenosis may be discrete or can encompass diffuse parts of the LVOT. Critical neonatal aortic stenosis can have diffuse endocardial fibroelastosis within the left ventricle, which, if severe, can become a hypoplastic left heart syndrome. It often is associated with coarctation of the aorta, pulmonary stenosis, mitral valve abnormalities, PDA, and VSD.

It is three to four times more prevalent in males. Supravalvular stenosis is associated with peripheral pulmonary stenosis and Williams' syndrome. It is rare and usually found secondary to VSD, Marfan syndrome and other connective tissue disease, congential stenosis with secondary insufficiency, or rheumatic disease.

Valvular Stenosis This occurs in about 2 percent of the population; 75 percent have a bicuspid aortic valve with varying degrees of annular hypoplasia. A common finding is fusion of the right and left cusps with the undeveloped commissure represented by a median raphe that can extend to the ventricular wall. Thickening of the wall cusp and mild poststenotic dilatation of the ascending aorta occur.

With severe valvular stenosis, more severe deformities such as single-cuspid valve, a small annulus with annular hypoplasia, and diffuse ventricular fibroelastosis are common. The left ventricle can be so underdeveloped as to be unsalvageable. Subvalvular stenosis is rare; pathology ranges from a discrete fibrous ring with localized obstruction to diffuse fibromuscular obstruction. Diffuse fibromuscular subvalvular stenosis or tunnel-like subaortic obstruction results from diffuse fibromuscular narrowing of the subvalvular left ventricular outflow tract. The obstruction usually is concentric and severe.

Idiopathic hypertropic subaortic stenosis (IHSS) is an inherited hypotrophic cardiomyopathy that results in asymmetric septal hypertrophy, systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, and dynamic LVOT obstruction. Symptoms are angina, dyspnea, and syncope. With progressive disease, atrial fibrillation, systemic emboli, and sudden death are significant events.

Supravalvular Stenosis Peripheral pulmonary stenosis should be ruled out; focal stenosis may be present. Thirty percent of patients have associated involvement of the aortic valve cusps; coronary abnormalities are common.

Pathophysiology Physiologic abnormality is directly related to the severity of the obstruction. Some neonates present with severe heart failure and metabolic acidosis requiring intensive therapy and urgent intervention with balloon angioplasty or operative correction. Milder forms may remain asymptomatic for years and slowly develop findings of left ventricular hypertrophy and cardiomegaly, which can lead to significant concentric ventricular hypertrophy or congestive heart failure. Correction should be performed for patients whose gradient is greater than 50–60 mmHg and the cross-sectional area is less than 0.5 cm/m^2 and for patients with deteriorating left ventricular systolic function.

Decreased exercise capacity, an abnormal drop in ejection fraction in response to exercise, arrhythmias, and pulmonary congestion on exercise are indications for operation. Operation is indicated when symptoms develop before the onset of irreversible cardiac damage.

Clinical Manifestations Neonates present with congestive heart failure, acidosis, and low-output syndrome. Older children may be asymptomatic or present with fatigue, dyspnea, angina, arrhythmias, and syncope. Physical findings include a systolic ejection murmur, a forceful left ventricular impulse, and a narrow pulse pressure. Pulse pressure can be decreased. Diastolic murmur may indicate concomitant aortic insufficiency.

ECG may indicate the degree of stenosis; echocardiogram accurately determines the transvalvular gradient and annular size and the subvalvular LVOT. MRI delineates anatomy and assesses the aortic arch and peripheral pulmonary arteries. It is indicated in patients with supravalvular stenosis.

Treatment *Valvular Aortic Stenosis* Neonates require balloon valvuloplasty and surgical valvotomy using cardiopulmonary bypass. Surgical valvotomy is performed with cardiopulmonary bypass and cardioplegic arrest, cutting the fused stenotic area up to the commissure. Overcorrection can result in tearing of the valve and aortic insufficiency.

With valvular stenosis, the fused commissures are incised along the center of the fibrous raphe, leaving a thick margin on each of the two cusps, which are separated. Primitive, thickened hypoplastic leaflet tissue is partially excised. In older children with isolated stenosis from a bicuspid valve, balloon valvuloplasty is the treatment of choice.

Valve replacement is reserved for patients with significant annular hypoplasia or those with recurrent stenosis. Most are treated with the Ross procedure (pulmonary autotransplant). Those with significant annular hypoplasia are treated with extended aortic root replacement using human homograft or the Ross procedure and root enlargement.

Operative mortality for neonates is 10–30 percent; for older children there is a less than 1 percent risk.

Subvalvular Stenosis For patients with a discrete subvalvular ring, the valve cups are retracted and the fibrotic ring excised. Excellent visualization is required to prevent injury to the base of the aortic valve, the mitral valve, or the conduction bundle in the ventricular septum. The fibrous ring usually involves 270 degrees of the circumference of the LVOT; complete excision is required.

To avoid late recurrence and restenosis, if fibromuscular obstruction is found, a block of muscle from the septum is resected.

Tunnel-like or diffuse subvalvular obstruction requires extensive resection of fibromuscular tissue from the LVOT. Patients with severe LVOT obstruction may require aortoventriculoplasty with extended root replacement using homograft or with a combination of the Ross procedure and patch enlargement of the LVOT. These procedures obviate the need for anticoagulation therapy.

IHSS Surgical myotomy and myectomy are indicated in symptomatic patients with an outflow gradient of greater than 50 mmHg despite medications. Using a transaortic approach, a rectangular

block of ventricular muscle is excised from the septum, stopping at the level of the anterior leaflet of the mitral valve. Relief of the gradient should be confirmed.

Supravalvular Stenosis With the hourglass type of stenosis, widening the stenotic area by adding a patch of Dacron or pericardium produces excellent results. Before the patch is placed, the fibrous ridge above the sinotubular junction should be excised completely. An alternative is to excise totally the supravalvular ridge of stenosis and perform an end-to-end anastomosis between the distal aorta and the aortic root. Incidence of reoperation is low.

Congenital Mitral Valve Disease

Rheumatic heart disease, endocarditis, and cardiomyopathy can produce mitral valve pathology during childhood; it represents 1 percent of all cases.

Pathology Four types of congenital mitral valve abnormalities are (1) typical congenital mitral stenosis with varying degrees of obliteration and fusion of the chordae tendineae and subvalvular apparatus and mild to moderate deficiency of leaflet tissue (50 percent), (2) "parachute mitral valve," which is rare and refers to insertion of all the chordae tendineae into a single, shortened papillary muscle, resulting in restricted leaflet mobility with valvular obstruction, (3) mitral stenosis with hypoplasia as part of diffuse LVOT obstruction, representing the most extreme form of this condition (40 percent), and (4) supraannular mitral stenosis, which is rare and results from a supraannular ring of connective tissue in the left atrium.

Associated cardiac malformations occur in 75 percent of patients and include VSD (30 percent), valvular aortic stenosis (29 percent), aortic atresia and hypoplastic left heart syndrome (29 percent), and less severe subvalvular LVOT obstruction (30–60 percent). Abnormal left ventricular muscle with endocardial fibroelastosis occurs in most patients with mitral stenosis and diffuse LVOT obstruction and in nearly 50 percent of patients with mitral valve stenosis.

Clinical Manifestations Symptoms appear in infancy and include dyspnea, orthopnea, and pulmonary edema. Chest x-ray and ECG will demonstrate an enlarged left atrium, pulmonary congestion, and P mitrale of stenotic lesions. Transesophageal echocardiography will identify lesions in the left atrium and the degree of stenosis.

Treatment Operation should be timed to avoid further deterioration of left ventricular function. Repair might not be feasible, and valve replacement might be required.

Cor Triatriatum

This is a variant of total anomalous pulmonary venous drainage, but the unreabsorbed common pulmonary venous sinus empties into the left atrium through a restricted aperture. The common venous chamber is superior and posterior to the left atrium with a diaphragm separating this from the true left atrium. A small opening in the thick muscular diaphragm is the only communication between the upper pulmonary venous chamber and the lower true atrial chamber. This severely obstructs pulmonary venous return and produces supraannular mitral obstruction with left-to-right shunting across any defect in the atrial septum (present in about 70 percent).

Clinical Manifestations This produces severe pulmonary congestion with pulmonary artery hypertension. Congestive heart failure usually is severe. Gradients can be as high as 20 mmHg. If not corrected, 70–75 percent of patients die in the first year of life.

Chest x-ray demonstrates pulmonary congestion and an enlarged right ventricle. ECG shows right ventricular hypertrophy and some pulmonary hypertension.

Treatment Operation should be performed promptly in patients with severe obstruction; less severely obstructed patients with significant left-to-right shunting may be operated on later in childhood.

At operation, the defect is approached through the right atrium, enlarging the septal defect and excising the left atrial membrane to create a common unobstructed left atrial chamber. The atrial defect is closed with a patch of pericardium.

INCREASED PULMONARY BLOOD FLOW (LEFT-TO-RIGHT SHUNTS)

Patent Ductus Arteriosus (PDA)

This is a common form of congential heart disease (10 percent) and is a normal physiologic state in severely premature infants. It is two to three times more common in females than in males. In premature infants, the prostaglandin effect is pronounced, resulting in in-

creased ductal patency. Closure of a PDA can be hastened by administration of indomethacin.

Associated anomalies occur in 15 percent of patients; the most common are VSD and coarctation of the aorta. Depending on the diameter of the ductus, a varying amount of blood is shunted from the aorta to the pulmonary artery. If pulmonary resistance has been elevated for a long period, only partial regression may occur at closure of the ductus; otherwise, resistance decreases immediately to normal.

Clinical Manifestations In premature infants, a large patent ductus can cause serious heart failure; most full-term infants and older children are asymptomatic. When symptoms are present, the most common are palpitations, dyspnea, and decreased exercise tolerance. Symptoms of congestive heart failure may present in adults.

The hallmark of PDA is the continuous "machinery" murmur. With a large ductus, wide pulse pressure usually is evident, produced by a decrease in diastolic pressure. In an extremely large ductus, low-level diastolic pressure may be associated with peripheral vascular findings. Signs of pulmonary congestion may be present. There is an increased risk of bacterial endocarditis.

Diagnosis may be made in premature infants from the widened pulse pressure detected through an umbilical arterial catheter and confirmed by echocardiography. Chest x-ray shows increased pulmonary blood flow. In children, the diagnosis is made from the characteristic murmur and echocardiography. In adults, catheterization measures the pulmonary vascular resistance to assess ductal length and calcification.

Treatment In premature infants, PDA closure can be achieved with indomethacin therapy. Operation is indicated when there is severe respiratory insufficiency. In full-term infants without congestive heart failure, PDA closure can be performed at 6 months to 2 years. Insertion of a specially designed coil results in successful occlusion in most older children. Surgical division is indicated for those with a large-diameter ductus or extremely short length.

For operative closure, the patent ductus is exposed through a short, posterolateral incision in the fourth intercostal space; in premature infants, the patent ductus is doubly ligated. Surgical division is performed in older children by placing a partial occlusion clamp on the aorta adjacent to the ductus, and an angled vascular clamp is placed on the pulmonary artery side of the ductus. The ductus is divided sharply, and each side is oversewn, being careful that the suture line is flush with the aorta to avoid late aneurysm formation because of an unobliterated ductus diverticulum.

Aortopulmonary Window

This is a rare anomaly that results from the incomplete development of the spiral septum dividing the primitive truncus arteriosus into the aorta and pulmonary artery. It usually is located proximally near the ostium of the coronary arteries. The disease progresses rapidly because of the tremendous amount of shunting, resulting in early development of severe congestive heart failure.

Diagnosis is made readily by echocardiography and confirmed by MRI. Operation should be performed on diagnosis. A transaortic approach is used, and large defects are closed with a prosthetic patch.

Ventricular Septal Defects

Ventricular septal defect (VSD) is a common form of congential heart disease (20–30 percent) with no known etiologic factors. Associated anomalies are PDA, coarctation of the aorta, ASD, right ventricular outflow tract obstruction, tetralogy of Fallot, double-outlet right ventricle, TGA, truncus arteriosus, and aortic insufficiency from prolapse of an aortic valve cusp into the VSD.

Pathophysiology The defects are classified according to position: perimembranous, posterior inlet or atrioventricular canal type, outlet or supracristal, and muscular. Perimembranous defects are the most common (80 percent) requiring surgery. These involve the membranous septum. The bundle of His is located along the posterior, rightward rim of the septum, where it bifurcates into left and right conduction bundles. It may extend superiorly into the outlet septum next to the aortic valve annulus.

Inlet or atrioventricular canal type defects are perimembranous defects that extend posteriorly beneath the conal papillary muscle and the tricuspid valve involving the inlet septum. The conduction tissue runs adjacent to the rim of the septum.

Outlet or supracristal defects are in the infundibular septum adjacent of the pulmonary and aortic valves. Aortic insufficiency is common. These defects are away from the conduction bundle.

Muscular VSDs are the most common but may close spontaneously before age 2–3 years and do not require surgery. They are located inferiorly in the muscular septum and often are multiple. VSDs may be classified as restrictive or nonrestrictive depending on whether the right ventricular pressure is elevated to systemic levels. The nonrestrictive defect is equal in diameter to the aortic annulus. With a large, nonrestrictive defect, the right ventricular pressure is equal to systemic pressure, and the left-to-right shunt

may be 4:1 or greater. With long-standing defect, the pulmonary resistance may increase significantly, leading to irreversible pulmonary vascular changes, and a right-to-left shunt may develop, which leads to cyanosis (Eisenmenger's syndrome). Small restrictive defects have increased risk of bacterial endocarditis.

Clinical Manifestations Patients with small defects usually are asymptomatic but may have a loud murmur and thrill. With large defects, severe heart failure, dyspnea, and pulmonary congestion are common. Patients may have frequent respiratory symptoms, pneumonia, and lag in growth and development. Severe cardiac failure can occur in the first few months of life or much later in adulthood. Patients may be asymptomatic until cyanosis and hemoptysis develop. Chest x-rays appear normal. ECG usually shows left ventricular or biventricular hypertrophy.

Treatment Small defects should be observed (60–70 percent will close early, 90 percent by 8 years). Large defects depend on cardiac failure and increased pulmonary vascular resistance. Infants with severe cardiac failure require immediate operation; children with large left-to-right shunts require operation at 3–6 months. Criteria for nonoperability vary but include a nonreactive, fixed pulmonary vascular resistance of greater than 10 Woods units.

Operation is performed through a median sternotomy with extracorporeal circulation. The VSD is closed through a right atrial approach, which minimizes the risk of ventricular dysfunction and arrhythmias, or through a short transverse ventriculotomy. It is critical to avoid heart block.

Atrial Septal Defect (ASD)

Malformations involve the atrial septum or the pulmonary veins and include ostium secundum defects, sinus venosus defects with partial anomalous pulmonary venous return, and ostium primum defects. They are common (10–15 percent) and twice as frequent in females as in males.

Pathophysiology ASDs vary in size and location, but the majority are located in the middle part of the atrial septum in the area of the ostium secundum. A high subcaval defect near the orifice of the superior vena cava is referred to as a *sinus venosus defect.* It is associated with anomalous entry of one or more right pulmonary veins into the superior vena cava with drainage of the upper and middle lobe veins, which enter below the entry site of the azygos vein. Unusual defects include the common atrium, "unroofing" of

the coronary sinus, and low ostium secundum defects that extend toward the inferior vena cava. Right pulmonary veins may have a common atrium or be associated with a large posterior ostium secundum defect. Part of the septum may be fenestrated.

Partial anomalous pulmonary veins entering the inferior vena cava is a "scimitar" syndrome and is associated with hypoplasia of the right lung and left-to-right shunt.

A rare variant is ostium secundum defect combined with mitral stenosis (Lutembacher's syndrome). Mitral stenosis retards blood flow from the left atrium to the left ventricle and produces a large left-to-right shunt through the septal defect with massive dilation of the pulmonary arteries.

Clinical Manifestations Children may have symptoms of fatigue, palpitations, and exertional dyspnea. Adults may have congestive heart failure or arrhythmias. Chest x-ray may show mild to moderate cardiac enlargement, as well as an enlarged right atrium and pulmonary artery. ECG will show a right-axis deviation.

Treatment Most children are asymptomatic; operation is recommend on the basis of a large echocardiographic defect with significant left-to-right shunting. Contraindication is increased pulmonary vascular resistance and Eisenmenger's syndrome.

At operation, the patient is placed on cardiopulmonary bypass; the heart is electrically fibrillated or arrested with cardioplegia. The right atrium is opened and the defect closed. Large ostium secundum defects may require patch closure; those with partial anomalous venous drainage are corrected by placement of a pericardial patch so as to recreate the atrial septum, redirecting the anomalous veins into the newly created left atrial chamber. Sinus venosus defects are closed by rerouting the anomalous pulmonary venous blood from the right upper and middle lobe veins across the high sinus venosus defect.

Incomplete Atrioventricular Septal Defect

The terms *incomplete atrioventricular septal defect, incomplete atrioventricular canal defect,* and *ostium primum atrial septal defect* are interchangable and account for 4–5 percent of ASDs. Associated abnormalities are an unroofed coronary sinus, PDA, persistent left superior vena cava, coarctation of the aorta, and LVOT obstruction. Twenty percent of patients have Down syndrome.

Pathophysiology There are two anatomic defects. One is a partial cleft in the anterior leaflet of the mitral valve. The other is a complete defect, which separates the entire anterior leaflet in halves. Physiologic abnormalities are a left-to-right shunt and mitral insufficiency.

Clinical Manifestations With significant mitral insufficiency, cardiac failure with pulmonary congestion and dyspnea may be fatal in the first year of life unless corrected. Chest x-ray shows moderate cardiac enlargement; increased pulmonary vascularity is common. ECG will show a left-axis deviation with counterclockwise rotation.

Treatment Operative correction often is performed when the patient is between 1 and 4 years of age. Operation is through a median sternotomy or a small right anterior thoracotomy incision with the patient on extracorporeal circulation. The cleft in the anterior mitral valve leaflet is closed, and the ASD is repaired. To avoid heart block, the sutures are inserted superficially and leftward along the annulus of the mitral valve or rightward in relation to the coronary sinus.

Complete Atrioventricular Septal Defects

Pathophysiology This also is referred to as *complete atrioventricular canal defect* or *complete endocardial cushion defect,* and it results from failure of fusion of the endocardial cushions in the central portion of the heart, which causes a large defect involving the atrial and ventricular septum. The central portion of the annulus between the mitral and tricuspid valves also does not form. Eighty percent of patients have Down syndrome.

Rastelli's classification divides the deformity into types A, B, and C based on the presence of clefts or septal attachments in the bridging superior common leaflet. The common atrioventricular valve is a six-leaflet structure that overlies a large septal defect involving the ventricular and the atrial septum. Intermediate or transitional atrioventricular septal defect occurs when all components are present but the VSD is restricted. When a single atrioventricular valve overrides one ventricle by more than 50 percent and the other ventricle is underdeveloped, it is termed *unbalanced.*

Diagnosis is by echocardiography; catheterization should be done for evaluation of pulmonary hypertension and elevated

pulmonary vascular resistance, particularly if the child is more than 6 months old or other lesions are suspected. Catheterization shows a typical "gooseneck" deformity in the LVOT.

Treatment Early complete repair is recommended for most patients before 6 months of age or at 2–3 months if significant congestive heart failure is present. Operation consists of placement of a prosthetic patch to correct the underlying VSD, reattachment of the atrioventricular valve leaflets, and closure of the ostium primum ASD component. Repair may be performed using a single- or double-patch technique; the two-patch approach is preferred because it is more precise and has less late leaflet dehiscence.

CYANOTIC LESIONS

Cyanosis results from any intracardiac defect producing right-to-left shunting of unoxygenated venous blood resulting in systemic oxygen desaturation. Conditions include tetralogy of Fallot, pulmonary atresia, and tricuspid atresia. Conditions evidencing moderate cyanosis and increased pulmonary blood are TGA, double-outlet right ventricle, and truncus arteriosus.

Palliative Shunts The modified Blalock-Taussig (BT) shunt involves placement of an interposition between the subclavian and pulmonary arteries with a 4–5-mm expanded polytetrafluoroethylene (Gore-Tex) graft. It can be performed in neonates and lasts 1–2 years. Another option is a central systemic-to-pulmonary shunt performed through a sternotomy using a 3.4–4-mm Gore-Tex graft from the ascending aorta or the innominate artery to the pulmonary artery. It is technically easy to perform and produces minimal distortion of the pulmonary arteries.

A venous-to-pulmonary shunt is the bidirectional Glenn shunt or hemi-Fontan procedure, which is an end-to-side anastomosis between the divided superior vena cava and the pulmonary artery. This is performed using cardiopulmonary bypass or passive temporary cavoatrial shunt. This shunt improves oxygenation without overperfusion of the lungs and is used in patients with tricuspid atresia, single-ventricle complex, or hypoplastic left heart syndrome.

Currently, transcatheter balloon dilation of the pulmonary valve and arteries combined with coil occlusion of large systemic-to-pulmonary collateral vessels is used for patients with tetralogy of Fallot and small pulmonary arteries.

Tetralogy of Fallot

The four features are (1) malalignment of the ventricular septal defect, (2) dextroposition of the aorta, (3) right ventricular outflow tract obstruction, and (4) right ventricular hypertrophy. All are a result of underdevelopment and anterior malalignment of the infundibular septum, which deviates anteriorly and cephalad, creating a large ventricular defect at the point of nonunion.

The anterocephalad deviation narrows the right ventricular outflow tract and allows the aortic root to "override" the ventricular septum in a rightward direction, producing the malalignment VSD, which is a large, perimembranous defect. This results in systemic pressures in the right ventricle, while concentric right ventricular hypertrophy results from obstruction of the right ventricular outflow tract.

Patients have decreased pulmonary blood flow, cyanosis secondary to right-to-left shunting, and systemic right ventricular pressures with right ventricular hypertrophy.

Clinical Manifestations Most patients with untreated tetralogy of Fallot die from progressive hypoxia with repeated cyanotic "spells" resulting in cardiac arrest, cerebral injury, pulmonary thrombosis, or infection. Brain abscess is a fatal late complication. Patients are symptomatic with exertional dyspnea and cyanosis. Squatting and clubbing of digits are classic manifestations. A systolic murmur of grade II to III is common along the left sternal border; 50 percent have a thrill.

Chest x-ray shows a normal-sized heart with an unusual boot-shaped contour (coeur en sabot). ECG shows right ventricular hypertrophy with right-axis deviation.

Treatment Early correction is the treatment of choice. Infants with early cyanotic spells, hypoplastic or discontinuous pulmonary arteries, and pulmonary atresia require emergent systemic-to-pulmonary shunt for palliation. Patients with underdeveloped pulmonary arteries are treated with balloon dilation of the pulmonary valve or pulmonary vessels.

Repair is performed through a median sternotomy with extracorporeal perfusion and cardioplegic arrest. The VSD is approached through the right atrium or through a right ventriculotomy, and the patch is placed through the tricuspid valve. All areas of potential obstruction are reexamined during operation. After repair, the infundibular outflow tract is inspected, and the main pulmonary artery is opened just above the valve. The main pulmonary artery, pulmonary bifurcation, left and right pulmonary arteries, the

pulmonary valve, and the pulmonary annulus are calibrated with Hegar dilators. A transannular incision is made only if the pulmonary annulus is hypoplastic.

If the annular size is adequate and leaflet mobility can be restored, the valve is preserved; a small ventriculotomy is made below the valve to correct any infundibular stenosis, or a resection of the infundibular obstruction is performed through the tricuspid valve. If the annulus is hypoplastic, the incision is extended across the annulus far enough to correct the infundibular stenosis while preserving as much right ventricular function as possible. The transannular incision is closed, tailoring the patch to prevent late aneurysmal formation in the patch.

When the distal pulmonary arteries are severely stenosed or hypoplastic, a valved pulmonary artery homograft may be required to reconstruct the outflow tract; the valve minimizes regurgitation of blood into the right ventricle and lowers the risk of long-term dysfunction.

After cardiopulmonary bypass is discontinued, intracardiac pressure is measured to confirm correction of right ventricular outflow. Right ventricular outflow should be 60–70 percent less than left ventricular pressure; if still elevated, additional correction should be considered. The ratio of right to left ventricular pressure is less than 0.50–0.60 after successful repair, with a pulmonary artery systolic pressure of 20–25 mmHg.

Pulmonary Stenosis/Pulmonary Atresia with Intact Ventricular Septum

This is a common defect (10 percent of congenital cardiac lesions); 50 percent have only valvular pulmonary stenosis. Pulmonary atresia with intact septum results in total obstruction of the outflow tract with atresia of the valve, hypoplasia of the annulus, and degrees of hypoplasia and maldevelopment of the right ventricle (1–3 percent).

Pathophysiology Pathologic findings range from isolated valvular stenosis to total valvular atresia with hypoplasia of the inlet, body, and outflow tract of the right ventricle. Pulmonary stenosis may be mild or critical with a pinhole opening. The valve usually is bicuspid or tricuspid and domed with fused commissures; the annulus may be normal or hypoplastic.

Approximately 40 percent of children with pulmonary stenosis have infundibular obstruction; 10 percent are severe. Pulmonary atresia with intact ventricular septum (PAIVS) presents in newborns with an atretic valve and no forward blood flow; the right

ventricle is underdeveloped. The right ventricle is classified according to its degree of development: unipartite, bipartite, and tripartite depending on the adequacy of the inlet, body, and outlet portions. A minimum of bipartite ventricle is necessary if the right heart is to be used in circulation. The ventricle is extremely small, thickened, and hypertensive with myocardial muscular disarray. In 10 percent of patients, sinusoids connect the right ventricle with the coronary circulation, resulting in right ventricular-dependent coronary circulation. The tricuspid valve often is regurgitant; if severely hypoplastic or totally atretic, the patient is treated as having single-ventricle physiology.

With moderate pulmonary stenosis, the obstruction produces an elevation in right ventricular pressure with subsequent ventricular hypertrophy. A gradient of less than 50 mmHg is mild; a gradient of 80–100 mmHg is more severe. With severe stenosis, suprasystemic right ventricular pressures can develop. In patients with critical pulmonary stenosis or PAIVS, most forward blood flow may be absent.

Clinical Manifestations Hypoxia, cyanosis, and acidosis develop shortly after birth. Ductal patency is maintained with prostaglandins until the diagnosis is made. Chest x-ray shows decreased pulmonary blood flow, a flat or concave pulmonary artery segment, and a normal or enlarged heart.

Diagnosis is made by echocardiography. Cardiac catheterization is used for intervention (e.g., balloon dilation). In PAIVS it is used to determine the presence or absence of sinusoids feeding the coronary circulation.

Treatment Treatment of choice for infants with critical pulmonary stenosis and adolescents with moderate to severe isolate pulmonary stenosis is balloon dilation. Patients with hypoplastic outflow tract obstruction or with PAIVS require surgical correction, but operative risk is high. Correction requires cardiopulmonary bypass, a valvotomy and systemic-to-pulmonary shunt, or a transannular patch to relieve outflow tract obstruction plus a systemic-to-pulmonary shunt.

Tricuspid Atresia

This affects 2–5 percent of children with cyanotic heart disease and consists of total atresia of the tricuspid valve and ventricular inlet, hypoplasia of the body and outlet portion of the right ventricle, and an ASD or VSD. Pulmonary atresia or severe pulmonary stenosis is seen in 85 percent. Most patients have total ductus-dependent pulmonary blood flow. TGA occurs in 30 percent. When the aorta and pulmonary artery are transposed, 70 percent have unrestricted

pulmonary blood flow with overperfusion of the lungs (single-ventricle complex). Hypoxia is severe because of the absence of blood flow through the atretic tricuspid valve combined with restricted or absent flow across the septal defect and through the rudimentary right ventricle into the pulmonary artery.

Clinical Manifestations Most patients are markedly hypoxic and dyspneic shortly after birth; most die without palliative shunting. Diagnosis is made during days 1–2 of life. Chest x-ray shows decreased vascularity. ECG shows a left-axis deviation. Echocardiogram can establish the diagnosis with certainty.

Treatment Emergency systemic-to-pulmonary shunt usually is required in the first few days or weeks to prevent death from hypoxia. A modified Blalock-Taussig shunt is satisfactory. In some patients, a balloon septostomy is necessary to increase the right-to-left shunt.

After palliative shunting, a modification of the Fontan procedure is performed in which a direct connection between the systemic venous circulation and the pulmonary arteries is constructed. A bidirectional Glenn shunt procedure often is performed at 3–8 months. This is coupled with a takedown of a previously performed systemic-to-pulmonary shunt, which minimizes volume overload and is the first step to a final corrective modified Fontan procedure. This is performed by connecting the superior vena cava to the pulmonary artery with a bidirectional Glenn shunt and connecting the inferior vena cava to the pulmonary artery; this is a total cavopulmonary connection. The inferior caval connection can be done with an intraatrial lateral Dacron tunnel or with an extracardiac conduit. Flow dynamics and clinical outcomes are better than with the direct atriopulmonary connection method. Modified Fontan procedures are delayed until 8–12 months.

Single-Ventricle Complex

This includes patients with a single atrioventricular connection and differing ventricular morphology, mitral atresia with unrestricted aortic outlet, unbalanced atrioventricular septal defects, and a variety of other anatomic configurations with a single functioning ventricular chamber.

Clinical Manifestations Some patients have unrestricted pulmonary blood flow and cyanosis. Others have severe hypoxia, cyanosis, and restricted pulmonary blood flow shortly after birth and require an emergency palliative shunt. With moderate degrees of restriction, patients do reasonably well in the first few years of life.

Treatment Unrestricted pulmonary blood flow with severe pulmonary congestion requires urgent pulmonary artery banding; severe cyanosis and hypoxia require emergency placement of a palliative shunt. After palliative treatment, the final planned surgical correction is some modification of the Fontan procedure (total cavopulmonary procedure). For most patients with single-ventricle complex, placement of a bidirectional Glenn shunt is performed at 3–6 months while taking down the pulmonary artery band or the palliative shunt. At 12–18 months, a bidirectional Glenn shunt is converted to a modified Fontan total cavopulmonary connection, which often is fenestrated.

Ebstein's Anomaly

This is uncommon (0.5 percent). It is a malformation of the septal and posterior leaflets of the tricuspid valve. The origin of the leaflets is displaced downward, creating a third chamber on the right side of the heart. Leaflet tissue and chordae are abnormal. The anterior tricuspid leaflet may be unusually large and prominent (sail-like). The segment of right ventricular wall between the true annulus becomes functionally part of the right atrium with hypoplasia. The atrialized segment has some muscle fibers with little paradoxical motion. The distal functioning right ventricle is small. A patent foramen ovale or ostium secundum defect usually is present with right-to-left shunting. The right atrium usually is dilated.

Malformation varies from minor valvular abnormalities to atresia of the valve leaflets with severe regurgitation. Disturbances include restricted pulmonary blood flow, inadequate cardiac output from right ventricular dysfunction, tricuspid insufficiency, and right-to-left shunting at the atrial level. Arrhythmias commonly occur, with frequent supraventricular tachycardias and Wolff-Parkinson-White syndrome and accessory pathways and preexcitation occurring in 5 percent. Moderate cyanosis occurs in 50 percent.

Clinical Manifestations Patients present in the first month of life with tachypnea and cyanosis. Fifty percent are severely symptomatic and die. After the first month, symptoms decrease, and disability becomes minimal. Onset of symptoms after surviving childhood is gradual; average age at diagnosis is the midteens.

Systolic and diastolic murmurs are present; chest x-ray shows cardiac enlargement. Echocardiogram is diagnostic. Cardiac catheterization may be considered.

Treatment Depending on the degree of anatomic abnormality, valve reconstruction may be considered; valve replacement is necessary in patients with severe valvular deformity.

TRANSPOSITION OF THE GREAT ARTERIES (TGA)

TGA is common (5–8 percent) and is responsible for 25 percent of neonatal deaths. It results from abnormal division of the bulbar trunk. The aorta originates from the right ventricle and the pulmonary artery from the left ventricle. This circulatory arrangement is incompatible with life. A PDA, a patent foramen ovale, or a VSD must be present for the patient to survive. LVOT obstruction resulting in pulmonic stenosis occurs frequently. Coarctation of the aorta, pulmonary atresia, and dextrocardia also may occur.

Hypoxia and progressive pulmonary congestion occur, leading to severe, progressive cardiac failure. Patients with TGA and intact ventricular septum and patients with TGA, VDS, and LVOT obstruction develop severe cyanosis. TGA is lethal if untreated. TGA and VDS patients develop rapid pulmonary vascular changes.

Clinical Manifestations Many infants are cyanotic at birth. Pulmonary congestion with cardiac failure is frequent. Cyanosis often is severe. Chest x-ray shows a heart that may be egg-shaped, the base of the cardiac shadow may be unusually narrow, and pulmonary congestion often is marked. ECG shows severe right ventricle hypertrophy. Echocardiogram is diagnostic.

Treatment The most critically ill are those neonates with TGA and an intact ventricular septum. A Rashkind balloon septostomy often is necessary shortly after birth. The atrial switch operation should be performed at 7–14 days. After 2 weeks of age, infants may require preliminary banding of the pulmonary artery to induce hypertrophy in the left ventricle before it is feasible to perform the arterial switch operation. With TGA and VSD, the arterial switch is done within the first 2 weeks of life.

Repair often is done with the patient in deep hypothermia and circulatory arrest. After cardiopulmonary bypass and cardioplegia, the great vessels are transected distal to the sinotubular ridge. A small button of aorta that includes the ostium of the coronary artery is resected from the posterior sinus of the anterior great vessel and transferred to the corresponding sinus of the posterior great vessel. A similar transfer is made with a button of the anterior right coronary artery. The anterior aorta is relocated posteriorly and sutured end-to-end to the posterior great vessel distal to the coronary artery reimplantation site. The pulmonary artery is brought anteriorly and connected to the anterior great vessel, which exits from the right ventricle.

Patients with TGA, VSD, and LVOT obstruction may require palliation with a systemic-to-pulmonary shunt followed by a Rastelli

operation at 4–5 years. This procedure uses a prosthetic patch to reroute the anterior aorta to connect internally to the posterior left ventricle across the VSD. The systemic venous ventricle is connected extraanatomically into the pulmonary artery with a valved homograft conduit or a prosthetic valve and graft.

Double-Outlet Right Ventricle (DORV)

This is a congenital malformation in which both great arteries arise from the morphologic right ventricle (5 percent of CHD patients). Patients are classified by location: (1) subaortic, (2) subpulmonic, (3) doubly committed, and (4) uncommitted. The aorta rotates anteriorly, arising from the right ventricle, and the great vessels usually are side by side; in extreme cases, the aorta is completely anterior.

When the aorta rotates to a greater degree anteriorly and the pulmonary artery begins to rotate posteriorly, a condition of DORV and subpulmonic VSD occurs (Taussig-Bing syndrome). The aorta and the pulmonary artery arise from the right ventricle, allowing some mixing of venous and arterial blood with some bidirectional shunting. The amount of cyanosis varies.

Clinical Manifestations In patients with DORV and a large subaortic VSD or doubly committed VSD, there is a large, isolated VSD with markedly increased pulmonary blood flow. Patients develop congestive heart failure early with pulmonary hypertension, early pulmonary vascular resistance changes, and cyanosis.

DORV and subaortic VSD with pulmonary stenosis patients have hypoxia and cyanosis. Patients with DORV and subpulmonic VSD (Taussig-Bing syndrome) have increased pulmonary blood flow with pulmonary congestion and moderate hypoxia with cyanosis. Echocardiography can determine diagnosis.

Treatment Most forms of DORV can be corrected with an intracardiac tunnel to channel blood from the left ventricle across the VSD to the aorta. The right ventricular outflow tract is enlarged with a patch or homograft valved conduit. Mortality is 2–5 percent. In patients with Taussig-Bing syndrome, some have used the arterial switch procedure along with VSD closure to redirect blood through the neoaorta. Mortality is 5–10 percent.

Truncus Arteriosus

This is a rare malformation (3 percent) that results from a failure of the fetal truncus to separate into the pulmonary arteries, resulting in a single arterial trunk. The entire circulation (the aortic valve,

the aorta, the pulmonary arteries, the coronary arteries) arises from a common arterial trunk. A single truncal semilunar valve is present that may be bicuspid (30 percent), tricuspid (50 percent), or quadricuspid (20 percent). There is an underlying VSD.

Pathophysiology In Type I truncus arteriosus there is a single main pulmonary trunk off the aorta, in Type II the right and left pulmonary arteries originate from the dorsal wall of the truncus arteriosus from separate orifices, in Type III the pulmonary arteries arise as separate ostia, and in Type IV the pulmonary blood supply is provided by systemic aorta-to-pulmonary collateral vessels arising from the descending aorta. In most, the ductus arteriosus is absent.

Physiologic abnormality is severe; 50 percent die in the first month of life, 90 percent in first year. Death is from unrestricted pulmonary blood flow with severe pulmonary congestion, congestive heart failure, and progressive pulmonary vascular changes. Patients develop early dyspnea and respiratory distress.

Shunting is bidirectional, and arterial oxygen desaturation is always present with cyanosis. Severe pulmonary vascular disease develops rapidly.

Clinical Manifestations Chest x-ray shows cardiomegaly and pulmonary congestion. Right and left hypertrophy are evident on ECG. Echocardiogram is diagnostic.

Treatment Operation should be performed when the diagnosis is made. The pulmonary arteries are detached from the truncus, the right ventricle is opened, the VSD is closed with a patch, and a homograft valve conduit is used to reconstruct flow into the pulmonary vascular bed.

OTHER COMPLEX MALFORMATIONS

Hypoplastic Left Heart Syndrome (HLHS)

HLHS is made up of a group of malformations that include aortic hypoplasia or atresia and poorly developed or absent left ventricle (2–4 percent).

Pathophysiology The pathology produces severe LVOT obstruction with almost no forward blood flow. The ascending aorta and proximal aortic arch are diminutive, providing retrograde flow to

the coronary arteries. The left ventricle is severely hypoplastic or absent, and the myocardial muscle fibers are in disarray with severe endocardial fibroelastosis. The mitral valve is hypoplastic or totally atretic (85 percent); some have a severely malaligned common atrioventricular valve (15 percent).

Clinical Manifestations Infants become symptomatic 24–48 h after birth; they develop cyanosis, tachypnea, respiratory distress, severe acidosis, and ashen color. Death occurs if the ductus arteriosus is not reopened with prostaglandin infusion.

Examination reveals congestive heart failure (e.g., rales), hepatomegaly, diminished peripheral pulses, and poor perfusion. Chest x-ray shows significant pulmonary congestion, and ECG shows an absence of left-sided forces, right-axis deviation, and right ventricular hypertrophy. Echocardiogram is diagnostic.

Treatment Initial treatment is with prostaglandin E_1. Acidosis is corrected with sodium bicarbonate. Best results are obtained with staged palliative treatment. The initial operation is in first week of life with the patient in deep hypothermia and circulatory arrest; a stage I Norwood procedure establishes unobstructed flow from the right ventricle to the systemic circulation by anastomosis of the pulmonary artery to the aortic arch. Controlled pulmonary blood flow is established by a systemic-to-pulmonary modified Blalock-Taussig shunt. At 4–6 months, a stage 2 bidirectional Glenn shunt is performed. Cardiac catheterization is performed beforehand to evaluate the aortic arch and aortic outflow tract, the pulmonary arteries, and pulmonary vascular resistance. The Blalock-Taussig shunt is taken down, and the pulmonary arteries are augmented as necessary. At l year, the stage 3 Fontan procedure is performed.

Total Anomalous Pulmonary Venous Return (TAPVR)

Pathophysiology This is classified according to the path of the anomalous venous drainage: supracardiac—the common venous channel usually is a vertical vein that enters the innominate vein (40–50 percent); intracardiac—the anomalous venous channel typically enters the coronary sinus (25 percent); infracardiac—the common venous channel traverses the diaphragm and enters the portal system (25 percent); and mixed (5 percent). Pulmonary venous obstruction producing severe pulmonary congestion and respiratory distress is common. Untreated, 50 percent of patients die in first month, 80 percent in first year.

Clinical Manifestations Severe tachypnea is the dominant symptom. Infants with severe obstruction have severe pulmonary congestion and hypoxemia and diminished peripheral perfusion. Chest x-ray may show a double contour (snowman). Echocardiography can be diagnostic, but cardiac catheterization and angiography are necessary.

Treatment Operation is urgent; total repair is done using hypothermia and circulatory arrest. Correction includes construction of large (2.5–3.0 cm) side-to-side anastomosis between the common venous trunk and left atrium followed by closure of the ASD and ligation of the left vertical vein.

Corrected Transposition

In this situation the anatomic right ventricle and the anatomic left ventricle are switched or inverted (ventricular inversion). The most common associated defects are VSD (80 percent), conduction abnormalities, pulmonic stenosis, and left-sided (tricuspid) atrioventricular valvular insufficiency.

Clinical Manifestations Heart block is present at birth (5–10 percent). Left-to-right shunting and pulmonary congestion are common. Hypoxia and cyanosis are present in 30 percent. ECG is abnormal, echocardiogram is diagnostic, and cardiac catheterization may be necessary.

Treatment Closure of the VSD is technically difficult. A standard transatrial approach through the right atrium and tricuspid valve is preferred. Heart block is common after operation (10–20 percent). Patients with severe pulmonic stenosis require placement of an extracardiac valve homograft to the pulmonary artery. Valve repair or replacement may be necessary.

OTHER ANOMALIES

Anomalous Origin of the Left Coronary Artery

This occurs in 1 in 300,000 births. The flow of blood in the anomalous left coronary artery is retrograde into the low-pressure pulmonary artery. Patients are symptomatic early, with myocardial infarction and left ventricular failure within 3 months of birth. Other

symptoms include tachypnea, sweating, poor feeding, respiratory distress, and heart failure.

Chest x-ray shows extensive enlargement of the left ventricle with pulmonary congestion. ECG is diagnostic. Transesophageal echocardiography is confirmatory. Cardiac catheterization and angiography are done before repair.

Treatment Operative repair is early. Coronary transfer is performed with the patient on cardiopulmonary bypass and cardioplegic arrest. The left main pulmonary artery is transected distal to the sinotubular junction. The ostium is excised from the sinus and reimplanted on the appropriate point of the lower medial ascending aorta. The posterior pulmonary sinus may be augmented; the pulmonary artery is closed. If significant mitral insufficiency is present, mitral valve annuloplasty is performed.

Vascular Rings

These are congenital defects in which an anomalous arterial formation can result in compression of the esophagus or trachea. The five types of anomalies include double aortic arch, right aortic arch with left ligamentum arteriosum, retroesophageal subclavian artery, anomalous origin of innominate artery, and anomalus origin of left common carotid artery.

Clinical Manifestations Most symptoms result from compression of the trachea. Dyspnea, stridor, and periodic episodes of serious respiratory distress are common. Feeding often precipitates respiratory crisis. Recurrent pneumonia is common. Some patients with mild symptoms may recover spontaneously.

Examination of the esophagus with a barium swallow is diagnostic. MRI and MR angiography establish diagnosis. Bronchoscopy usually is performed.

Treatment No treatment is necessary without symptoms. Mild symptoms require observation. Clear symptoms require prompt operation. At operation, the aorta and aortic arch are completely dissected. With a double aortic arch, the smaller of the two arches should be divided. With a left descending aorta, the anterior arch is smaller and can be divided between the left common carotid and left subclavian arteries. If the posterior arch is smaller, it can be divided behind the esophagus. With a right descending thoracic aorta, the posterior arch usually is smaller, and it is divided. With a right aortic arch and retroesophageal ligamentum or ductus arteriosus, division of the ligamentum or ductus is all that is necessary.

Pulmonary Artery Sling

The left pulmonary artery arises from the right pulmonary artery, coursing to the left between the trachea and the esophagus to reach the left pulmonary hilus and forming a sling or ring around the trachea. The trachea often is segmentally narrowed at the site of compression. Fifty percent have severe tracheal stenosis with complete cartilaginous rings.

Clinical Manifestations Most infants develop symptoms in the first months of life with feeding difficulty, wheezing, stridor, and severe respiratory distress. Chest x-ray shows a density separating the trachea from the esophagus on the lateral view. An esophageal barium swallow is diagnostic. MRI is the examination of choice; if uncertain, catheterization and angiography are performed. Bronchoscopy is routine.

Treatment Older patients with minimal or no symptoms require no specific treatment. In the absence of severe tracheal stenosis, the repair is performed through a left lateral thoracotomy, dividing the anomalous pulmonary artery at its origin and reanastomosing it to the main pulmonary artery anteriorly. The ligamentum arteriosum is divided. With significant tracheal stenosis, the segmental tracheal stenosis should be resected at the time of sling repair, reanastomosing the trachea end to end.

For a more detailed discussion, see Galloway AC, Artman M, and Colvin SB: Congenital Heart Disease, chap. 17 in *Principles of Surgery,* 7th ed.

CHAPTER

18

ACQUIRED HEART DISEASE

DETERMINATION OF CARDIAC FUNCTION

Evaluation of cardiac function, both preoperatively and postoperatively, requires an understanding of the heart as a pump. Cardiac output (CO) measures the ability of the heart to supply metabolic substrates and remove waste. CO is proportional to heart rate (HR) multiplied by stroke volume (SV) (that is, $CO = HR \times SV$). CO divided by the patient's body surface area (BSA) equals cardiac index (that is, $CI = CO/BSA$), which allows a normal value for all patients. SV has three major determinants: preload, afterload, and contractility.

Preload This is measured as the end-diastolic pressure within the ventricle. A normal value is 8 mmHg. Within limits, the ventricle can be volume loaded to increase preload. This results in increased force of contraction. Sarcomere length of 2.2 nm results in maximal force of contraction. In a normal heart, this occurs with an end-diastolic pressure of 14 mmHg. A Swan-Ganz catheter is often used to measure left ventricular end-diastolic pressure. When there are no obstructions between the pulmonary vascular bed and the left ventricle, the wedge pressure reflects left ventricular end-diastolic pressure.

Afterload This is the impedance to left ventricular emptying. The greater the afterload, the lower is the SV. The mean systolic pressure approximates afterload.

Contractility This represents the intrinsic ability of the cardiac muscle to contract and relax. It is measured as a maximal velocity of fiber shortening.

Each of these factors may be manipulated postoperatively to alter CI. Hazard function curves show increased mortality postoperatively with a CI of less than 2 $L/min/m^2$. It is important to realize that blood pressure, urine output, temperature, and cerebral

function are all unreliable determinants of cardiac function in the postoperative state. If the CI falls below 2 L/min/m^2, the first intervention is usually to infuse fluid to increase preload to 14–18 mmHg. In stiff ventricles, left ventricular (LV) end-diastolic pressure may need to be 20 mmHg to optimize LV performance. Depending on mean systolic pressure, afterload reduction with vasodilators may be required. Contractility can be improved with the addition of inotropic agents. In severe LV failure, the intraaortic balloon pump may be required.

EXTRACORPOREAL CIRCULATION

Gibbon accomplished the first open heart operation in 1953 using cardiopulmonary bypass. Currently, most centers use a roller pump, originally designed by DeBakey. Since 1985, most centers have used membrane oxygenators. Priming solutions are usually crystalloid or colloid. Hemodilution is allowed to a hematocrit of 20 percent. Starting heparin doses are usually 4 mg/kg, and the activated clotting time is maintained greater than 600 s. Perfusion rate is usually 2.5 L/min/m^2, keeping mean systematic pressure to at least 50–60 mmHg. Core body temperature is lowered to about 30°C. In most cases, myocardial preservation is obtained using cold crystalloid or blood cardioplegia in combination with body hypothermia (28–30°C) and topical cooling. Myocardial temperatures below 15°C can be obtained, extending the possible cross-clamp time up to 4 h.

POSTOPERATIVE COMPLICATIONS

Bleeding Blood coagulation mechanics are abnormal for at least 18–24 h after coronary artery bypass. Unless bleeding is excessive, transfusion of platelets or fresh frozen plasma is seldom required. Brisk bleeding requires urgent return to the operating room.

Cardiac Tamponade Classic findings include elevated central venous pressure, equalization of diastolic pressures, hypotension, low CI, and mediastinal widening. Findings may be subtle. If a low CI is present and does not respond rapidly to specific treatments, reexploration for cardiac tamponade needs to be considered.

Inadequate Cardiac Index A CI of 2–2.5 L/min/m^2 early postoperatively is adequate. A CI below 2 L/min/m^2 requires rapid diagnosis and treatment, since death from inadequate perfusion may occur rapidly.

Preload, afterload, and contractility should be manipulated to optimize LV performance. The combination of fluid resuscitation and afterload reduction often restores cardiac index. Inotropes may be required. An intraaortic balloon pump (IABP) may be required if the preceding interventions fail.

Early postoperative cardiac rhythm disturbances require close attention. Temporary pacing wires are placed on the right ventricle and right atrium before leaving the operating room. Cardiac pacing with atrial or atrioventricular (AV) sequential pacing may be useful to ensure normal sinus rhythm. Premature ventricular contractions should be suppressed medically or overridden with a pacemaker because ventricular fibrillation or ventricular tachycardia can result. Potassium levels should be checked and kept well above 4 mEq/L. Lidocaine given as a bolus (75–100 mg) and infused at 2–4 mg/min can be used. Atrial fibrillation, the most common postoperative arrhythmia, is treated by rate control (calcium-channel or beta blocker) followed by a class IA antiarrhythmic agent; occasionally, electrocardioversion is required for hemodynamic instability.

Respiratory Insufficiency With current pump oxygenators, respiratory insufficiency is uncommon unless severe preexisting disease is present. The simplest numerical expression of this failure is elevation of the A-a gradient, representing the inability of oxygen to diffuse across the alveolar membrane.

Low-Grade Fever Low-grade fevers are common in the first 24–48 h after surgery and are due to pulmonary atelectasis and the use of blood products. After this time, postpericardiotomy syndrome may be present, usually treated with an anti-inflammatory medication. Specific causes, such as infection, need to be sought. The most serious cause is a mediastinal wound infection, which requires prompt return to the operating room. This complication occurs in 1–2 percent of open heart patients.

Renal Failure Urine output should be 0.5–1.0 mL/kg/h. Renal failure is uncommon with postoperative cardiac indices above 2 L/min/m^2, unless there is preexisting disease. Renal failure may be treated with hemodialysis or peritoneal dialysis.

Central Nervous System Dysfunction Stroke risk is increased in the elderly and patients with atherosclerotic aortas. Every effort should be made to remove air and debris from cardiac chambers before unclamping the aorta. Mean pressures during the pump run should be kept at least 60 mmHg, especially in the elderly.

SPECIFIC DISEASES

Coronary Artery Disease

Atherosclerosis is the fundamental cause, with the basic lesion being a segmental atherosclerotic plaque often localized in the proximal 5 cm of the coronary vessel. Clinical manifestations include angina pectoris, sudden death, myocardial infarction, and congestive heart failure. Angina pectoris is most common, and the differential diagnosis includes anxiety states, musculoskeletal disease, and esophageal reflux. In 25 percent of the patients, symptoms are atypical. Laboratory investigations include a variety of stress tests using electrocardiographic (ECG) monitoring, radionuclide scanning, or echocardiography. Coronary angiography remains the "gold standard." A stenosis is considered significant when the diameter is reduced by more than 50 percent, corresponding to a reduction in the cross-sectional area of 75 percent. Ventriculography is used to measure ejection fraction (EF), with normal EF 55–70 percent, moderately depressed EF 35–55 percent, and severely depressed EF under 35 percent. Regional wall motion is described as normal, hypokinetic (impaired), akinetic (no visible contraction), and dyskinetic (paradoxical contraction). Positron emission tomographic (PET) or thallium scanning may reveal areas of viable yet nonfunctional myocardium (hibernating) that will benefit from revascularization.

Coronary artery disease can be treated either medically or surgically, which involves coronary artery bypass grafting (CABG). Indications for CABG are determined by symptoms, number of stenotic major coronary arteries, and left ventricular ejection fraction (LVEF).

Coronary surgery (CABG) results in improved survival in patients with unstable symptoms, severe proximal coronary disease (triple-vessel and/or left main), depressed LVEF, or a poor response to stress testing. Unstable situations such as postinfarction angina or structural defects require more urgent intervention. Angioplasty and other intracoronary therapies are used for single and occasionally multivessel disease. Survival is superior for CABG versus angioplasty in diabetic patients, those with triple-vessel disease, and those with double-vessel disease with a tight left anterior decending (LAD) artery stenosis.

Surgical techniques include the use of cold blood cardioplegia with systemic hypothermia and topical cooling. Saphenous vein grafts are used, whereas mammary arteries are preferred, with sequential and bilateral mammary grafts increasing in frequency. Recently, an increased use of other arterial conduits has emerged, including the radial (most common), gastroepiploic, inferior epigastric, and other arteries. Hospital stay is usually 5–7 days, and

full return to activity usually occurs in 6–8 weeks. Mortality risk is approximately 1–3 percent, with a morbidity rate of 5 percent and an overall frequency of stroke of 2 percent (up to 10 percent for patients over age 70). Carotid artery surgery is not used unless acute cerebral symptoms (transient ischemic attacks) are present.

Postoperatively, relief of angina is seen in 90–95 percent of patients, correlating with improvement in wall motion abnormalities. Vein graft patency at 1 month exceeds 95 percent, with an attrition rate of approximately 1–2 percent per year up to 5 years. Thereafter, rapid progression of atherosclerotic disease can be seen, and at 10 years, patency rate is about 60 percent. The 10-year patency rate of left internal mammary artery grafts is over 95 percent, whereas the long-term patency of other arterial conduits remains to be determined. Progression of native disease is a major factor, which may be reduced by decreasing the serum cholesterol level. Recurrent angina occurs at a rate of 3–5 percent per patient-year. If LV damage or scarring is present, arrhythmia is usually not improved after CABG. Longevity in patients with coronary artery disease tends to favor operation versus medical treatment when the LVEF is depressed, moderate to severe angina is present, or two or more coronary arteries are stenotic. New developments for the treatment of coronary artery disease include MIDCAB (minimally invasive direct coronary artery bypass (MIDCAB), port-access surgery, transmyocardial laser revascularization (TMLR), and gene therapy.

Left Ventricular Aneurysm

A left ventricular aneurysm (LVA) develops over a period of 4–8 weeks in 10–15 percent of patients after a transmural myocardial infarction. Mural thrombus is present in 50 percent of the patients, whereas emboli and rupture are rare. Most LVAs (> 80 percent) are anterolateral. In 30–40 percent of patients, single-vessel disease is present, and large aneurysms impair ventricular function. Longevity is probably related to underlying ventricular function. Distinction must be made at operation between akinetic scar and true aneurysm. Surgical considerations include (1) not disturbing the aneurysm until the aorta is cross-clamped, avoiding emboli, (2) subtotal resection of the aneurysm, maintaining LV muscle and geometry, (3) possible endocardial resection to treat arrhythmias, and (4) appropriate coronary artery grafts to improve global circulation.

Valvular Diseases

MITRAL STENOSIS

Mitral stenosis is almost always due to rheumatic heart disease. Rheumatic fever produces a pancarditis, but it is the endocardial

changes that predominate, resulting in scarring of the valve tissue. Turbulent flow results, and hemodynamic changes cause commissural fusion, valve fibrosis, and calcification. Leaflet mobility decreases while the subvalvular apparatus (chordae tendineae) and papillary muscles become thickened, fibrotic, and contracted. Thus the pathologic changes of mitral stenosis do not develop from multiple episodes of rheumatic fever but rather from the turbulent flow resulting from the initial episode. Repair of the mitral valve and decreasing leaflet turbulence may result in a good long-term result.

Normal mitral valve orifice area is 4–6 cm^2. Reduction to 2–2.5 cm^2 constitutes mild mitral stenosis (class I). Patients with a cross-sectional area less than 1 cm^2 are severely disabled (class IV). Mitral stenosis results in the following significant physiologic derangements:

1. Increased left atrial pressure, enlargement, and eventually atrial fibrillation with a risk of embolization.
2. Low CO due to a fixed, stenotic orifice.
3. Variable increases in pulmonary vascular resistance, primarily a result of vasoconstriction in the pulmonary arterioles. In the majority of patients, pulmonary hypertension abates after surgical repair.

The main symptoms in mitral stenosis are exertional dyspnea and fatigue. Dyspnea develops when left atrial pressure rises to exceed the oncotic pressure of plasma leading to transudation of fluid across the pulmonary capillaries. When this interstitial fluid load exceeds lymphatic capacity, pulmonary edema occurs. Systemic emboli occur with increases in left atrial size and atrial fibrillation. Hemoptysis may occur but is usually not severe. Right-sided heart failure occurs later secondary to elevated pulmonary vascular resistance (PVR). Physical examination usually shows cardiac cachexia. Pulmonary congestion is frequent. The “auscultatory triad” includes an increased first heart sound, an opening snap, and an apical diastolic rumble.

The chest radiograph demonstrates a left atrium as a double shadow behind the heart. The usual concavity between the aorta and left ventricle appears as a “straight” left heart border. Mitral valve calcification also may be seen. Pulmonary hypertension causes large pulmonary arteries, and Kerley lines may be present.

Echocardiography (transthoracic or transesophageal) can determine the degree of atrial enlargement, estimate the degree of mitral stenosis, and provide information about leaflet mobility. Cardiac catheterization provides additional information but may not be necessary in patients under age 40 if good echocardiographic data are available. Cardiac catheterization helps delineate the severity of the

mitral stenosis, the level of PVR, and the status of the coronary arteries.

Operation should be considered routinely with hemodynamically significant mitral stenosis even if symptoms are minimal. The operative risk is approximately 1 percent, and in early mitral stenosis, reconstruction rather than replacement is often possible (90 percent). The presence of systemic emboli is an indication for surgery because recurrent emboli are common. Most important, mitral stenosis may be repaired successfully regardless of the severity of PVR. The left ventricle in pure mitral stenosis is protected, and PVR is reduced postoperatively in most patients.

MITRAL INSUFFICIENCY

Etiologies include degenerative disease (50 percent), rheumatic fever (20–30 percent), ischemic disease (15–20 percent), endocarditis, congenital abnormalities, and cardiomyopathy. Type I insufficiency due to annular dilatation or leaflet perforation is usually caused by ischemia or endocarditis. Type II insufficiency is secondary to increased leaflet motion with prolapse, commonly of degenerative or ischemic origin. Type III occurs with restricted leaflet motion, usually from rheumatic disease. Annular dilatation is an important component of insufficiency and is usually found with types II and III.

The physiologic derangement of this condition is regurgitation of blood from the left ventricle to the left atrium during systole. This results in decreased forward flow and elevated left atrial pressure, causing pulmonary congestion and volume overload of the left ventricle. The left ventricle undergoes dilatation but may function adequately for long periods of time before failure. A systolic murmur radiating to the axilla is characteristic of mitral regurgitation, becoming pansystolic with increased severity. Symptoms, primarily dyspnea, are mild until late in the course.

Diagnosis and anatomic characterization are made by echocardiography. Cardiac catheterization is indicated in advanced insufficiency and cardiac enlargement, uncertain diagnosis, and when coronary disease is a concern. Timing of the operation is difficult, especially since the symptoms are mild until late in the course. An operation should be done before the onset of LV failure.

Operative Technique The standard operative approach is through a median sternotomy with exposure of the valve through a lateral, transseptal, or superior approach. The atrial appendage should be ligated if atrial fibrillation is present preoperatively. Reconstruction techniques (commissurotomy, repair of subvalvular apparatus) are always preferable to replacement. This preserves LV function and

avoids the complications of a prosthetic device. Open, precise repair using cardiopulmonary bypass is preferred to the "blind," closed commissurotomy. Commissurotomy and repair can be performed if the leaflets are pliable and an adequate opening can be obtained. Carpentier and others have used chordi shortening, chordi transplantation, and quadrangular resection with annuloplasty with excellent results. After discontinuing cardiopulmonary bypass, the repair is evaluated using intraoperative transesophageal echocardiogram or direct measurement of the transvalvular gradient. Significant residual stenosis (gradient 5–7 mm) or regurgitation requires additional procedures or valve replacement.

If reconstruction cannot be accomplished, replacement with a bioprosthesis or mechanical valve is performed. Excision of the valve should preserve the chordae to the posterior leaflet in order to preserve the LV geometry and function (especially in mitral insufficiency). In addition, there is some evidence that posterior leaflet preservation protects against LV rupture in the early postoperative period. Sutures for valve replacement should be placed carefully to avoid the circumflex artery (posterior) and the conduction system (anterior). As with repair, care is taken to remove air from all cardiac chambers before LV ejection.

Antibiotics are given perioperatively and continued until all intracardiac lines are removed. Anticoagulation is started within the first 3 days. With a bioprosthesis, warfarin can be stopped after 3 months if normal sinus rhythm is present and left atrial size has decreased. Currently, no ideal cardiac prosthesis exists. Mechanical valves are durable but thrombogenic, with the frequency of thromboembolism approximately 4 percent per patient-year. The frequency of prosthetic thrombosis is 1 percent per year and necessitates the need for lifelong anticoagulation with its attendant risks. Bioprosthetic valves, however, deteriorate over time, and in 10 years, 20–40 percent of the bioprostheses may require replacement. In general, for patients less than 60 years old who can reliably take warfarin, a metal valve is recommended. Older patients often receive the bioprosthesis.

AORTIC STENOSIS

A normal aortic valve has a cross-sectional area of 2.5–3.5 cm^2, whereas moderate aortic stenosis is present at 1.0 cm^2. Valve areas as low as 0.4–0.6 cm^2 may be found with severe aortic stenosis. The effective valve area is determined by the transvalvular gradient and the CO (Gorlin's formula). Aortic stenosis results in progressive concentric hypertrophy of the left ventricle. Causes of aortic valve stenosis are congenital deformity, rheumatic disease, and acquired calcific disease. Calcified congenital bicuspid valve steno-

sis (46 percent) is characterized by heavy infiltration with calcium on the leaflets, aorta, and ventricle. Rheumatic aortic stenosis with commissural fusion and calcification accounts for 35 percent. Ten percent of the patients have acquired or sclerotic aortic stenosis, where the leaflets are of normal size without commissural fusion. Leaflet immobility occurs because the bases of the cusps are heavily infiltrated with calcium. In older patients (> 40 years old), coronary atherosclerosis occurs in 30–50 percent of patients. Characteristically, there is a long asymptomatic period, up to 10–20 years. The classic symptoms include angina pectoris, syncope, and failure. Once symptoms develop, life expectancy is about 3 years, with sudden death accounting for 15–20 percent of fatalities. Syncope develops in 10 percent of patients and may be related to cerebral blood flow or arrhythmia. Angina unrelated to coronary artery disease occurs in 30–40 percent as a result of left ventricular hypertrophy, elevated LV systolic pressures, and subendocardial ischemia. This problem is obviously made worse with coronary artery disease.

Congestive heart failure is an ominous symptom, with a risk of death of 40 percent over the next 2–3 years. Atrial fibrillation also may occur as ventricular failure progresses. The principal physical finding is a harsh systolic murmur at the base of the heart. A prolonged heave is present at the apical impulse instead of the forceful thrust found in mitral regurgitation or aortic insufficiency. Peripheral pulses have a delayed upstroke. Heart size is usually normal. Echocardiography is the principal diagnostic study demonstrating (1) leaflet mobility and Ca^{2+}, (2) transvalvular gradient, (3) degree of ventricular hypertrophy, and (4) ventricular dimensions. Cardiac catheterization with coronary angiography is usually necessary. Valve replacement is indicated for all symptomatic patients, for those demonstrating progressive ventricular decompensation, and for those with critical stenoses. Operative replacement of the aortic valve for significant aortic stenosis remains the best long-term treatment. Valve dilatation with balloon angioplasty is possible but is reserved for nonoperative candidates.

AORTIC INSUFFICIENCY

Aortic insufficiency is caused by a variety of diseases. Bacterial endocarditis commonly results in valvular insufficiency, whereas fever is decreasing in frequency. Annular ectasia is a collagen disease associated with cystic medial necrosis and increases in frequency in the older population. In its most severe form (Marfan syndrome), the aortic root and aorta dilate, producing aortic insufficiency and aneurysmal enlargement of the sinuses of Valsalva and ascending aorta.

Atherosclerotic aneurysms have different underlying pathologies and may cause aortic insufficiency from annular dilatation. Aortic dissection with valve cusp detachment from the aortic wall can result in aortic insufficiency. The clinical course is highly variable depending on the degree and rate of increased aortic insufficiency.

Aortic insufficiency causes diastolic volume overload of the LV. The regurgitant volume may be two to three times the normal stroke volume, 60–70 mL. The LV adaptation is quite different from aortic stenosis, in which concentric muscular hypertrophy occurs. Because of the compensatory mechanism of chamber dilatation, LV end-diastolic pressure and left atrial pressure remain normal until late in the course, when LV failure occurs. Mitral regurgitation might develop at this point as a result of annular dilatation. Death may occur within 4–5 years because of progressive LV failure.

Symptom-free intervals of 8–10 years are common. Symptoms usually develop once LV failure begins in the chronic form. The left ventricle maintains its SV by dilatation, causing massive cardiac enlargement. Anginal symptoms also may be present with severe disease. On physical examination, the murmur is a high-pitched decrescendo diastolic murmur along the left sternal border starting immediately after the second heart sound. Systolic blood pressure remains stable, but diastolic pressure drops. Peripheral pulses increase and often can be visualized because of the widened pulse pressure.

Timing an operation is difficult because once symptoms develop, some degree of LV failure is usually present. Means of detecting the early LV failure have been attempted, and echocardiography, showing an end-systolic dimension greater than 55 mm, has been recommended. A decreased ejection fraction with exercise also has been used to improve surgical results. Even with moderate or severe LV dysfunction, operation is recommended, since death is almost always a certainty otherwise. In this subset of patients, the degree of improvement following surgery is difficult to predict.

Operative Technique Aortic valve surgery is usually performed through a median sternotomy with cardiopulmonary bypass and antegrade or retrograde cardioplegia. A left ventricular vent is placed by way of the right superior pulmonary vein. An aortotomy is performed, and the valve is inspected and completely excised; the annulus is debrided as necessary. Most commonly pledgeted horizontal mattress sutures are placed; alternatively, simple, interrupted figure-of-eight or continuous sutures can be used. Currently, a number of prostheses are available: bioprosthetic valves, including porcine, pericardial, stentless porcine, homograft, and autograft

(Ross procedure), and a variety of mechanical valves. Postoperative care includes anticoagulation and observation for arrhythmias. Operative mortality is low (1–2 percent). Five-year survival is 80–90 percent for good ventricles.

TRICUSPID STENOSIS AND INSUFFICIENCY

Distinction needs to be made between organic and functional tricuspid valve disease. Organic tricuspid valve disease is almost always due to rheumatic fever; 10–30 percent of patients with left-sided disease also will have tricuspid valve involvement. The pathology is similar to the more familiar mitral valve disease. Organic tricuspid stenosis is more frequent than insufficiency, which can be caused by endocarditis and trauma. Functional tricuspid valve disease is more common and occurs when normal leaflets do not coapt as a result of annular dilatation. This valvular insufficiency is due to left-sided heart disease with subsequent pulmonary hypertension and right-sided heart failure.

Normal right atrial pressure is 4–5 mmHg. When the tricuspid orifice becomes smaller than 1.5 cm^2, the atrial pressure rises, with a mean gradient of 5–15 mmHg, resulting in symptoms similar to right-sided heart failure with edema, ascites, and hepatomegaly. A characteristic murmur of tricuspid stenosis is a diastolic murmur at the lower sternum. Inspiration will increase its intensity. A moderate degree of tricuspid insufficiency may be tolerated with little adverse effect. Tricuspid insufficiency produces a systolic murmur at the lower sternum.

Diagnosis of tricuspid valve disease can be accomplished with ultrasound and right-sided heart catheterization. A transvalvular gradient of 4–5 mmHg is significant. At the time of operation, palpation can be a useful indicator of tricuspid insufficiency, whereas both anatomic findings and preoperative symptoms determine the decision for surgical repair. With minor symptoms and anatomic changes, the tricuspid valve should be left alone. If right atrial hypertrophy and/or dilatation is present and the annulus is mildly dilated, repair almost always should be performed. Repair can be accomplished by posterior leaflet annuloplasty, DeVega annuloplasty, or the ring annuloplasty technique of Carpentier. Tricuspid stenosis usually can be handled with a commissurotomy. When leaflet destruction precludes repair, replacement needs to be carried out. Mechanical valves have a higher incidence of thrombotic complications than bioprostheses, which are preferred. When the prosthesis is placed, care must be taken to preserve the septal leaflet, avoiding the complications of heart block. The conduction bundle lies between the coronary sinus and the ventricular septum. With bacterial endocarditis, there is controversy over whether the

prosthetic device should be placed at the initial operation or at a later time if right-sided heart failure occurs. Operative mortality is low (1–2 percent). Long-term prognosis depends on underlying myocardial dysfunction.

MULTIVALVULAR DISEASE

With rheumatic heart disease, more than the cardiac valve may be involved. Prominent signs of disease in one valve can readily be masked by disease in other valves. Echocardiography is a valuable tool to determine the contribution of each valve.

CARDIAC TUMORS

Metastases are the most common cardiac tumors, occurring in 4–12 percent of autopsies performed in patients with neoplastic disease. The most frequent primary cardiac tumor is myxoma, comprising 50–60 percent of all primary cardiac tumors. Sarcoma and rhabdomyoma are less common. Benign but extremely rare neoplasms include fibromas, angiomas, lymphomas, and teratomas. Two-dimensional echocardiography is now the keystone of diagnostic studies.

Between 60 and 75 percent of cardiac myxomas develop in the left atrium, almost always from the atrial septum near the fossa ovalis. Most other myxomas develop in the right atrium, and less than 20 have been found in either the right or left ventricle. Myxomas are true neoplasms. They are usually polypoid, arising from superficial layers of the septum, and invasion does not occur. Metastases are rare. The tumor is friable, so emboli can occur. Myxomas cause symptoms by growing large enough to restrict flow or prolapsing through the mitral or tricuspid valve. The tumor is friable in 40–50 percent of patients. Some myxomas produce generalized symptoms resembling an autoimmune disorder, including fever, weight loss, arthralgias, and myalgias.

Treatment is prompt operative removal. A biatrial incision is used for good exposure and complete exploration. The tumor and septum are removed, and the resulting atrial septal defect is closed with a patch. Cardiac rhabdomyomas are probably hamartomas and are most common in children. About 50 percent of patients have tuberous sclerosis of the brain, and the tumor is usually fatal.

PERICARDITIS

Acute pericarditis can be caused by infection, myocardial infarction, trauma, neoplasm, radiation, autoimmune diseases, drugs, and

others. Treatment is directed by etiology (e.g., antibiotic therapy for infection or nonsteroidal anti-inflammatory drugs for postinfarction pericarditis) and drainage either by aspiration or operation.

Chronic constrictive pericarditis is usually idiopathic. The physiologic derangement due to limitation of diastolic filling of ventricles results in decreased SV and CO and increased systemic venous pressure. This disease rarely develops after an open heart operation.

Cardiac catheterization results are characteristic, showing the "square root" sign and equalization of pressures. Treatment is surgical removal of pericardial constriction. The approach is through median sternotomy. The pericardium is removed as completely as possible from both ventricles along with the atria and cavae. The plane of resection is usually between the pericardium and epicardium, which, if thickened, may require removal or incision in a gridlike fashion.

ARRHYTHMIA SURGERY

Current ablative therapies are now done for Wolff-Parkinson-White (WPW) syndrome, paroxysmal supraventricular tachycardia, sustained ventricular tachycardia, or atrial fibrillation. The Maze procedure can treat chronic atrial fibrillation successfully.

PACEMAKERS/ IMPLANTABLE DEFIBRILLATORS/ INTRAAORTIC BALLOON PUMP/ ASSIST DEVICES

Technology in this field is changing rapidly. The two most common methods of pacing are R wave–inhibited demand ventricular (VVI) and AV synchronous (DDD). Both require an electrode in the right ventricle, and the second requires an additional wire in the right atrium. These electrodes are usually placed transvenously to engage the endocardial surface. Both methods of pacing prevent syncope by pacing the heart during periods of bradycardia. The latter technique (DDD) allows AV synchrony. Current pacemakers are programmable, allowing rate, pulse amplitude, duration, AV delay, and other variables to be changed. Recently, a code has been developed to describe all pacemakers. Three or more letters are used, representing chamber pace, chamber sensed, and the mode of generator function. Operative techniques usually involve surgical exposure of the cephalic vein, with other options including external jugular, internal jugular, and subclavian percutaneous introduction. Endocardial electrodes require threshold testing, which should be

between 0.4 and 0.8 mA and 0.2 and 0.4 V. The most common indicator for pacemaker insertion today is heart block in the elderly (Lev disease). It is uncommon to require a pacemaker after heart block from myocardial infarction. Telephone ECG surveillance is used for pacemaker follow-up, helping to decrease the morbidity from heart block. Another use of cardiac pacemakers and electrodes is the automatic implantable defibrillator, which allows successful detection and termination of malignant ventricular arrhythmias.

Temporary assisted circulation is a valuable clinical modality when transient cardiac injury is present. It is seldom effective if required for more than 2–3 days. Intraaortic balloon pumping (IABP) is an effective method to augment coronary blood flow and decrease LV work. The IABP is alternately inflated during diastole and deflated during systole. CI is usually increased 0.5–0.7 L/min/m^2. Ischemia of the extremity is the most common complication. If the IABP is not effective, left-sided heart bypass or assist also can be used. Blood is removed from the left atrium or ventricle and returned to the systemic circulation, reducing left-sided work and improving CO. As opposed to the IABP, ventricle assist can be used for prolonged periods of time. Newer devices are implantable and often are used as a bridge to transplantation, some even on an outpatient basis. Research continues on the total artificial heart.

For a more detailed discussion, see Galloway AC, Colvin SB, Grossi EA, Spencer FC: Acquired Heart Disease, chap. 18 in *Principles of Surgery,* 7th ed.

CHAPTER

19

THORACIC ANEURYSMS AND AORTIC DISSECTION

THORACIC ANEURYSMS

General Considerations Excisional therapy and endoaneurysmorrhaphy with internal graft replacement have been used for repair of thoracic aortic aneurysms. If the aneurysm is well localized, total excision is feasible, and the involved area is replaced with an end-to-end Dacron graft (graft interposition method). This method is associated with a lower risk of reoperation for pseudoaneurysm. Patients with more extensive aneurysmal disease may require replacement of the diseased segment from within by placing a Dacron graft without excising the aorta itself. An end-to-end anastomosis is performed within the open aneurysm; the wall of the aneurysm is wrapped around the graft for tissue coverage (graft inclusion method).

Etiology An aortic aneurysm is a localized or diffuse aortic dilatation greater than 5–6 cm in diameter that develops from a weakness or defect in the aortic wall. Atherosclerosis associated with increased proteolytic enzyme activity has been implicated. There is a degeneration of elastin and collagen within the vessel wall, as well as decreased protease inhibitor activity, resulting in progressive dilation of the vessel. Late in the process, there is degradation of the adventitial layer with additional dilation or rupture of the aneurysm.

Causative factors are age, hypertension, smoking, atherosclerosis, aortic dissection, and connective tissue disorders. Chronic atherosclerosis is responsible in a minority of patients usually in conjunction with other factors such as inflammation or a genetic tendency for increased proteolytic activity. The most common connective tissue disorders associated with aneurysm formation are Erdheim's cystic medial necrosis, Marfan syndrome, and Ehlers-Danlos syndrome. Familiarity with genetic defects associated with aneurysmal disease can lead to earlier, more effective operative treatment. Less common causes are trauma, infection (mycotic), inflammatory disease, and autoimmune diseases.

Classification Aneurysms are classified by anatomic location: aortic root and ascending aorta, transverse arch, descending thoracic, and thoracoabdominal aneurysms. The most common are aneurysms of the aortic root and ascending aorta. Other classifications are as follows: Aortoannular ectasia is degenerative dilatation of the aortic annulus and the sinuses of Valsalva; traumatic aneurysms may occur after blunt trauma; and aortic dissection may occur as a result of an intimal tear in the aortic wall.

Clinical Manifestations Sudden and severe pain is the most common symptom associated with a large or expanding aneurysm. Chronic pressure or low-grade, aching pain may suggest chronic aneurysm. In a patient with known aneurysms, new onset of pain may indicate rapid expansion, leakage, or impending rupture. Large aneurysms may produce symptoms from compression of adjacent structures, which can result in pain, pulmonary symptoms, and hoarseness. Most patients with moderate-sized aneurysms are asymptomatic and are discovered incidentally.

Diagnosis Diagnosis is established by echocardiography, computed tomographic (CT) scan, magnetic resonance imaging (MRI), and rarely, aortography. Patients often have associated coronary artery disease, and screening studies or coronary angiography should be performed before repair.

Natural History and Operative Indications The history is one of progressive enlargement with rupture. Risk factors for rupture include size of the aneurysm, change in size, smoking, and chronic obstructive pulmonary disease (COPD). Risk of rupture by size is as follows: $<$ 3 cm, 0 percent; 3–4 cm, 6 percent; 4–5 cm, 12 percent; 5–6 cm, 36 percent; 6–7 cm, 50 percent; and 7–8 cm, 100 percent. A few patients with smaller aneurysms that were not enlarging have had sudden ruptures; if treated nonoperatively, patients should be aware of this fact. Overall survival if untreated is 60 and 13 percent at 1 and 5 years, respectively. Operation should be strongly considered in patients with saccular aneurysms or connective tissue diseases when the aneurysm is greater than 4.5–5 cm in size.

AORTIC ROOT AND ASCENDING AORTIC ANEURYSMS

Operative Treatment Standard operative repair is through a median sternotomy incision using cardiopulmonary bypass and car-

dioplegia. When the aneurysm is confined to the ascending aorta without involvement of the aortic root, the ascending aorta is replaced with a woven Dacron graft, beginning just distal to the sinotubular ridge and ending proximal to the innominate artery. Concomitant valve replacement is performed if aortic valve disease is present.

The operation most commonly used for root replacement is a composite valve graft, which involves replacement of the aortic valve and aortic root with aortic valve–Dacron graft conduit placed from the aortic annulus to the distal aorta beyond the aneurysm; this requires reimplantation of the coronary arteries into the composite graft. The need for root replacement can be determined preoperatively by MRI, CT, echocardiogram, or angiogram during cardiac catheterization. Long-term operative results are excellent with low mortality (2–5 percent) depending on the number of associated risk factors.

AORTIC ROOT AND AORTIC ARCH ANEURYSMS

These may be isolated or part of a continuous aneurysmal process involving the ascending and descending aorta. Most common causes are atherosclerosis, aortic dissection, and connective tissue disorders. Diagnosis is made after chest x-ray by MRI, CT, or aortography. The innominate, carotid, or subclavian artery also may be aneurysmal. The extent of disease and great vessel involved should be defined preoperatively in order to determine the operative approach.

Treatment The extent of arch involvement may make it necessary to perform total arch replacement with reimplantation of the arch vessels into the graft or partial hemiarch replacement with placement of a beveled graft leaving the arch vessels to arise from the native aortic arch superiorly. Hemiarch repair allows replacement of 25–85 percent of the aortic arch as necessary. The elephant trunk technique is used for patients who require a subsequent operation for a descending aneurysm. In this technique, the distal graft is invaginated into itself while the anastomosis is constructed, and the invaginated portion is subsequently unfolded so that it lies free in the descending aorta, allowing easier access to the distal graft during the subsequent descending aneurysm repair.

Use of hypothermic circulatory arrest for cerebral protection allows blood flow to be stopped so that a precise, sound technical arch anastomosis can be performed and avoids clamping and

manipulation of the disease aorta, lessening the risk of aortic injury or embolization. Risk of permanent neurologic injury (stroke), caused by embolic events, after circulatory arrest is low if the cerebral ischemic time does not exceed 45 min. Temporary neurologic dysfunction such as transient confusion, agitation, or obtundation occurs in 20–30 percent of patients in whom circulatory arrest exceeds 50 min.

A new technique for cerebral protection involving retrograde cerebral perfusion through the superior vena cava has minimized the risk of cerebral ischemia when the circulatory arrest time is greater than 45 min.

Descending Thoracic Aneurysms

Etiology Descending thoracic aneurysms may result from atherosclerosis, cystic medial necrosis, connective tissue diseases, dissection, infection, inflammation, or prior trauma. Most begin in the proximal descending thoracic aorta, just distal to the left subclavian artery and can extend to involve the entire descending thoracic aorta. Atherosclerotic aneurysms usually are fusiform; some are localized and saccular. Concomitant abdominal aneurysms occur in 25–30 percent of patients; the entire thoracoabdominal aorta may be involved in 10 percent of patients.

Clinical Manifestations Most are asymptomatic and diagnosed on routine chest x-ray. Aneurysmal enlargement or compression of adjacent structures may produce symptoms that result in pain, cough, dyspnea, vocal cord paralysis, or hemoptysis. Physical examination usually is normal.

Diagnosis Thoracic aneurysm is usually diagnosed after chest x-ray and is confirmed by CT or MRI. Concomitant atherosclerosis often is present in the coronary, renal, or carotid arteries. Stress testing, coronary arteriography, and carotid studies should be performed to determine whether concomitant cardiovascular disease requires treatment. Patients with symptomatic coronary artery disease or a positive stress test should undergo cardiac catheterization and revascularization before aneurysm repair.

Operative Indications In patients with descending aneurysms larger than 5–6 cm in diameter, elective repair is suggested. Patients with aneurysms less than 5 cm in diameter require frequent follow-up and imaging studies; operation is indicated if the aneurysm expands or the patient becomes symptomatic.

Treatment Operative techniques include *unprotected cross-clamping*, in which cross-clamps are placed proximally and distally without distal perfusion or with a single proximal cross-clamp with controlled distal exsanguination. In *perfusion* or *shunting*, bypass or passive shunts are used to maintain distal aortic perfusion during the cross-clamp time. Perfusion may be done with left atriofemoral bypass, with femoral-femoral bypass with an oxygenator, or with a Gott shunt from the proximal to the distal aorta.

Operative exposure is achieved with a left posterolateral thoracotomy through the fourth, fifth, or sixth interspace; the fifth is used for most middle descending aneurysms. The aorta initially is mobilized and encircled proximal and distal to the aneurysm; occasionally, the aorta is controlled proximally between the left carotid and left subclavian arteries. Almost 25 percent of descending aneurysms require placement of the cross-clamp proximal to the left subclavian artery. Operative dissection is facilitated by opening the pericardium to expose the intrapericardial portion of the transverse aortic arch. The vagus nerve and recurrent laryngeal nerve should be mobilized and protected.

To place the graph, an initial dissection is performed to isolate the aorta proximally and distally. The aorta must be sufficiently mobilized to allow precise placement of the cross-clamps, with proximal control usually obtained first. Decision is then made as to whether a simple cross-clamp or perfusion technique is to be used.

When the aorta is clamped and opened widely, thrombus is removed from the lumen. Ostia of intercostal vessels are oversewn from within the aneurysm unless they are to be reimplanted into the side of the graft. In most patients, the aneurysm is not resected; the graft is placed internally after the aneurysmal contents are evacuated. A woven Dacron graft is inserted; end-to-end anastomoses are performed proximally and distally with continuous vascular suture. After graft placement, the clamps are temporarily opened to remove air or thrombus; the suture lines are then tied. The cross-clamps are removed slowly; the distal body is perfused through the graft. Reperfusion can result in transient hypotension, which is corrected by volume infusion and sodium bicarbonate. When hemostasis is obtained, the aneurysmal sac is wrapped around the graft.

Complications after repair can include paraplegia. Unprotected cross-clamping for more than 20 min is associated with an increased risk of paraplegia. Data suggest that when cross-clamp time is greater than 30–40 min, maintaining perfusion of the distal aorta at more than 60 mmHg reduces the risk of paraplegia, renal insufficiency, intestinal ischemia, and reperfusion-related white blood cell activation with multiorgan dysfunction.

Perfusion Technique Perfusion options include using femoral vein–femoral artery perfusion with an oxygenator or left atriofemoral artery bypass using heparin-bonded circuits, no oxygenator, minimal heparin, and a cell-saver–rapid infuser. Left atriofemoral bypass is preferred because it allows better control of the proximal blood pressure and minimizes the need for nitroprusside.

In addition, somatosensory evoked potential monitoring (SEP) can evaluate spinal cord ischemia or the adequacy of perfusion while the aorta is occluded, although some have reported no decreased incidence of paraplegia when using distal perfusion and SEP monitoring versus the simple cross-clamp method.

Single Cross-Clamping with Controlled Distal Exsanguination Controlled distal exsanguination reduces venous distention and lowers cerebrospinal fluid pressure, improving spinal cord perfusion during the cross-clamp period (as long as the cross-clamp period is not more than 30–40 min). This method limits spinal cord ischemia and edema. Because no bypass circuit for distal perfusion is required and no heparin is used, the risk of bleeding and coagulopathy may be lower.

Results Long-term prognosis after repair depends on concomitant coronary artery disease, cerebrovascular disease, or aneurysmal disease in other parts of the aorta. Approximately 30 percent of patients with descending thoracic aneurysms develop aneurysmal disease elsewhere; follow-up imaging studies on a yearly basis are recommended.

Thoracoabdominal Aneurysms

Etiology and Classification These usually are a result of atherosclerosis, connective tissue disease, or aortic dissection and are classified as follows:

Type I—proximal descending to upper abdominal
Type II—proximal descending to below renal arteries
Type III—distal descending and abdominal
Type IV—suprarenal and infrarenal abdominal

Operative Treatment Because thoracoabdominal aneurysms usually involve the segment of aorta where the celiac axis, superior mesenteric artery, and renal arteries arise, surgical repair may result in transient spinal cord, renal, and visceral organ ischemia, with subsequent ischemia-reperfusion-related white blood cell activation, which can lead to multiorgan injury. Coagulopathy and

bleeding may be significant; if massive transfusion is needed, the risk of multiple organ failure is increased.

Operative exposure requires a large thoracoabdominal incision in the sixth or seventh intercostal space of the left chest; the costal cartilage is divided; the incision is extended below the umbilicus. The diaphragm is divided circumferentially along the radius, preserving the central innervation. The descending thoracic aorta is isolated proximal to the aneurysm; the spleen, left colon, and kidney are reflected medially; the retroperitoneum is entered to expose the aorta distally to the bifurcation; the retroperitoneal lymphatics are tied in continuity.

When the aorta is exposed, the aorta is clamped proximally. Distally, the aorta is left open or clamped and perfused. The aneurysm is incised, and an anastomosis is performed between the graft and the proximal aorta. Segmental intercostal arteries or the cluster of arteries above and below the diaphragm are reimplanted into the graft. The cross-clamp is sequentially moved distally beyond the reimplanted intercostal arteries. The visceral vessels are reimplanted and reperfused, and an anastomosis between the graft and the distal aorta is performed.

Reimplanting large intercostal vessels or clusters of vessels in the aortic graft can reduce the risk of paraplegia. Other methods of spinal cord protection include bypass methods to increase spinal cord blood flow; the use of intrathecal vasodilators such as papaverine, systemic steroids, intravenous lidocaine, systemic hypothermia, barbiturates, calcium channel blockers, and oxygen radical scavengers; and cerebrospinal fluid drainage to decrease spinal cord pressure.

AORTIC DISSECTION

Etiology This begins as a tear in the intima with entry of blood and separation of the media, which results in blood flow down a "false lumen." A localized aneurysm may develop immediately or months or years later. The disease is three to four times more common in males, occurring mostly in older patients (after the fifth decade). Dissection may occur in any age group; certain cases occur in childhood secondary to coarctation of the aorta.

Aortic dissection usually results from a combination of hypertension and degenerative connective tissue disease. The strongest predisposing factor is cystic medial necrosis, but it also may be associated with congential bicuspid aortic valve. Aortic dissection is a disease of the media, usually originating in the thoracic aorta, and it may continue distally to the aortic bifurcation.

Pathology A transverse tear of intima and media is the initial event, which permits blood to enter into the media and dissect distally. Most prominent sites are 70 percent ascending, 10 percent arch, 20 percent upper thoracic, and 2 percent abdominal aorta. The aortic wall progressively separates ("dissects") with an inner (true) lumen composed of intima and an outer (false) lumen composed of media and adventitia. It usually extends rapidly through the thoracic and abdominal aorta in the peripheral arteries.

As dissection proceeds, branches are obliterated unless communication with the false lumen is established. Proximally, the coronary arteries may be involved, and often one or more aortic valve commissures are detached, creating aortic insufficiency. The commissure between the right sinus and the noncoronary sinus is most commonly involved. Distally, any vessel may be involved. Innominate or carotid artery involvement may produce neurologic injury. Obstruction of a subclavian artery may produce arm ischemia, and occlusion of intercostal arteries may cause spinal cord injury with paraparesis or paraplegia. Dissection of renal arteries may produce renal insufficiency, hematuria, oliguria, or anuria. Acute obstruction of the iliac or femoral arteries may cause leg ischemia.

Rupture into the pericardial cavity with cardiac tamponade is the most common fatal complication.

Clinical Manifestations Abrupt onset of excruciating pain is characteristic. Pain may radiate from the anterior chest to the neck, arms, epigastrium, or legs. Other presenting symptoms include congestive heart failure, tamponade, syncope, stroke, peripheral neurologic injury, leg or arm ischemia, paraplegia, gastrointestinal hemorrhage, hematuria or anuria, hoarseness, dysphagia, superior vena cava syndrome, and aortic insufficiency.

Classification The Stanford classification based on clinical course and surgical significance is as follows: Stanford type A dissection includes any dissection involving the ascending aorta, and Stanford type B dissection involves only the descending aorta.

Diagnostic Studies A chest x-ray will show a widened mediastinum or left pleural effusion. Transesophageal echocardiography (TEE) is the procedure of choice. CT and MRI can be useful; aortography is seldom necessary.

Medical Treatment Immediate drug therapy is initiated to control blood pressure and decrease the contractility of the left ventricle (dp/dt). Combination drug therapy is used to achieve beta-

adrenergic blockade and afterload reduction. The systolic blood pressure should be kept below 110–120 mmHg.

Natural History and Operative Indications Patients with Stanford type A dissections are at risk for early death and need an emergent operation. Patients with Stanford type B dissections are treated medically initially, and early operation is recommended only for those with complications such as rupture, hemodynamic compromise, prolonged pain, aneurysm expansion, visceral or limb ischemia, and neurologic signs. Close observation is essential, including serial hematocrits, chest x-rays, and imaging studies.

Operative Treatment *Stanford Type A Dissection* The objective is to remove the intimal tear, replace the diseased aorta, obliterate the false lumen and redirect flow into the true lumen, and correct associated valvular insufficiency or coronary ischemia. This is accomplished usually with deep hypothermia and circulatory arrest with performance of an "open" distal anastomosis. Alternatively, the aorta may be excised totally with removal of the tear site and aneurysmal segments; the risk of early bleeding may be increased with this method.

When the aortic valve is involved, resuspension of the valve is highly effective. If a competent valve cannot be ensured, aortic valve replacement should be performed.

Stanford Type B Dissection Most advocate initial medical therapy. Urgent operation is indicated for complications such as recurrent pain, progressive mediastinal hematoma, leakage, acute expansion, rupture, visceral organ ischemia, extremity ischemia, progressive neurologic dysfunction, and retrograde dissection with aortic valve involvement. Operation is performed through a left thoracotomy. The goal is to exclude the tear site from the circulation, to obliterate the false lumen, and to redirect blood flow into true lumen distally. The technique is that previously described for aneurysms of the descending thoracic aorta.

For a more detailed discussion, see Galloway AC, Miller JS, Spencer FC, and Colvin SB: Thoracic Aneurysms and Aortic Dissection, chap. 19 in *Principles of Surgery*, 7th ed.

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CHAPTER

20

ARTERIAL DISEASE

For purposes of study, arterial diseases are more appropriately categorized into five general topics: peripheral arterial occulsive disease, aneurysms, cerebrovascular occlusive disease, nonatherosclerotic arterial disorders, and vascular trauma.

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Atherosclerotic peripheral arterial occlusive disease can be split into four categories, specified on the basis of the anatomic distribution of the symptomatic stenoses. These categories are clinically relevant with respect to treatment as well, since the choice of intervention depends on the anatomic location of the problem.

I. Lower extremity occlusive disease
   A. Aortoiliac
   B. Infrainguinal
II. Visceral occlusive disease
   A. Renal
   B. Mesenteric
III. Upper extremity occlusive disease

Within each category, patients may present with acute or chronic symptoms. While acute symptoms are encountered most commonly with embolic problems and bypass graft occlusions, chronic symptoms are associated more frequently with stenotic or occlusive disease within native arterial segments.

Lower Extremity Occlusive Disease

The symptoms of lower extremity occlusive disease are as follows:

1. *Claudication symptoms.* Claudication is defined as pain occurring with ambulation. The symptoms are reproducible and subside with cessation of ambulation. The pain is located in the calves in patients with infrainguinal disease. Patients with suprainguinal (aortoiliac) disease also may experience calf claudication, but the

symptom progresses to involve the thighs and buttocks with continued walking. Claudication is a marker for generalized atherosclerotic occlusive disease with its well-known complications of myocardial and cerebrovascular events. It is not, however, well correlated with lower extremity complications; limb loss occurs only in a small minority of untreated patients.

2. *Limb-threatening symptoms.* Limb-threatening signs and symptoms are those complaints which, unlike claudication, are harbingers of limb loss. These include the presence of pain at rest (almost always in the forefoot and not in the calf, relieved by dependency), ulceration, and gangrene. Acute limb ischemia most often presents with limb-threatening symptoms as a result of the paucity of preexisting collaterals. These patients often present with signs and symptoms that begin with the letter *p*, including pulselessness, pain, pallor, poikilothermia, paresthesia, and paralysis.

The diagnosis of lower extremity arterial occlusion begins with palpation of the pulses in the leg, including the femoral pulse in the groin, the popliteal pulse behind the knee, and the dorsalis pedis and posterior tibial pulses at the ankle level. Noninvasive testing, in the form of Doppler segmental pressure determinations, is useful to localize the involved arterial segment and as a quantitative index to gauge the severity of the problem. Arteriography is employed only after the patient has been deemed an appropriate candidate for open surgical or endovascular intervention.

The treatment of lower extremity arterial disease can take one of three forms:

1. *Open surgical intervention.* Bypass or endarterectomy can be employed to improve arterial flow. Endarterectomy is limited to occasional patients with disease localized to the aorta and common iliac arteries and rare patients with focal superficial femoral disease at the adductor canal. Bypass of aortoiliac lesions is best accomplished with polyester or expanded polytetrafluoroethylene (ePTFE) bifurcated aortobifemoral bypass grafts. Infrainguinal bypasses are best constructed with autogenous conduits (usually greater saphenous vein), especially if the outflow site is a tibial artery, but ePTFE is an appropriate alternative if the outflow site can be kept above the knee joint.

2. *Endovascular intervention.* Short stenotic or occlusive lesions of the iliac arteries are well treated with balloon angioplasty, with or without the placement of a stent. Long-term success decreases as the lesion is more distal; excellent results are seen with iliac lesions, but angioplasty of the superficial femoral and certainly tibial arteries is dismal enough that the modality should be reserved for patients in whom open surgery is contraindicated.

3. *Thrombolytic therapy.* Thrombolysis should be reserved for patients in whom the primary process is that of an occluding, nonorganized thrombus. Generally, this is synonymous with acute occlusion of a bypass graft or embolic occlusion of a native artery. Nevertheless, acceptable results are realized with thrombolysis of an acutely occluded native arterial segment. Urokinase is the agent of choice in the United States today. Successful thrombolysis in most cases, however, must be followed by an appropriate endovascular or open surgical procedure to correct any underlying lesion responsible for the occlusive event.

Mesenteric and Renal Occlusive Disease

Mesenteric occlusive disease can present in a chronic or acute form; occasionally, acute mesenteric ischemia develops in the setting of chronic symptoms, probably when a critical stenosis of the superior mesenteric artery undergoes sudden thrombosis. Patients with chronic symptoms present with postprandial abdominal pain and weight loss; the diagnosis is unlikely without a history of both. Therapy is directed at revascularization of the superior mesenteric artery and celiac axis, through either a bypass from the aorta or transaortic endarterectomy of the vessels. Acute mesenteric ischemia can develop from embolism, thrombosis overlying a preexisting stenosis, or nonocclusive problems related to low cardiac output or the use of vasopressors. Patients with acute mesenteric ischemia should undergo urgent arteriography to define the problem, with revascularization (e.g., embolectomy or superior mesenteric artery thrombectomy and reimplantation onto the aorta) undertaken for occlusive lesions.

Renal arterial disease can present with hypertension, renal insufficiency, or both. Arteriography is the mainstay of diagnosis, and selective renal function testing (e.g., renal vein renin determination) may help to identify the symptomatic kidney. Therapy may comprise balloon angioplasty for nonostial lesions, stenting for ostial lesions, or a variety of operative revascularization procedures (e.g., aortorenal bypass, transaortic renal endarterectomy, or hepato/splenorenal bypass).

Upper Extremity Occlusive Disease

Atherosclerotic disease of the upper extremity vessels is almost always confined to the origin of the subclavian arteries. More distal disease implies a nonatherosclerotic etiology such as giant cell arteritis or embolism. The left subclavian artery is affected much

more often than the right. Symptoms comprise arm claudication from hypoperfusion, but digital ischemia or vertebrobasilar symptoms may result from embolism to the fingers or vertebral circulation, respectively. Identifying a pressure gradient between the right and left arms readily makes the diagnosis. The "subclavian steal syndrome" is actually the anatomic (arteriographic) finding of reversed vertebral arterial flow ipsilateral to a proximal subclavian stenosis and is rarely symptomatic. Treatment of symptomatic subclavian lesions is directed at bypassing the offending lesion (e.g., subclavian-to-carotid transposition or carotid-subclavian bypass), and one must be sure to exclude the embolic source if the indication for operation is embolism.

ANEURYSMAL DISEASE

Abdominal aortic aneurysms most commonly are confined to the infrarenal segment of the aorta, with suprarenal extension in only 5 percent of cases. Males predominate, with a ratio of 9:1. Aortic aneurysms exhibit a familial tendency, especially when found in female patients. Aneurysmal dilatation of the common iliac arteries is found commonly in association with aortic aneurysms and, rarely, as an isolated finding. Although hypogastric artery aneurysms are observed occasionally, aneurysms of the external iliac artery are virtually nonexistent. Other less common sites of nonthoracic peripheral aneurysms are the following: (1) the popliteal artery (bilateral in the majority of patients and in conjunction with aortic dilatation in over 50 percent of patients), (2) the splenic artery (with a high rate of rupture during pregnancy), (3) the renal arteries, (4) the mesenteric vessels (commonly found in patients with periarteritis nodosa), and (5) the subclavian artery (when distal, in association with a cervical rib and poststenotic dilatation). Most extraaortic aneurysms are repaired with bypass and ligation, e.g., femoropopliteal bypass with saphenous vein and proximal and distal ligation for popliteal aneurysms. The risk of complications outweighs the risk of intervention when the diameter reaches a remarkably constant value of 2 cm, irrespective of the specific anatomic site.

Abdominal aortic aneurysms are repaired to prevent rupture, which, when it occurs, is associated with a mortality rate that approximates 50 percent and is probably closer to 90 percent when one includes those patients who die prior to reaching the hospital. The risk of rupture of abdominal aortic aneurysms is related to size. When the diameter exceeds 6 cm, the risk of rupture is great. Smaller aneurysms, however, also can rupture, especially in smaller

patients. A useful paradigm for timing intervention is illustrated in the following table, although treatment must be individualized on the basis of more than the three variables listed:

Aneurysm Diameter	Medical Status/ Life Expectancy	Treatment
< 4.0 cm	Favorable or unfavorable	Observation
4.0–4.9 cm	Favorable	Consider repair
	Unfavorable	Observation
5.0–5.9 cm	Favorable	Repair
	Unfavorable	Observation
≥ 6.0 cm	Favorable or unfavorable	Repair

The treatment of aortic aneurysms traditionally was performed though a midline transperitoneal incision, although the use of a retroperitoneal exposure has the advantages of (1) better patient tolerability and (2) facilitation of access to the more proximal aorta. Recently, endovascular techniques have been used to repair abdominal aortic aneurysms, inserting a sheathed stent-graft through the femoral artery, removing the sheath, and allowing the stent to expand within the aorta, effectively sealing the aneurysm sac from the path of blood flow. Although yet experimental, endovascular aneurysm repair holds promise as a less invasive method of aneurysm repair.

CEREBROVASCULAR OCCLUSIVE DISEASE

Focal carotid bifurcation atherosclerosis is the most common manifestation of cerebrovascular disease, and its main complication is embolization and stroke. Symptoms, when present, include (1) transient ischemic attacks (TIAs), defined as neurologic deficits that clear completely within 24 h, (2) reversible ischemic neurologic deficits (RINDs) that resolve within 3 weeks, (3) completed strokes, and (4) amaurosis fugax (reversible) and retinal strokes (fixed). Occasionally, the etiology of symptoms is cerebral hypoperfusion rather than embolization. In these cases the symptoms are usually global and in many instances referable to the hindbrain (vertebrobasilar symptoms).

The presence of a carotid lesion is best ascertained with duplex ultrasonography, and arteriography is being used less frequently as clinicians gain comfort with duplex scanning as the sole preoperative imaging modality. Treatment of carotid bifurcation lesions is

possible with endarterectomy, since the lesions are remarkably well localized to within a few centimeters of the internal carotid artery origin. Carotid stenting is presently being evaluated as an alternative to endarterectomy, but current results suggest that the new procedure is not as safe as traditional endarterectomy in standard patients. Newer stent devices and delivery systems can be expected to improve future results. Presently, patients with recurrent carotid stenosis, those with radiation-associated disease, and those with severe medical comorbidities represent categories that may benefit from carotid stenting in its current stage of evolution.

The risk of stroke appears most closely related to the degree of internal carotid artery stenosis, irrespective of the presence or absence of symptoms. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) found that patients with stenoses greater than 70 percent of the vessel diameter fared better with endarterectomy than with aspirin alone. Similarly, the Asymptomatic Carotid Artery Study (ACAS) demonstrated improved results when asymptomatic patients with carotid stenoses greater than 60 percent were treated with surgical repair. Patients with less severe carotid bifurcation disease should be treated with antiplatelet agents to prevent both carotid embolization and the complications of coexisting coronary artery disease.

NONATHEROSCLEROTIC DISORDERS

Thoracic Outlet Syndrome The thoracic outlet, bounded by the clavicle, first rib, and scalene muscles, is a tight space that the brachial plexus, subclavian artery, and subclavian vein must traverse. As such, compression of any of these structures may result in symptoms. Neurologic symptoms are most common, due to the susceptibility of nerve tissue to compressive injury. Venous symptoms are next in frequency, usually manifested by acute thrombosis of the axillary and subclavian veins associated with trauma, exercise, or protracted shoulder abduction. Arterial symptoms (digital embolization from a poststenotic aneurysm) are infrequent, and when they are observed, one should suspect the presence of a cervical rib. Treatment involves resection of the cervical rib, if present, removal of the first rib in the absence of a cervical rib, and repair of the artery for significant dilatation.

Popliteal Artery Occlusion There exist two entities that are associated with popliteal artery occlusion, adventitial cystic disease and popliteal entrapment. If the artery is stenotic but not yet occluded from adventitial cystic disease, operative evacuation of the

contents of the cyst will ameliorate the problem. Similarly, patients with popliteal stenoses from entrapment will benefit from lysis of the medial head of the gastrocnemius muscle. With either entity, however, operative bypass becomes necessary once the popliteal artery occludes.

Vasospastic Disorders The vasospastic arterial disorders affect the fingers more frequently than the toes. The prototypic vasospastic disorder is Raynaud's syndrome, a primary benign or secondary (related to collagen vascular disease) more virulent process. Characteristically, patients describe cold-induced cutaneous color changes of pallor, cyanosis, and finally, rubor accompanied by pain and numbness. Treatment entails avoidance of cold, tobacco, and drugs such as beta blockers. Calcium-channel blockers may provide symptomatic relief. Cervical sympathectomy has been used, but with limited long-term success.

Inflammatory Arteritides A number of vasculitides produce arterial symptoms, including giant cell arteritis (temporal arteritis and Takayasu's disease), Buerger's disease (tobacco-associated arterial and venous angiitis), periarteritis nodosa, systemic lupus erythematosus, and other collagen vascular disorders. The success of operative intervention for these entities has been disappointing, especially when performed during the acute phase of the disease.

ARTERIAL TRAUMA

Arterial trauma is best handled by understanding a set of caveats relating to the problem:

1. It is safest to approach arterial injuries only after adequate proximal and distal control has been achieved. By contrast, proximal and distal control is not helpful in venous injuries, and control must be achieved using direct compression with the digits or a sponge stick.
2. Early restoration of perfusion is important, and if orthopedic instability precludes an effective arterial repair, a shunt should be used while stabilization is being accomplished.
3. Proximity of an injury to an arterial structure should make one suspicious of a vascular injury, even if distal pulses are intact. Traumatic arteriovenous fistulas, false aneurysms, and intimal defects all may occur in the presence of normal distal pulsations. Maintaining a high index of suspicion is important, with liberal indications for arteriography.

4. Preoperative arteriography is undertaken unless (a) the patient is actively bleeding, (b) there is an unstable hematoma, or (c) the limb is severely ischemic.
5. Suspected carotid arterial injury should be managed with preoperative arteriography if the process is above the angle of the mandible or below the level of the clavicle. Midcervical injuries may be explored without arteriography, but exploration is unnecessary if the injury does not traverse the platysma muscle.
6. Neither autogenous nor prosthetic grafts have been shown to be clearly superior in reconstruction of traumatic large vessel injuries.
7. It is important to repair the vein as well as the artery in combined arterial and venous injuries of the lower extremity.
8. If saphenous vein is used for the arterial reconstruction, it should be taken from the contralateral extremity because the ipsilateral saphenous vein may provide an important route for venous return in the presence of combined arterial and venous injury.
9. Right subclavian injuries are best approached via a median sternotomy, whereas left subclavian injuries are best managed with a left anterolateral thoracotomy or "open book" incision.

For a more detailed discussion, see Ouriel K and Green RM: Arterial Disease, chap. 20 in *Principles of Surgery,* 7th ed.

CHAPTER

21

VENOUS AND LYMPHATIC DISEASE

ANATOMY OF THE VENOUS SYSTEM

The veins of the extremities are divided into three systems. There is a deep system, below the level of the fascia of the muscles. The valves in the deep system serve to direct blood flow toward the heart. There is a superficial system, residing in the subcutaneous tissue of the extremities. The valves in the superficial system also are oriented so that the direction of blood flow is toward the heart. Finally, there is a system of communicating veins connecting the superficial system with the deep system. The communicating veins have valves oriented so that the flow of blood is from the superficial to the deep system. The communicating veins are most prominent along the medial aspect of the calf, where they are known as *perforating veins.*

The flow of blood in veins is phasic with respiration. During inspiration, abdominal pressure increases, and venous flow in the lower extremities decreases transiently. During expiration, abdominal pressure decreases, and lower extremity venous flow increases. The "calf muscle pump" facilitates the flow of blood back to the heart. Within the muscle of the calf, venous sinuses exist, most prominently in the soleus and gastrocnemius muscles. With each contraction of the calf muscles, blood is forced into the longitudinally oriented deep veins, and the valves preferentially direct the flow toward the heart. In the absence of competent venous valves, however, muscle contraction forces blood in all directions. Incompetent communicating veins are especially problematic because calf muscle contraction ejects blood in a retrograde direction through the communicators. These spurts of blood with each contraction of the muscle produce localized venous hypertension, edema, and rupture of small venules in the subcutaneous tissue overlying the communicators—the genesis of the skin (hemosiderin deposits and ulceration) and subcutaneous changes (brawny edema and fibrosis) associated with chronic venous insufficiency.

DEEP VENOUS THROMBOSIS

Virchow postulated three mechanisms for the development of venous thrombosis: endothelial damage, hypercoagulability, and stasis. These factors account for the high incidence of deep venous thrombosis (DVT) after an operation. Thrombi that form in areas of rapidly flowing blood (arteries) are generally gray in color and primarily composed of platelets. By contrast, thrombi occurring in relatively slowly flowing systems (veins) are red and primarily composed of fibrin and red blood cells.

Etiology of Deep Venous Thrombosis

I. Endothelial cell damage
   A. Immune vasculitis
      1. Systemic lupus erythematosus
      2. Buerger's disease
      3. Giant cell arteritis
      4. Takayasu disease
      5. Vasculitis with anticardiolipin factor
II. Hypercoagulability
   A. Activated protein C resistance
   B. Antiphospholipid syndrome
   C. Antithrombin III deficiency
   D. Protein C and S deficiencies
   E. Dysfibrinogenemia
III. Stasis
   A. Congestive heart failure
   B. Hyperviscosity
   C. Prolonged immobility (bed rest, airplane and automobile trips)
   D. Neurologic disorders with loss of muscle pump

Diagnosis of Deep Venous Thrombosis The clinical diagnosis of DVT is notoriously inaccurate, and objective tests have become the cornerstone of diagnosis. Contrast phlebography is the "gold standard" test. Duplex ultrasound is very accurate, especially when the patient is symptomatic or the thrombus is present in the femoral segment. Duplex is less sensitive for isolated thrombi of the calf veins or of the iliac veins. Isolated iliac vein thrombosis is rare.

Prophylaxis of Deep Venous Thrombosis Patients at high risk for venous thrombotic events can be treated with a variety of means to diminish the chance of deep venous thrombosis. These patient groups include those undergoing major operative procedures, par-

ticularly orthopedic procedures. Other high-risk groups include patients with malignancy, major trauma, paralysis, and a history of previous DVT. The following represent prophylactic methods used in these high-risk groups:

1. Elastic compression stockings to reduce stasis
2. Intermittent pneumatic compression to reduce stasis and enhance intrinsic fibrinolysis
3. Low-dose subcutaneous heparin administration
4. Low-molecular-weight heparin administration
5. Warfarin anticoagulation in patients undergoing major joint replacement

Treatment of Deep Venous Thrombosis The treatment of deep venous thrombosis depends on the location of the thrombus. Isolated calf vein thrombi may be treated without anticoagulation, especially if they develop as a result of an identifiable event such as trauma or surgery. De novo calf vein thrombi may represent a hypercoagulable state, whether identified or not, and anticoagulation is prudent. Proximal deep venous thrombi should be treated with anticoagulation to prevent propagation of thrombus and pulmonary embolism. Therapy is begun with intravenous heparin, with the goal of achieving an activated partial thromboplastin time (APTT) of more than two times control. Oral anticoagulation with warfarin can be instituted concurrently, aiming for an international normalized ratio (INR) of approximately 2.0. Heparin may be discontinued after the INR stabilizes at a therapeutic level.

As an alternative to intravenous heparin, subcutaneous low-molecular-weight heparin (LMWH) therapy has been used successfully on an outpatient, ambulatory basis. APTTs are not assessed with LMWH; their use is meaningless because LMWH does not reproducibly alter the APTT. Randomized studies have not detected an increased frequency of pulmonary embolism with outpatient LMWH therapy for DVT.

Chronic Venous Insufficiency

Chronic venous insufficiency, also known as the *postthrombotic* or *postphlebitic syndrome,* develops in the majority of patients who have sustained a significant DVT. The underlying pathophysiology consists of recanalization of the deep system with subsequent incompetence of the valves. The high venous pressure then promotes fluid and protein loss into the subcutaneous tissues, resulting in subcutaneous fibrosis probably secondary to inadequate tissue oxygenation and metabolism. This “liposclerosis” produces the brawny

edema characteristic of the postphlebitic syndrome. Chronic microscopic hemorrhage into these tissues produces deposition of hemosiderin and the characteristic brown pigmentation. Ulceration occurs frequently and generally is located above the medial malleolus. The chronic edema predisposes the patient to recurrent bouts of cellulitis. The therapy of chronic venous insufficiency is supportive initially. Compression stockings usually are used, as is bed rest with leg elevation and paste boots. Operative therapy is reserved for patients with persistent ulceration despite adequate conservative measures. The perforating veins may be ligated, usually via a subfascial approach; however, wound infection and recurrent ulceration frequently accompany this procedure. An endoscopic method of perforating vein ligation has been developed, and the initial results are promising. Venous reconstruction is indicated in a minority of patients with nonhealing venous ulceration. Ascending and descending phlebography and ambulatory venous pressure measurements are mandatory in determining whether patients are candidates for venous reconstructive procedures. Venous valve repair (congenital incompetence) and venous valve transposition (acquired incompetence) have been used in patients with pure valvular incompetence without outflow obstruction, whereas a number of venous bypass techniques have been used in others with documented, persistent venous hypertension.

Inferior Vena Caval Interruption

Vena caval interruption has been used in an effort to prevent pulmonary emboli. The procedure is percutaneous, with the introduction of a variety of filters into the inferior vena cava. The indications for vena caval interruption include pulmonary embolus with a contraindication for anticoagulation, recurrent pulmonary embolism on adequate anticoagulation, and as prophylaxis against recurrent embolism after pulmonary embolectomy. A relative indication for caval interruption occurs in patients with large iliofemoral DVT with a contraindication to anticoagulation.

Other Types of Venous Thrombosis

Superficial Thrombophlebitis This process is characterized by aseptic thrombosis of the superficial veins. In the lower extremities, it usually is associated with varicose veins, occasionally after trivial trauma, and it is dangerous only when it propagates to the common femoral vein. Therapy is usually supportive, including bed rest, warm packs, and anti-inflammatory agents. Superficial thrombophlebitis in the upper limbs usually is secondary to intravenous

infusions. Excision of the vein is indicated when the process is purulent.

Subclavian Vein Thrombosis Thrombosis of the subclavian vein occurs in two settings. The first is in the presence of an indwelling catheter. Removal of the catheter is indicated. It also may occur as an "effort thrombosis," usually in the setting of thoracic outlet syndrome. Thrombolytic therapy has been helpful when an effort thrombosis occurs, and subsequent thoracic outlet decompression (clavicle or first rib resection) with or without venous reconstruction (patch angioplasty or venous bypass) frequently is necessary.

PULMONARY EMBOLISM

Diagnosis of Pulmonary Embolism A patient with a pulmonary embolism classically presents with chest pain, cough, dyspnea, and tachypnea. Hemoptysis occurs late and is associated with pulmonary infarction. The electrocardiogram (ECG) and chest radiographs are used primarily to exclude other diagnoses. Arterial blood gases usually reveal room air PO_2 below 60 mmHg and decreased PCO_2. If a Swan-Ganz catheter is placed, the pulmonary arterial pressures frequently are elevated, and the wedge pressure is normal or diminished (Table 21-1).

Documentation of the pulmonary embolism is made most accurately with a pulmonary angiogram. The relatively invasive nature of this modality has accounted for reluctance to use the test, especially in frail, medically compromised patients. Other, less invasive modalities have supplanted pulmonary angiography for diagnosing a pulmonary embolism. Foremost is the ventilation-perfusion ($\dot{V}/\dot{Q}$) scan, although the accuracy of this test is variable and depends on the experience of the reader. Spiral computed tomography (CT) and magnetic resonance imaging (MRI) have been reported as highly accurate, noninvasive alternatives to pulmonary angiography.

Management of Pulmonary Embolism There are three methods of managing pulmonary embolus. The first is heparin anticoagulation, which continues to be the most commonly used modality. Anticoagulation prevents propagation of thrombus and could prevent recurrent thromboembolism from the deep veins. It has never been shown to result in acceleration of clearance of the thrombus from the pulmonary vasculature. Patients with compromised right ventricular function on the basis of pulmonary artery obstruction continue to demonstrate echocardiographic changes long after the embolic event.

TABLE 21-1
STRATIFICATION OF PULMONARY THROMBOEMBOLISM

Category	Signs and Symptoms	Gases	PA Occlusion (%)	Hemodynamics
Minor	Anxiety Hyperventilation	$PaO_2 < 80$ mmHg $PaCO_2 < 35$ mmHg	20–30	Tachycardia
Major	Dyspnea Collapse	$PaO_2 < 65$ mmHg $PaCO_2 < 30$ mmHg	30–50	CVP elevated, PA > 20 mmHg Responds to resuscitation
Massive	Dyspnea Shock	$PaO_2 < 50$ mmHg $PaCO_2 < 30$ mmHg	> 50	CVP elevated, PA > 25 mmHg Requires pressors, inotropes
Chronic	Dyspnea Syncope	$PaO_2 < 70$ mmHg $PaCO_2 < 30$–40 mmHg	> 50	CVP elevated, PA > 40 mmHg Fixed low cardiac output

Thrombolytic therapy with intravenous urokinase or streptokinase, by contrast, results in the dissolution of pulmonary vascular thrombus and improvement in right ventricular function. The relatively small, randomized trials of the 1970s did not demonstrate

mortality differences between patients treated with heparin versus thrombolysis, but their small size precluded a meaningful analysis of the endpoint of mortality. It is likely that thrombolytic therapy holds great potential to improve the clinical outcome of patients with pulmonary embolism, especially in those with sufficient thrombus burden to compromise right ventricular function. The cost of these benefits is a small but significant risk of distant bleeding complications.

Pulmonary embolectomy represents the third treatment modality for pulmonary embolism. It is indicated in patients with severe hemodynamic decompensation. The procedure carries a mortality of 50 percent when done through an open technique. A transvenous, percutaneous technique has been developed recently, and it holds potential as an isolated procedure or an adjunct to thrombolytic therapy (Fig. 21-1).

VARICOSE VEINS

The prevalence of varicose veins increases with age and usually is greater in females. It is important to distinguish between primary varicose veins and varicosity secondary to underlying deep venous disease. Primary varicose veins may be inherited and are associated with incompetent valves within the superficial system alone. Secondary varicose veins occur as a result of incompetence in the communicating and deep veins of the leg. This results in high pres-

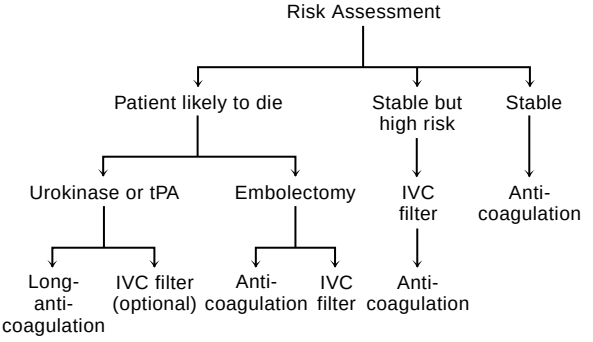

FIGURE 21-1 Algorithm for the management of pulmonary embolism. IVC = inferior vena cava; tPA = tissue plasminogen activator.

sures within the superficial veins and subsequent dilatation and superficial venous incompetence. Complications are unlikely with primary varicose veins, but stasis dermatitis and ulceration frequently accompany secondary varicosities.

Patients with varicose veins are treated initially with conservative care, using compression stockings and limitation of prolonged standing. Injection sclerotherapy may be used if the veins are small or localized. Surgical excision is indicated when conservative measures fail. This frequently requires stripping of the greater saphenous vein in its entirety, including ligation of the adjoining branches in the groin. Accessory varicosities usually are excised through multiple small incisions.

LYMPHEDEMA

Lower extremity edema occurs in three clinical settings: edema of fluid overload, venous insufficiency, and lymphedema. Lymphedema is unilateral or bilateral and is very slow to clear with elevation. The diagnosis of lymphedema frequently is based on clinical grounds. Management is supportive, with compression stockings and care taken to avoid factors that predispose the patient to cellulitis.

Lymphedema may be classified into primary and secondary varieties. The primary lymphedemas are classified as follows:

1. Congenital: present at birth
2. Praecox: onset in childhood
3. Tarda: onset in adulthood

Lymphography has been useful in clarifying the primary lymphedemas into hyperplastic and hypoplastic varieties. Secondary lymphedema is frequently secondary to lymph node metastases and also may occur after radiation, trauma, surgical excision, or parasitic invasion.

Operative treatment is used rarely in patients with lymphedema. The attempts have been directed at removing the subcutaneous tissues of the extremity. The original procedure of Charles consisted of wide excision of the lymphedematous tissue followed by skin grafting of the extremity. Direct lympho-venous anastomoses have been undertaken at a few centers but have yet to be proved effective.

For a more detailed discussion, see Green RM, Ouriel K: Venous and Lymphatic Disease, chap. 21 in *Principles of Surgery,* 7th ed.

CHAPTER

22

MANIFESTATION OF GASTROINTESTINAL DISEASE

PAIN

Pain is the most common symptom of gastrointestinal disease. The amount and quality of perceived pain are determined by physiologic and psychological variables.

Pain Pathways Pain impulses from the abdomen reach the central nervous system (CNS) through (1) visceral sympathetic afferents and (2) visceral parasympathetic afferents and (3) from the parietal peritoneum, the diaphragm, and the root of the mesentery via somatic afferents of segmental spinal nerves or phrenic nerve. The visceral peritoneum is innervated by autonomic C-type fibers, which are slow transmitters; therefore, the sensation is dull, poorly localized, gradual in onset, and longer in duration. The fibers are insensitive to stimuli such as cutting and crushing; stimuli causing visceral pain include changes in diameter of a hollow viscus perceived as cramping, the stretching of capsules of solid viscera (e.g., subcapsular liver hematoma), ischemia, and chemicals (e.g., acids, alkalis, hypertonic solutions, potassium, and bradykinin). The pain is described as deep in the cutaneous areas and zones supplied by the somatic sensory nerve originating from the same segments of the spinal cord as the visceral afferent fibers from the viscus in question. Autonomic reflexes such as sweating, nausea, vomiting, tachycardia, bradycardia, hypotension, hyperesthesia, and involuntary abdominal muscle contraction may accompany severe visceral or deep somatic pain. Abdominal pain could be visceral pain, referred visceral pain, parietal pain, unreferred parietal pain, or any combination thereof.

VISCERAL PAIN

The abdominal viscera have bilateral afferent autonomic innovation, except the kidneys, ureter, cecum, and ascending and descending colon, which are unilaterally innovated. Visceral pain usually is perceived as midline because of the embryologic development of the gut; e.g., midgut pain is manifest as periumbilical pain.

Referred Visceral Pain This pain is more localized and is referred to the dermatomes and myotomes that are supplied by the same spinal cord segment as the affected viscus; e.g., increased distention of the abdomen causes abdominal wall discomfort and backache.

PARIETAL PAIN

Pain sensation is transmitted by A-delta fibers. The pain is well localized; nerve endings are stimulated by chemicals, changes in pH, inflammatory mediators, bacteria, and neutrophil breakdown products.

Referred Parietal Pain This is the result of afferent neurons that innervate two separate, anatomically distinct structures having a common embryologic origin, e.g., left shoulder pain with ruptured spleen.

Pain of intraabdominal origin may arise from the peritoneum, hollow or solid viscera, mesentery, or the pelvic organs and be caused by inflammation, mechanical processes, and vascular disturbances. Extraperitoneal disorders also can manifest as abdominal pain. Common sites of referred pain from intraabdominal pathology are illustrated in Table 22-1.

TABLE 22-1
POSSIBLE ORIGINS FOR REFERRED PAIN

Right shoulder	*Left shoulder*
Diaphragm	Diaphragm
Gallbladder	Spleen
Liver capsule	Tail of pancreas
Right-sided pneumoperitoneum	Stomach
	Splenic flexure (colon)
Right scapula	Left-sided pneumoperitoneum
Gallbladder	
Biliary tree	*Left scapula*
	Spleen
Groin/genitalia	Tail of pancreas
Kidney	
Ureter	
Aorta/iliac artery	
Back-midline	
Pancreas	
Duodenum	
Aorta	

Other pain is back pain as a result of neural infiltration, e.g., infiltration of the celiac plexus by pancreatic cancer or gastric cancer.

ACUTE ABDOMINAL PAIN

Sudden pain is seen with perforation, obstruction, acute arterial ischemia, and acute intraperitoneal bleeding. Pain of gradual onset is seen with inflammatory pathology (Table 22-2). The site and character of pain, radiation, aggravating and relieving factors, and the progression of pain help find the anatomic area and nature of the process; e.g., patients with colic move around compared with patients with peritonitis, who lie still; acute mesenteric vascular ischemia produces pain disproportionate to physical findings. Vomiting, bowel movements, flatus history, menstrual history, previous similar episodes, similar episodes in family members, and medications should be elicited.

Physical Examination *General Visual Assessment* Is the patient looking sick? What is the breathing pattern? What is the state of hydration? Is the patient writhing in pain or lying still? Examine for distention, masses, visible peristalsis, and herniae.

Auscultation This should include the lungs and the abdomen. Crepitations, rales, and bronchial breathing indicate pulmonary pathology with referred pain to the abdomen. Hypoactive bowel sounds are seen with inflammation and ileus (e.g., hypokalemia, hypomagnesia, narcotic overdose). In the early phases of arterial occlusion, bowel sounds are hyperactive and may disappear when gangrene sets in.

Percussion distinguishes between gas and fluid causes of distention; liver dullness is obliterated by large amounts of free air, indicating a hollow viscus perforation.

Examine for masses; make a diligent search for herniae. Remember that light touch is essential when there is peritoneal inflammation. Guarding may be overcome by distracting the patient while palpating. Rebound tenderness indicates inflammation of the parietes, and in advanced stages of peritonitis, boardlike rigidity can occur. Hyperesthesia may be appreciated over the involved intraabdominal viscera. Bimanual pelvic and rectal examinations and stool examination for occult blood are mandatory.

Laboratory Evaluation Complete blood count with differential, pregnancy testing in females of childbearing age, serum electrolytes, serum amylase, lipase and liver profile, sickle cell screen-

TABLE 22-2
DIAGNOSIS RELATED TO THE MODE OF ONSET OF ABDOMINAL PAIN

Sudden Onset	Gradual Onset	Intermittent Pain	Constant Pain with Acute Exacerbation
Perforated viscus	Appendicitis	Peptic ulceration	Alkaline reflux gastritis
Volvulus	Diverticulitis	Reflux esophagitis	Pancreatitis
Passage of stone (kidney or gallbladder)	Cholecystitis	Cholelithiasis	
	Lower intestinal obstruction	Crohn's disease	
High intestinal obstruction	Mesenteric ischemia insufficiency	Diverticulitis	
Mesenteric embolism/ arterial thrombosis	Leaking aortic aneurysm	Chronic pancreatitis	
Ruptured aortic aneurysm	Ectopic pregnancy	Chronic mesenteric ischemia	
Ruptured ectopic pregnancy	Endometritis	Pelvic inflammatory disease	
		Endometriosis	

Ovarian torsion/ruptured cyst	Gastroenteritis
Sickle cell crisis	Gastritis/peptic ulcer disease
Myocardial ischemia/ infarction	Pancreatitis
Mittelschmerz	Salpingitis
Porphyria	Endometriosis
Abdominal wall intramuscular hematoma	Regional enteritis/ulcerative colitis
Intraperitoneal bleeding	Pyelonephritis
Intussusception	Pneumonia
	Splenic vein thrombosis
	Hepatitis
	Diabetic acidosis
	Addisonian crisis
	Herpes zoster

ing in African-Americans, and an electrocardiogram in all adults are essential.

Radiologic Examination Upright anteroposterior (AP) and lateral chest x-rays and upright and supine abdomen views (free air series) show pulmonary pathology or free air under the diaphragm, abnormal gas patterns (air in the biliary tract indicating gallstone ileus, extraluminal air indicating perforation or abscesses), displaced organs (gastric fundus indented by splenic hematoma), fluid levels of intestinal obstruction, radiopaque ureteric and biliary calculi, appendicular fecaliths, and abnormal vascular calcifications.

Ultrasound is useful in evaluating hepatobiliary and pancreatic disease, appendicitis, and gynecologic abnormalities. Computed tomographic (CT) scan is helpful especially if there is no contraindication to oral or rectal contrast agents. Arteriography is required early in suspected intestinal ischemia. Paracentesis, laparoscopy, culdoscopy, and culdocentesis may be useful, and celiotomy may be indicated in patients who are too sick to undergo prolonged testing.

Symptoms of an acute abdomen may be masked in the pediatric population, in elderly patients, in patients on steroids, and immunecompromised patients.

INTERMITTENT AND RECURRENT PAIN

Hemolytic disorders such as sickle cell disease, autoimmune hemolytic anemia, and thrombotic thrombocytopenia can present with abrupt severe abdominal pain; accompanying muscle spasm and rigidity can mimic an acute abdomen.

Chronic hemolytic anemias, hereditary spherocytosis, and thalassemia can cause abdominal pain, anemia, jaundice, splenomegaly, and cholelithiasis. Acute intermittent porphyria, an inherited dominant disorder, presents as abdominal pain; the mechanism is thought to be an autonomic neuropathy. Attacks are precipitated by drugs (e.g., barbiturates, sulfonamides), starvation, sex hormones, and infection.

Chronic Pain

Bouts of pain with entirely normal intervals are seen in acute intermittent porphyria, internal hernias, endometriosis, and occasionally, choledocholithiasis. Persistent chronic abdominal pain may be seen with chronic pancreatitis and pancreatic or colon malignancy.

Chronic pain also can be from abdominal wall pathology such as peripheral nerve injuries, hernias, myofascial pain syndromes, the rib tip syndrome, and spontaneous rectus sheath hematoma. In

addition, many psychiatric disorders are associated with chronic abdominal pain.

Intractable Pain

The control of intractable pain could be challenging, e.g., pain from unresectable carcinoma of the pancreas and chronic pancreatitis. Control may require large doses of opiate analgesics. Other modalities include neurologic interruption of the pain pathway (e.g., posterior rhizotomy, spinothalamic tract interruption, prefrontal lobotomy). Mechanical/electrical forms of pain control include the dorsal column stimulator.

FEVER

Fever indicates illness such as infection, inflammation, autoimmune disease, and neoplasia. In the normal postoperative phase, persistent fever may indicate an infectious complication. Unusually high fever, e.g., malignant hypothermia, could be dangerous.

Pathophysiology Cytokines activated by the inflammatory response and pyrogens from macrophages (interleukin-1, tumor necrosis factor, and interferon) that are released locally within the brain and peripherally into the bloodstream act on the hypothalamus in endocrine fashion. The resulting upward resetting of the thermal regulatory apparatus triggers vasoconstriction that limits heat loss and shivering, which increases heat production.

Patients also may establish the environmental temperature that is most comfortable for them. This temperature is called *thermoneutrality.* For example, burn patients and patients with large wounds, peritonitis, sepsis, and multi-organ system failure feel cold at temperatures that normal persons consider comfortable because they have a higher thermal regulatory set point.

Clinical Considerations Fevers of gastrointestinal origin usually result from intraabdominal infection, e.g., urinary tract infection, peritonitis. Postoperative fevers are common (15–30 percent) in patients after celiotomy, but only 10–20 percent of such fevers are from infections such as pulmonary complications, urinary tract infections, wound sepsis, and thrombophlebitis. Twenty percent of fevers of unknown origin are secondary to cancers that are primary or metastatic in the abdomen, e.g., hypernephroma, liver tumors, lymphomas, and carcinoma of the stomach, colon, and pancreas.

ANOREXIA

Anorexia is seen in many illnesses such as inflammatory diseases (indicates significant inflammation), endocrinopathies such as hyperparathyroidism, and adrenal cortical insufficiency. Anorexia is a manifestation of liver disease, probably mediated by a combination of ammonia and neuropeptide Y (NPY). Anorexia is very common in malignancy and indicates significant tumor burden. Postoperative anorexia may be associated with a loss of taste or poor appetite and may respond to zinc replacement (220 mg daily). Alcohol is a stimulant.

Pathophysiology The physiologic mechanisms that control feeding and satiety are complex and multifaceted, involving receptors in both the brain and the periphery; stimuli include changes in glucose utilization rate, changes in the rate of lipid metabolism, alterations in brain and peripheral peptides, imbalances in plasma and brain amino acid profiles, increases and decreases in neurotransmitter activity, and alterations in cytokine levels. The hypothalamus is the feeding center of the brain; afferents are important for communicating peripheral nutrition-related information from the gastrointestinal tract or from glucose-sensitive cells in the liver. Small decreases in blood glucose levels have been related to the onset of hunger. Increased lipolysis and oxidation of lipids reduce hunger and produce satiety. The obese gene protein (leptin) that is synthesized in adipose sites adversely affects the synthesis and release of hypothalamic NPY, resulting in reduced food intake and increased metabolic rate. Increased dopamine activity and elevated activity in serotonin neurons may inhibit feeding. Multiple peptides also control feeding and satiety; e.g., NPY, endorphins, and galanin stimulate feeding; others, such as cholecystokinin, corticotropin-releasing factor, calcitonin, glucagon, and insulin, produce satiety. Cytokines (e.g., tumor necrosis factor and interleukins) reduce food intake when infused peripherally or injected directly into the hypothalamus. Although many drugs cause anorexia, there is no medication to restore appetite.

Cancer Anorexia It is likely that cancer anorexia results from tumor-induced aberrations of neurochemical mechanisms that normally control hunger and satiety. Aberrations in plasma and brain amino acid profiles have been reported in tumor-bearing organisms. Studies have been unconvincing for cause and effect because some of the aberrations may be the result of the anorexia rather than the cause of it. Factors produced by tumor tissue such as lactic acid and

ammonia may produce anorexia. Cytokines also may be involved in tumor-related anorexia/cachexia, although treatment of tumor-bearing mice with tumor necrosis factor antibodies does not prevent the appearance of anorexia. NPY is a very potent appetite stimulator. It is dysfunctional in anorexic tumor-bearing rats.

WEIGHT LOSS AND CACHEXIA

Patients have significantly negative prognostic implications; a loss of 10–15 percent over a 3–4-month period is indicative of nutritional or immunologic impairment. Inability to carry out normal function, serum albumin levels of less than 3.0 g/dL, and decreased short-turnover proteins (e.g., albumin, transferrin) have seriously negative prognostic implications.

Decreased intake and weight loss may occur in obstruction to the esophagus or be secondary to postprandial pain, chronic infections, and malabsorption. Thyrotoxicosis, Addison's disease, and diabetes mellitus may produce rapid weight loss over a short period. The most common cause of weight loss is malignancy. Up to 70 percent of cancer patients die from the effects of starvation, with infection the final common pathway. Weight loss in the elderly could be from treatable causes such as poorly fitting dentures. In a small percentage of patients, weight loss is of psychological origin.

HICCUPS

Hiccups often is transient and benign but can be debilitating if persistent and may be a manifestation of an underlying severe pathologic process. Hiccups reflex consists of the phrenic and vagus nerve and the sympathetic chain from T6–T12.

Abdominal conditions such as gastric distention, pancreaticobiliary disease, bowel obstruction, and intraoperative surgical manipulation stimulate the afferent vagal branches. The vagus could be stimulated by intrathoracic pathology such as neoplasms, myocardial infarction, pulmonary edema, and infectious processes. Intraabdominal phrenic nerve stimulation can arise from diaphragmatic hernia or subphrenic abscesses. Within the chest, the phrenic nerve can be irritated by inflammation, tumor, infection, and trauma. Central causes of hiccups include anesthetics, drugs such as intravenous steroids and barbiturates, and metabolic causes such as alcohol toxicity, uremia, hypocalcemia, and hyponatremia. The treatment of hiccups is aimed at the cause, and symptomatic relief may

be obtained by nasopharyngeal stimulation and pharmacologic treatment, e.g., chlorpromazine, haloperidol, sodium valproate, or metachlorpromide.

SYMPTOMS RELATED TO SPECIFIC COMPONENTS OF THE GASTROINTESTINAL TRACT

Esophagus, Stomach, and Duodenum

HEARTBURN AND DYSPEPSIA

Frequent heartburn indicates gastroesophageal reflux disease. The defense mechanisms of the esophagus are a competent lower esophageal sphincter (LES), rapid esophageal clearing of refluxed material, neutralization of refluxed acid by bicarbonate-rich saliva, and an intact mucosal diffusion barrier; the most common clinical abnormality is an incompetent LES.

Heartburn is a substernal burning often associated with bitter taste, and when severe, it is associated with regurgitation of gastric contents. A minority of patients with gastroesophageal reflux dysmotility develop esophagitis (19 percent of patients undergoing upper endoscopy for upper abdominal symptoms have esophagitis).

Dyspepsia includes symptoms such as substernal pressure, epigastric distress, nausea, and bloating. Diseases of the esophagus, stomach, duodenum, biliary tree, and pancreas produce the symptoms. Classic esophageal pain radiates directly through to the back between the scapulae. It also can radiate to the left shoulder, mimicking angina. Esophageal disorders can be evaluated with cinefluoroscopy, contrast radiography, endoscopy and biopsy, 24-h pH study, and manometry.

The timing to food helps: Duodenal ulcer pain is relieved by food, and gastric ulcer pain is provoked by food. Fried, fatty, or greasy foods are found to provoke biliary colic. Alcohol may provoke pancreatitis.

DYSPHAGIA

Dysphagia (difficulty in swallowing) and painful swallowing (odynophagia) require investigation. Pain accompanying dysphagia is a result of inflammation or spasm. Because of the risk factors for squamous cell cancer of the esophagus, the history should include questions about chronic medications (e.g., nonsteroidal anti-inflammatory drugs), dietary habits, substance abuse, smoking, and the taking of undiluted alcohol. Regurgitation of undigested, foul-

smelling food is suggestive of Zenker's diverticulum. A barium swallow should be followed with upper gastrointestinal endoscopy with biopsy; if Barrett's esophagus is suspected, multiple biopsies at various levels should be performed. Studies include manometry and 24-h pH monitoring. The esophagus is the most common part of the gastrointestinal tract to be affected by scleroderma; lower esophageal dysmotility also can occur in association with other connective tissue disorders such as rheumatoid arthritis. Dysphagia lusoria is caused by an aberrant origin of the right subclavian artery or pulmonary artery; it is suspected when there is a posterior indentation of the upper esophagus on barium swallow. If neoplasm is suspected, CT scan of the chest and abdomen and bronchoscopy are indicated. In addition, dysphagia may be a symptom in patients with conversion hysteria, anxiety, and anorexia nervosa.

NAUSEA AND VOMITING

Nausea and vomiting may be related or unrelated to disease of the gastrointestinal (GI) tract. When the GI tract is excessively irritated or overdistended, vomiting may result. Impulses of the GI tract are transmitted by both vagal and sympathetic fibers to the vomiting center in the medulla; motor pulses are transmitted down to cranial nerves V, VII, IX, X, and XII and to the diaphragm and abdominal muscles through the phrenic and spinal nerves. The vomiting center also receives impulses from the higher cortical centers and from the chemoreceptor trigger zone (CTZ) on the floor of the fourth ventricle. Most drug-induced nausea and vomiting is mediated through the CTZ receptor; changes in the directions of motion (through the labyrinthine apparatus), distressing visual input, and foul odors also act through the CTZ on the vomiting center. The same impulses that produce vomiting also produce other autonomic changes such as pallor, perspiration, bradycardia, and hypotension.

Any CNS disorder that leads to increased intracranial pressure (hypoxia) can produce vomiting; inflammation or infectious agents affecting the GI tract, neoplastic disease, or mechanical obstruction can lead to acute nausea and vomiting. Antibiotics such as erythromycin and neomycin may cause nausea and vomiting through direct effects on the GI tract. Pain of any origin may be associated with nausea and vomiting. If bulimia is suspected, psychiatric evaluation is indicated.

Consequences of Vomiting Continued vomiting and resulting hypovolemia can produce hemodynamic instability. Metabolic and electrolyte abnormalities include elevated blood urea nitrogen (BUN) and creatinine levels and metabolic alkalosis (vomitus rich in potassium and hydrogen ions that are also lost in the urine, i.e.,

paradoxical aciduria). Increased cellular breakdown of protein and the use of fat storage cause a rise in the BUN level and the appearance of ketone bodies, respectively. The initial treatment is with saline solution. Once diuresis is established, potassium is added. Metabolic alkalosis may need correction with ammonium chloride, arginine hydrochloride, and even 0.1 N HCl.

Gaseous Distention, Eructation, and Flatulence Intestinal gas produces symptoms of bloating, left shoulder pain (splenic flexure syndrome), audible bowel sounds, eructation, and flatulence. Postoperative gas pains are not uncommon but usually resolve spontaneously in 3–4 months.

Chronic belching/eructation may be seen in cholelithiasis, peptic ulcer disease, and esophageal reflux disease. Patients who do not have decreased LES pressure should not undergo fundoplication because the procedure can cause severe distress/gas bloat syndrome. Small intestinal gas is a combination of swallowed gas and gas from bacterial fermentation; the total is less than 1 L/day. Distention of the colon may reflect partial obstruction. Lactase deficiency also can result in eructation and flatulence.

Treatment with activated charcoal, simethicone, and enzymes may be helpful in patients with no correctable cause.

Small and Large Intestine

Digestion starts in the stomach. Gastric emptying is achieved within 3–4 h. In the duodenum and small intestine, 3–4 L of biliary and pancreatic secretions and 2 L of succus entericus are added per 24 h. Protein absorption occurs in the first 120 cm and carbohydrate absorption within the first 150–180 cm. Water absorption is mostly in the right side of the transverse colon. Elimination occurs 24–72 h after food digestion.

CONSTIPATION

This is an abnormal retention of fecal material or delay in bowel evacuation compared with usual bowel habits. Investigation is required for a change in bowel habits to rule out neoplastic disease.

Defecation occurs when peristaltic waves move the fecal bolus stored in the sigmoid colon into the rectum. Relaxation of the circular muscles at the rectosigmoid junction and impulses from the rectum via the hypogastric and pelvic nerves to the canda equina generate efferent spinal cord impulses; this results in abdominal and diaphragmatic muscle contraction and voluntary relaxation of the external sphincter. Parasympathetic nerves augment intestinal motility, whereas sympathetic stimulation inhibits it. Anticholinergics and

opiates inhibit motility; cholinergic agents, caffeine, nicotine, potassium, and vasopressin stimulate intestinal motility.

Acute Constipation This is often a result of intestinal obstruction. Reflex acute constipation may occur in trauma associated with retroperitoneal hematoma. Painful perianal conditions such as fissures and thrombosed hemorrhoids also cause acute constipation. Other causes of constipation include psychological factors, lack of bulky foods, excess laxatives and drugs, decreased skeletal muscle power, and extrinsic pressure on the GI tract. Intestinal atony is seen in hypokalemia, hypercalcemia, and uremia; collagen and endocrine disorders also can cause intestinal atony (e.g., hypothyroidism). Spinal cord disorders and Hirschprung's disease are examples of neurogenic causes of constipation.

Evaluation includes a history of previous bowel habits; changes in stool caliber, color, and consistency; and the presence of blood, mucus, or undigested fat. Abdominal examination can reveal abdominal distention, and rectal examination may reveal a mass. Stool should be tested for occult blood, and rectosigmoidoscopy (rigid or flexible), barium enema, and colonoscopy may be needed for establishing a diagnosis. Remember to exhibit caution in testing when toxic megacolon or colon perforation is suspected.

Chronic Constipation Congenital disorders, motility disorders, functional problems of the defecatary mechanisms in the pelvic floor, specific problems of the elderly, medications, diverticulosis with chronic scarring, and neoplastic disease are causes of chronic constipation. The age at onset, endoscopy and biopsy, manometry, and motility studies help in the diagnosis. Rectal prolapse and pelvic floor laxity are some of the pelvic floor abnormalities in the elderly resulting in constipation. Laxative abuse, anticholinergic use, and phenothiazine use can result in chronic constipation. A palpable left colon associated with constipation can be seen in chronic diverticulitis with scarring. Chronic constipation in the elderly always should raise a suspicion of neoplastic disease.

DIARRHEA

Between 5 and 8 L per 24 h is the volume secreted by the stomach, hepatobiliary tree, and small bowel. Profuse diarrhea can result in hemodynamic instability.

Pathophysiology Secretory diarrhea is seen after ileal resection, in pancreatic insufficiency, and from improper mixing of bile and pancreatic juice after a Billroth II gastrectomy. Many pancreatic islet cell tumors also produce secretory diarrhea, e.g., gastrinomas,

Werner-Morrison syndrome. Carcinoid tumor produces diarrhea from many of its products such as serotonin, kallikrein, substance P, neuropeptides, and prostaglandins. High plasma calcitonin levels in medullary carcinoma increase jejunal water and electrolyte stimulation, leading to diarrhea; bacterial toxins such as in cholera and *Shigella* infection, and laxative abuse can cause secretory diarrhea. Exudative diarrhea results from release of serum proteins, blood, or mucus from sites of inflammation, ulceration, or infiltration. Osmotic retention of water can lead to diarrhea, e.g., lactase deficiency. Disordered contact of the luminal contents and the absorptive intestinal surface can lead to diarrhea and is seen after bowel resection, bypasses, and superinfection.

Clinical Evaluation Onset of diarrhea; frequency; associated symptoms such as pain, fever, nausea, and vomiting; family history; and character of the stool are important clues; e.g., diarrhea associated with fever and pain suggests an infectious cause. Small-caliber stools indicate partial distal colonic obstruction. A large amount of mucus with the stool is seen in inflammatory bowel disease, rectal cancer, and villous tumors of the rectum. In the physical examination, look for fever (inflammatory process), skin disorders (pyoderma gangrenosum or erythema nodosum in inflammatory bowel disease), abdominal distention (neoplasm or inflammation), perianal examination for fistulas (Crohn's disease), digital examination of the rectum for a mass, and fecal impaction. A stool test for occult blood may lead to a diagnosis.

Diagnostic Studies Tests include a full blood count, liver chemistry, determinations of serum electrolytes, calcium, phosphorus and magnesium, stool culture, *Clostridium difficile* toxin determination, stool fat examination, and a stool examination for ova and parasites. Colonoscopy and biopsy are appropriate. Celiotomy and small bowel biopsy may be necessary. Radiologic studies include barium enema and CT scan if pancreatic pathology is suspected.

Treatment This depends on the cause of the diarrhea. Nonspecific therapy includes opiate drugs, correction of fluid and electrolyte abnormalities, indomethacin (prostaglandin synthetase inhibitor), somatostatin (for secretory diarrheas from islet cell tumors of the pancreas), and cholestyramine (bile salt–induced diarrhea).

Intestinal Obstruction

Intestinal obstruction accounts for 20 percent of surgical admissions. It is classified according to the obstructing agent to the wall

of the intestine. Postoperative adhesions are the most common cause of intestinal obstruction; hernias are second, followed by malignant tumors.

MECHANICAL OBSTRUCTION

Pathophysiology The accumulation of fluid and gas above the point of obstruction and altered bowel motility resulting in loss of fluid and electrolytes from vomiting and sequestration in the bowel are the principle physiologic derangements. Fluid and electrolyte losses are a result of (1) losses into the bowel lumen, (2) losses into the edematous bowel wall, (3) transduction as free peritoneal fluid, and (4) vomiting or nasogastric suction. Significant fluid and electrolyte losses could lead to hypovolemia, renal insufficiency, shock, and death.

Most bowel distention is from fluid sequestration, and some of it is from intestinal gas. Peristalsis increases in an attempt to overcome the obstruction; the higher the obstruction, the more frequent are the high-pitched peristaltic sounds.

Strangulated Obstruction This is seen in adhesive band obstruction, hernia, and volvulus. The obstructed segment of the bowel loses its blood supply; in addition, toxic materials leak into the peritoneal cavity (e.g., exotoxins, endotoxins, toxic hemin breakdown products).

Closed-Loop Obstruction This is a dangerous form of obstruction. Both the afferent and efferent limbs of a loop of bowel are obstructed. There is rapid progression to ischemia of the involved segment, and widespread abdominal distention may be absent.

COLON OBSTRUCTION

The physiologic effects on the patient are less traumatic because the colon is mainly a storage organ with minor absorptive and secretory functions. However, progressive distention may be dangerous, especially if the ileocecal valve is competent, because the obstruction becomes that of a closed-loop type and can lead to rupture, especially of the cecum (Laplace's law).

Clinical Manifestations Symptoms are crampy abdominal pain, vomiting, constipation, and abdominal distention. Pain and vomiting occur early in high intestinal obstruction. Constipation and abdominal distention are most common in low intestinal obstruction.

Abdominal distention and hyperactive bowel sounds may be the only finding in simple mechanical obstruction. Fever, tachycardia, localized tenderness, and rebound tenderness suggest compromised

bowel. The disappearance of peristalsis in progressive mechanical obstruction indicates gangrenous bowel. In the early postoperative phase, intestinal obstruction is difficult to diagnose.

Laboratory Findings Abnormal tests include elevated BUN level, hemoconcentration, hyponatremia and hypokalemia, high urinary specific gravity, and abnormal acid–base balance depending on the nature of the fluid loss. A very high white blood cell count may indicate the presence of strangulated bowel. High amylase levels may be seen with strangulated bowel, but there is no specific laboratory test indicative of intestinal ischemia.

Management Once nasogastric decompression and intravenous fluid resuscitation have occurred and blood has been drawn for testing, a free air series of the abdomen is obtained; the bowel gas pattern, especially the absence of gas in the rectum, is noted. A barium enema may be done to rule out an obstruction in the colon. Water-soluble contrast examination is contraindicated in obstructed colon because the agent can draw fluid into the intestinal lumen, aggravating the distention.

A central venous line for monitoring fluid needs and fluid administration may be necessary. Patients should have an indwelling bladder catheter. Initial fluid resuscitation is with normal saline or lactated Ringer's solution. Potassium supplements should not be added until a good urine output is established. Appropriate antibiotics should be administered first. If strangulation is suspected, the preceding preparation should be vigorous and fast to get the patient to the operating room quickly.

The majority of small bowel obstructions resolve without operative treatment. The indications to operate are the presence or suspicion of vascular compromise, a patient getting sicker, and the obstruction gone beyond 3 days. With preoperative preparation, the morbidity and mortality are minimal in patients with simple mechanical obstruction when operated on within 24 h of the onset of the disease.

Operative Procedure The timing of the operation is critical. Strangulation, closed-loop obstruction, colon obstruction, and early simple mechanical obstruction require operation as soon as possible. General anesthesia and a generous incision, preferably a long midline, are preferred. The obstruction is relieved with appropriate procedures such as lysis of adhesions, reduction of intersussusption and incarcerated hernia, resection of an obstructive lesion or strangulated bowel, enterotomy for removing obturation such as gallstones, bypass procedure, or enterostomy.

When adhesions are present, multiple sites of obstruction may be encountered. Viability of bowel is determined by the return of color and peristalsis, palpable mesenteric pulses, Doppler evaluations, and fluorescein staining. Reexploration within 24 h may be necessary. At celiotomy, decompression of the bowel is best carried out by advancing the nasogastric tube into the distended proximal small intestine; an alternative is to use a long tube through a proximal jejunostomy.

Postoperative care includes adequate fluid and electrolyte replacement and correction and return of intestinal motility (5–6 days). Parenteral nutrition may be needed.

ILEUS

The most common type of ileus is adynamic or inhibition ileus from inhibition of normal neuromuscular activities; when the bowel is contracted without coordinated propulsive activity, it is described as spastic ileus. In low floor states or when there is vascular occlusion, ischemic ileus is seen.

Adynamic ileus is common after abdominal operations. Gastric ileus and colonic ileus last for approximately 2 days and 3–4 days, respectively. Prolonged ileus may result from metabolic causes (e.g., hypokalemia, hyponatremia, hypomagnesia, intraabdominal sepsis, anastomotic leak), drugs (e.g., narcotics), or epidural anesthesia. Adynamic ileus also is seen with retroperitoneal hematoma, spinal fractures, rib fractures, and pelvic fractures. Clinical manifestations include abdominal distention and hypoactive bowel sounds. Abdominal x-rays show copious gas diffusely distributed in the intestine.

Management consists of nasogastric suction or gastrostomy tube drainage, the correction of fluid and electrolyte abnormalities, and parenteral nutrition. Erythromycin (a motilin agonist), bethanechol, vasopressin, metoclopramide, and cisapride are used.

PARTIAL OBSTRUCTION AND PSEUDO-OBSTRUCTION

Partial obstruction or pseudo-obstruction is seen in Crohn's disease and motility disorders, e.g., diabetic and postvagotomy gastroparesis. Symptoms include chronic nausea and vomiting. Abdominal examination may reveal generalized or localized distention.

Chronic intestinal pseudo-obstruction is secondary to abnormalities in the intestinal muscles or the nervous system and is seen in many diseases, including endocrine disorders, chronic infections, autoimmune diseases, neurologic disorders, and paraneoplastic syndromes. Tricyclic antidepressants, opiates, antihistamines, beta-adrenergic agonists, and amitriptyline can cause prolonged pseudo-obstruction. Presenting symptoms include nausea, vomiting,

abdominal cramps, and distention. Constipation and diarrhea may occur. Recurrent attacks can lead to chronic obstruction with abdominal distention; if it occurs in the postoperative phase, it can result in multiple unnecessary operations with complications.

No specific test is diagnostic; hypokalemia, hypomagnesemia, and hypoalbuminemia are to be excluded. Endocrine tests, antinuclear antibody determinations, manometric studies, and intestinal biopsies may be necessary. Radiologic studies demonstrate prolonged transit times.

Operation should be avoided unless a specific site of obstruction is identified; support with total parenteral nutrition may be necessary. Many operations have been performed with very poor results. If the pseudo-obstruction is primarily colonic, a subtotal colectomy with ileorectal anastomosis has been found to be the most successful operation.

GASTROINTESTINAL BLEEDING

Bleeding can be occult, presenting as weakness, anemia, and orthostasis, or may be massive with sudden and rapid loss of blood. In one-third of patients it is the first symptom of GI disease, and in 70 percent there is no previous history of bleeding. Fifty percent of GI bleeding stops spontaneously. Hematemesis or vomiting of fresh blood implies bleeding above the ligament of Treitz. Altered blood vomitus is coffee ground emesis. Hematochezia or passage of blood per rectum can be of varied brightness and color and usually is seen in lower GI bleeding. Altered blood presents as black, tarry stool and is seen more commonly in upper GI bleeding. Between 50 and 60 mL of blood is required for a melanotic stool; guaiac-positive stool is seen with 10 mL of bleeding per day. Although iron produces a black stool, the stool is guaiac-negative. The consequences depend on the rate of bleeding and the site of bleeding.

Upper Gastrointestinal Bleeding

Peptic ulcer disease constitutes one-half to two-thirds of upper GI bleeding, followed by esophageal varices (10 percent). Other causes are nose bleed, Mallory-Weiss tears, reflux esophagitis, gastric neoplasms, and hematobilia. In the over 60 age group, the mortality is 20–25 percent. H_2-receptor antagonists and proton pump inhibitors decrease the need for elective operations but have not reduced the need for operative treatment for bleeding duodenal ulcers.

Reflux esophagitis more commonly causes chronic occult bleeding. Variceal bleeding is a result of ulceration of the varix sec-

ondary to reflux esophagitis or increased pressure within the varix. A failing liver and its inability to synthesize coagulation factors aggravate the bleeding. In 25 percent of patients with cirrhosis and portal hypertension, bleeding can occur from gastritis and gastric or duodenal ulcers. Mallory-Weiss tears in the esophagus are secondary to recurrent vomiting and retching.

Acute gastritis can be seen with nonsteroidal anti-inflammatory drugs, alcohol, steroids, and oral potassium. Chronic gastritis is most commonly associated with *H. pylori* infection.

Stress ulcers and acute gastroduodenal lesions may be seen in patients in shock, with sepsis, after major surgery, trauma, or burns, and with intracranial pathology; they are the result of decreased gastric blood flow, bile reflux, infection, coagulopathy, and activation of cytocrines.

Among neoplasia, benign lesions such as leiomyomas can present with hematemesis. Dieulafoy's vascular malformations are rare submucosal dilated arterial lesions that can present with massive GI bleeding, as do aortoenteric fistulas. Patients should be questioned about past peptic ulcer disease, medications, alcohol abuse, and the onset of pain and vomiting as it relates to bleeding (in duodenal ulcers, pain disappears with bleeding). Prior aortic reconstructive surgery should raise suspicion for an aortoenteric fistula. Examination focuses on icterus, evidence of liver failure, and evidence of peritonitis.

Resuscitation is by the placement of a wide-bore intravenous line, restoring blood volume, Foley catheter, and nasogastric tube (iced saline lavage of the stomach may be useful). Laboratory tests include complete blood count, prothrombin time (PT), partial thromboplastin time (PTT), blood chemistry, and cross-match of adequate blood.

Esophagogastroduodenoscopy is performed as soon as the patient is hemodynamically stable and is of diagnostic and therapeutic value, e.g., injection or ligation of varices, coagulation of bleeding vessels, etc. Radionuclide scan is unhelpful but may be a useful precursor to arteriography, which can localize the bleeding point.

Specific therapies for variceal bleeding are intravenous vasopressin, Sengstaken-Blakemore tube, transjugular intrahepatic portal systemic shunting (TIPS), and an emergency portal caval shunt. Tamponade is very effective in controlling bleeding from Mallory-Weiss tears. When blood need exceeds 4 units in 24 h and continues, operative treatment should be considered. Operation is tailored to the underlying pathology, e.g., ulcer-reducing operation for duodenal ulcer bleeding, gastric resection for gastritis.

Gastric neutralization with antacids and sucralfate, inhibition of secretion with H_2 antagonists and proton pump blockers, the cor-

rection of coagulation defects, invasive cardiac monitoring, and ICU care are recommended.

Lower Gastrointestinal Bleeding

Small intestinal bleeding (10–15 percent) is diagnosed by exclusion of upper GI bleeding and colonic bleeding. The causes include vascular malformations, neoplasia, Meckel's diverticula, enteric infections, and ulcers. Investigation includes radionuclide scanning, arteriography, and celiotomy.

Colon bleeding can be acute and massive or chronic. Massive lower GI bleeding occurring in the right colon usually is from angiodysplasia. Diverticular disease is a common cause of massive bleeding from the left colon.

Management starts with fluid resuscitation, placement of a nasogastric tube to rule out upper GI bleeding, Foley catheter placement, and proctosigmoidoscopy. Radionuclide scanning is sensitive and specific but does not pinpoint the site of bleeding accurately. Arteriography is definitive in locating the point of bleeding. CT scan and MRI may be useful. Barium study interferes with endoscopy and angiography. Celiotomy, intraoperative enteroscopy, and colectomy may be indicated if bleeding continues and the site of bleeding cannot be localized.

In chronic lower GI bleeding, neoplasia should be excluded. Investigations include rectosigmoidoscopy, colonoscopy, and barium enema. Rectal and anal bleeding, especially when associated with pain, is from fissures, proctitis, and hemorrhoids. A careful history and physical examination should exclude more proximal colon lesions.

JAUNDICE

Jaundice (excess bile pigments in the tissues and serum) is recognizable when the serum level of bilirubin approximates 2–3 mg/dL.

Normal Bilirubin Metabolism Bilirubin is formed when heme is oxidized and the resulting biliverdin reduced. Eighty percent of bilirubin comes from the destruction of red cells, and 20 percent comes from the rapid turnover of hepatic heme proteins and ineffective erythrocytes. Bilirubin, when first formed, is water-insoluble and bound to albumin and is carried to the liver, where the hepatocytes conjugate it to mono-and diglucuronides catalyzed by bilirubin uridine diphosphate glucuronic acid transferase (UDPGA). Conjugated bilirubin is water-soluble, is secreted across

the liver canaliculi, and is carried down the bile ducts into the intestines, where bacteria convert the conjugated bilirubin to urobilinogen and urobilin, which are excreted in the feces and urine.

Etiology The causes of jaundice include

1. Congenital, as in (*a*) enzymatic deficiencies, e.g., Crigler-Najjar syndrome and Gilbert's syndrome, (*b*) conjugative disorders, e.g., Dubin-Johnson syndrome and rotor syndrome, and (*c*) the slow production of bilirubin from hemolytic diseases.
2. Physiologic, as in neonatal jaundice and increased pigment production secondary to tissue infarction and large hematomas.
3. Inflammatory, as in hepatitis and sepsis.
4. Metabolic/nutritional, as in drug-impaired uptake of bilirubin and drug-induced hemolysis and cholestasis, alcoholic malnutrition, and gallstones, including common hepatic and common bile duct stones.
5. Neoplastic, as in primary and metastatic tumors to the liver, extrahepatic tumors such as cholangiocarcinoma (including Klatskin tumour), carcinoma of the gallbladder, ampullary and periampullary carcinomas, carcinoma of the pancreas, and metastatic lymph nodes in the porta hepatis.

Congenital or familial types of hyperbilirubinemia are characterized by increases in unconjugated or conjugated bilirubin. Hemolytic disorders result in increased production of unconjugated bilirubin; pigment gallstones may produce common bile duct obstruction, resulting in an elevated conjugated bilirubin level. Unconjugated hyperbilirubinemia is rarely a surgical condition. The ratio of unconjugated to conjugated bilirubin will not differentiate between intra-or extrahepatic causes of jaundice but may help differentiate between a parenchymal and obstructive etiology. In parenchymal dysfunction, serum transaminase levels are elevated, unlike in obstructive jaundice, where the alkaline phosphatase level is high.

Clinical Manifestations Ask questions concerning loss of appetite (hepatitis), loss of weight, previous episodes of jaundice, the color of urine and stool, exposure to hepatitis, blood transfusions, drug (e.g., chlorpromazine, tetracycline, chlorthiazide, acetaminophen) and alcohol abuse, family history, abdominal pain (painless jaundice in carcinoma of the head of the pancreas), or pruritus (obstructive jaundice). Signs of liver dysfunction, lymph node enlargement, enlargement of the liver and spleen, and a palpable gallbladder (Courvoisier's Law) should be sought on examination.

Laboratory Studies Do a complete blood count and urinalysis (e.g., the presence of bilirubin and absence of urobilinogen indicates obstructive jaundice, the absence of bilirubin but presence of urobilin indicates excessive hemolysis or failure of conjugation); do liver enzyme determinations and fractionated bilirubin levels.

The initial radiologic examination is ultrasound to demonstrate a dilated biliary system and gallstones. If ducts are dilated, endoscopic retrograde cholangiopancreatography (ERCP) or a percutaneous transhepatic cholangiogram (PTC) can be performed depending on the expertise available. Both studies can localize the obstruction and also can be used for therapy, e.g., the removal of stones, sphincterotomy, placement of stent, placement of decompressive tube, obtain biopsies or brushings, and cytology. CT scan identifies masses in the porta hepatis, the head of the pancreas, and the liver. In carcinoma of the pancreas, a dynamic CT scan can define invasion of the portal vein.

MULTIPLE ORGAN FAILURE SYNDROME (MOFS)

This is a progressive, potentially reversible physiologic dysfunction of two or more organs or organ systems. It may be a sequel to resuscitation from an acute life-threatening event, e.g., operations for intraabdominal sepsis, ruptured abdominal aortic aneurysm with hypotension, and intestinal ischemia. Once MOFS is established, the mortality exceeds 70 percent. Although the GI tract may be the primary source of sepsis (e.g., perforated diverticulitis with fecal peritonitis), it also can be an unseen generator of the septic syndrome in a critically ill patient, e.g., bacterial translocation across the gut wall when the immunoregulatory function of the gut is compromised; immunologic activities of the liver also can be impaired in critical illness.

Several organ systems may show impairment. Pulmonary failure is manifest as the acute respiratory distress syndrome; poor urine output and a rise in BUN and creatinine levels indicate renal dysfunction. Liver failure presents as ischemic hepatitis (shock liver) and jaundice combined with associated abnormalities in liver chemistry and coagulation disorders. If septic shock syndrome is not reversed at this point, other organ systems fail. Cardiovascular dysfunction manifests as ventricular failure followed by CNS dysfunction causing altered states of consciousness. Anemia, leukopenia, and thrombocytopenia (heparin can cause thrombocytopenia) indicate hematologic dysfunction. Failure of the GI system may manifest as stress ulceration and diarrhea (exclude pseudomembra-

nous colitis as a cause). Acute pancreatitis is frequent in MOFS. Acalculous cholecystitis may have its origin in mucosal ischemia, stasis, or infection.

For a more detailed discussion, see Fischer JE, Nussbaum MS, Chance WT, and Luchette F: Manifestations of Gastrointestinal Disease, chap. 22 in *Principles of Surgery,* 7th ed.

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CHAPTER

23

ESOPHAGUS AND DIAPHRAGMATIC HERNIA

SURGICAL ANATOMY

The esophagus is a muscular tube that starts as the continuation of the pharynx and ends as the cardia of the stomach. The esophagus lies in the midline but deviates to the left in the lower portion of the neck and returns to the midline near the bifurcation of the trachea. In the lower thorax, the esophagus again deviates to the left to pass through the diaphragmatic hiatus (Fig. 23-1).

Three normal areas of esophageal narrowing are evident on the barium esophagogram. The uppermost is caused by the cricopharyngeal muscle. The middle narrowing is caused by the crossing of the left mainstem bronchus and aortic arch. The lowermost narrowing is caused by the gastroesophageal sphincter mechanism. These constrictions tend to hold up swallowed foreign objects and corrosive liquids because of their slow passage through these areas.

The cervical portion of the esophagus is approximately 5 cm long and descends between the trachea and the vertebral column to the level of the suprasternal notch anteriorly. The recurrent laryngeal nerves lie in the right and left grooves between the trachea and the esophagus. On the left and right sides of the cervical esophagus are the carotid sheaths and the lobes of the thyroid gland.

The thoracic portion of the esophagus is approximately 20 cm long. In the upper thorax, it is in intimate relationship with the posterior wall of the trachea and the prevertebral fascia. Just above the tracheal bifurcation, the esophagus passes to the right of the aorta. From the bifurcation of the trachea downward, both the vagal nerves and the esophageal nerve plexus lie on the muscular wall of the esophagus.

The thoracic esophagus follows the curvature of the spine and remains in close contact with the vertebral bodies. In the thorax, the thoracic duct lies dorsal to the esophagus between the azygos vein on the right and the descending thoracic aorta on the left.

The abdominal portion of the esophagus is approximately 2 cm long. This portion of the esophagus is subjected to the positive-pressure environment of the abdomen.

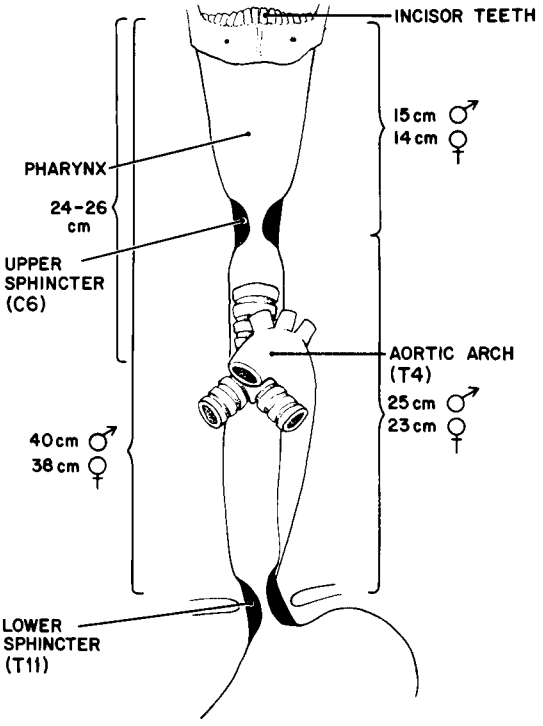

FIGURE 23-1 Important clinical endoscopic measurements of the esophagus in adults. (From: Rothberg M, DeMeester TR: Surgical anatomy of the esophagus, in Shields TW (ed): *General Thoracic Surgery*, 3d ed. Philadelphia, Lea & Febiger, 1989, p 78, with permission.)

The musculature of the esophagus can be divided into an outer longitudinal and an inner circular layer. The upper 2–6 cm of the esophagus contains only striated muscle fibers. More distally, smooth muscle fibers gradually become more abundant. Most of the clinically significant esophageal motility disorders involve only the smooth muscle in the lower two-thirds of the esophagus.

The circular muscle layer of the esophagus is thicker than the outer longitudinal layer. The geometry of the circular muscle is

helical and makes the peristalsis of the esophagus assume a worm-like drive as opposed to segmental and sequential squeezing. As a consequence, severe motor abnormalities of the esophagus assume a corkscrew-like pattern on the barium swallow radiogram.

The cervical portion of the esophagus receives its main blood supply from the inferior thyroid artery. The thoracic portion receives its blood supply from the bronchial arteries. Two esophageal branches arise directly from the aorta. The abdominal portion of the esophagus receives its blood supply from the ascending branch of the left gastric artery and from the inferior phrenic arteries. On entering the esophagus, the arteries form a longitudinal plexus, giving rise to an intramural vascular network in the muscular and submucosal layers.

The esophageal veins empty into the inferior thyroid vein, into the bronchial, azygos, or hemizygous vein, and into the coronary vein. The submucosal venous networks of the esophagus and stomach are in continuity with each other, and in portal venous obstruction, this communication functions as a collateral for portal blood to enter the superior vena cava via the azygos vein.

The parasympathetic innervation of the pharynx and esophagus is provided mainly by the vagus nerves. The cricopharyngeal sphincter and the cervical portion of the esophagus receive branches from both recurrent laryngeal nerves. Damage to these nerves interferes not only with function of the vocal cords but also with function of the cricopharyngeal sphincter, predisposing to pulmonary aspiration.

Afferent visceral sensory pain fibers from the esophagus using a combination of sympathetic and vagal pathways are also occupied by afferent visceral sensory fibers from the heart; hence both organs have similar symptomatology.

The lymphatics located in the submucosa of the esophagus are dense and constitute a single plexus. Lymph flow runs in a longitudinal direction. In the upper two-thirds of the esophagus the lymphatic flow is mostly cephalad and in the lower third caudad. In the thoracic portion of the esophagus, the submucosal lymph plexus extends over long distances in a longitudinal direction before penetrating the muscle layer. The cervical esophagus has a more direct segmental lymph drainage into the regional nodes.

Lymphatics from the cervical esophagus drain into the paratracheal and deep cervical lymph nodes and those from the upper thoracic esophagus empty mainly into the paratracheal lymph nodes. Efferent lymphatics from the lower thoracic esophagus drain into the subcarinal nodes and nodes in the inferior pulmonary ligaments. The superior gastric nodes receive lymph not only from the abdominal portion of the esophagus but also from the adjacent lower thoracic segment.

PHYSIOLOGY

The tongue and pharynx function as a piston pump with three valves. The esophagus and cardia function as a worm-drive pump with a single valve (Fig. 23-2). The three valves in the pharyngeal cylinder are the soft pallet, the epiglottis, and the cricopharyngeus. The valve of the esophageal pump is the lower esophageal sphincter. Failure of the valves or the pumps leads to abnormalities in swallowing.

Swallowing, once initiated, is entirely a reflex. With the posterior movement of the tongue, the soft palate is elevated. This pre-

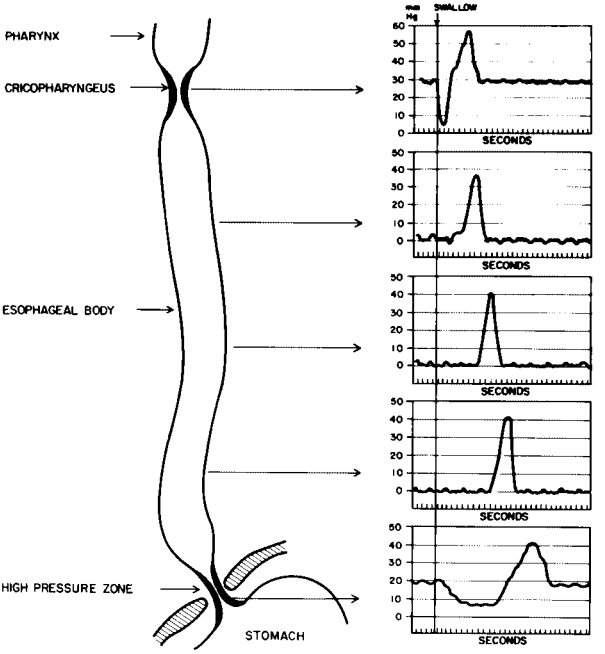

FIGURE 23-2 Intraluminal esophageal pressures in response to swallowing. (From: Waters PF, DeMeester TR, *Med Clin North Am* 65:1238, 1981, with permission.)

vents pressure generated in the oropharynx from being dissipated through the nose. During swallowing, the backward tilt of the epiglottis covers the opening of the larynx to prevent aspiration.

During swallowing, a sizable pressure difference develops between the hypopharyngeal pressure and the less-than-atmospheric midesophageal or intrathoracic pressure. This pressure gradient speeds the movement of food. The bolus is propelled by peristaltic contraction of the posterior pharyngeal constrictors and sucked into the thoracic esophagus. When esophageal compliance is lost because of muscle pathology, dysphagia can result.

Swallowing can be started at will, or it can be reflexly elicited by the stimulation of areas in the mouth and pharynx. The swallowing center in the medulla coordinates the complete act of swallowing by discharging impulses through cranial nerves V, VII, X, XI, and XII, as well as the motor neurons of C1 to C3. Operative damage to the innervation can interfere with laryngeal, cricopharyngeal, and upper esophageal function and predispose the patient to aspiration.

The lower esophageal sphincter (LES) provides a pressure barrier between the esophagus and stomach. Sphincter-like function is related to the architecture of the muscle fibers at the junction of the esophageal tube with the gastric pouch. The LES actively remains closed to prevent reflux of gastric contents into the esophagus and opens by a relaxation that coincides with a pharyngeal swallow.

The antireflux mechanism in human beings is composed of three components: a mechanically effective LES, efficient esophageal clearance, and an adequately functioning gastric reservoir. A defect of any one of these three components can lead to increased esophageal exposure to gastric juice and the development of mucosal injury.

Physiologic Reflux Healthy individuals have occasional episodes of gastroesophageal reflux. They are more common when awake and in the upright position than during sleep in the supine position. Normal subjects rapidly clear the acid gastric juice from the esophagus regardless of their position. LES pressure in normal subjects is significantly higher in the supine position than in the upright position. This is due to the hydrostatic pressure of the abdomen to the abdominal portion of the sphincter when supine.

The LES has intrinsic myogenic tone, which is modulated by neural and hormonal mechanisms. Beta blockers stimulate the LES, and alpha-blockers decrease its pressure. Peppermint, chocolate, coffee, ethanol, and fat are all associated with decreased LES pressure and may be responsible for esophageal symptoms after a sumptuous meal.

DIAGNOSTIC STUDIES

Tests to Detect Structural Abnormalities *Radiographic Evaluation* The first test in patients with suspected esophageal disease should be a barium swallow followed by full assessment of the stomach and duodenum. Esophageal motility is optimally assessed in the horizontal position. Hiatal hernias are best demonstrated with the patient prone because the increased intraabdominal pressure promotes displacement of the esophagogastric junction above the diaphragm. Fully distended views of the esophagogastric region are crucial. Esophageal disorders shown well by a full-column technique include circumferential carcinomas, peptic strictures, large esophageal ulcers, and hiatal hernias. The full-column technique should be supplemented with mucosal relief or double-contrast films to enhance detection of smaller or more subtle lesions.

The radiographic assessment of the esophagus is not complete unless the entire stomach and duodenum have been examined. A gastric or duodenal ulcer, partially obstructing gastric neoplasm, or scarred duodenum and pylorus may contribute significantly to symptoms otherwise attributable to an esophageal abnormality.

Endoscopic Evaluation In any patient complaining of dysphagia, esophagoscopy is indicated even in the face of a normal radiographic study. The flexible esophagoscope is the instrument of choice because of its technical ease, patient acceptance, and the ability to simultaneously assess the stomach and duodenum. The rigid esophagoscope may be an essential instrument when deeper biopsies are required or the cricopharyngeus and cervical esophagus need closer assessment.

When gastroesophageal reflux disease is suspected, particular attention should be paid to the presence of esophagitis and Barrett's columnar-lined esophagus. *Grade I esophagitis* is defined as reddening of the mucosa without ulceration. *Grade II esophagitis* is defined by the presence of linear erosions lined with granulation tissue. *Grade III esophagitis* represents a more advanced stage where the linear ulcerations coalesce, leaving islands of epithelium. *Grade IV esophagitis* is the presence of a stricture.

Barrett's esophagus is a condition in which the tubular esophagus is lined with specialized columnar epithelium as opposed to the normal squamous epithelium. Its presence is confirmed by biopsy. Barrett's esophagus is susceptible to ulceration, bleeding, stricture formation, and most important, malignant degeneration.

A *hiatal hernia* is determined by a pouch lined with gastric rugal folds lying 2 cm or more above the margins of the diaphrag-

matic crura. When a submucosal mass is identified, biopsies are usually not taken. If a biopsy is taken, the mucosa may become fixed to the underlying abnormality. This complicates the surgical dissection by increasing the risk of mucosal perforation.

Tests to Detect Functional Abnormalities *Stationary Manometry* Esophageal manometry is a widely used technique to examine the motor function of the esophagus and its sphincters. It is particularly necessary to confirm the diagnosis of specific primary esophageal motility disorders, i.e., achalasia, diffuse esophageal spasm, "nutcracker" esophagus, and hypertensive LES. It also identifies nonspecific esophageal motility abnormalities and motility disorders secondary to systemic disease such as scleroderma, dermatomyositis, polymyositis, or mixed connective tissue disease. In patients with gastroesophageal reflux, manometry can identify a mechanically defective LES and evaluate the adequacy of esophageal peristalsis and contraction amplitude.

A mechanically defective LES is identified by having one or more of the following characteristics: an average LES pressure of less than 6 mmHg, an average length exposed to the positive-pressure environment in the abdomen of 1 cm or less, or an average overall sphincter length of 2 cm or less.

24-Hour Ambulatory Manometry In both normal volunteers and symptomatic patients, esophageal motor activity increases with the state of consciousness and focus on eating activity. In patients with nonobstructive dysphagia, the circadian esophageal motor pattern is characterized by an inability to organize the motor activity into peristaltic contraction during a meal period. In patients with noncardiac chest pain, ambulatory motility monitoring can document a direct correlation of abnormal esophageal motor activity with the symptom and shows that the abnormal motor activity immediately preceding the pain episodes is characterized by an increased frequency of simultaneous, double- and triple-peaked, high-amplitude, and long contractions. In patients with gastroesophageal reflux disease, ambulatory motility monitoring shows that the contractility of the esophageal body deteriorates with increasing severity of esophageal mucosal injury, compromising the clearance function of the esophageal body. The combination of ambulatory 24-h esophageal manometry with esophageal and gastric pH monitoring is currently the most physiologic way to assess patients with foregut motility disorders.

Esophageal Transit Scintigraphy The esophageal transit of a 10-mL water bolus containing technetium-99m (^{99m}Tc) sulfur

colloid is recorded with a gamma camera. Its best use is to quantify the effect of an esophageal motility disorder by measuring esophageal emptying time.

Video- and Cineradiography High-speed cinematic or video recording of radiographic studies allows reevaluation by reviewing the study at various speeds. Observations suggesting dysfunction include misdirection of barium into the trachea or nasopharynx, prominence of the cricopharyngeal muscle, a Zenker's diverticulum, a narrow pharyngoesophageal segment, and stasis of the contrast medium in the valleculae or hypopharyngeal recesses. The simultaneous computerized capture of videofluoroscopic images and manometric tracings is now available and is referred to as *manofluorography.* It is presently the best means available to evaluate complex functional abnormalities.

Tests to Detect Increased Exposure to Gastric Juice The most direct method of measuring increased esophageal exposure to gastric juice is by an indwelling pH electrode. A 24-h period is necessary so that measurements are made over one complete circadian cycle. The 24-h esophageal pH monitoring should not be considered a test for reflux but rather a measurement of the esophageal exposure to gastric juice. The detection of increased esophageal exposure to acid gastric juice is more dependable than the detection of increased exposure to alkaline gastric juice. The presence of duodenal contents within the esophagus can now be determined via an indwelling spectrophotometric probe capable of detecting bilirubin over a 24-h period.

Standard Acid Reflux Test The development of powerful acid reduction agents such as omeprazole has created difficulties in the measurement of esophageal acid exposure. Standard acid reflux testing (SART) is performed following manometry by placing a pH electrode 5 cm above the upper border of the LES. The manometry catheter is then advanced temporarily into the stomach, and 300 mL of 0.1 *N* HCl is infused. The pH of the esophagus is monitored while the patient performs deep breathing, Valsalva and Mueller maneuvers, and coughs. A decrease in esophageal pH to less than 4 is considered evidence of reflux.

Patients with severe reflux may be unable to clear acid from the esophagus after reflux has been documented. SART has a sensitivity of 59 percent and a specificity of 98 percent and an overall accuracy of 81 percent.

Radiographic Detection of Gastroesophageal Reflux The radiographic demonstration of spontaneous regurgitation of barium into

the esophagus in the upright position is a reliable indicator that reflux is present.

Tests for Duodenogastric Function Abnormalities of the gastric reservoir or increased gastric acid secretion can be responsible for increased esophageal exposure to gastric juice. Reflux of alkaline duodenal juice, including bile salts, pancreatic enzymes, and bicarbonate, is thought to have a role in the pathogenesis of esophagitis and complicated Barrett's esophagus. Duodenogastric function is assessed by studying gastric emptying with radionuclide-labeled meal, by gastric analysis, cholescintigraphy, and 24-h gastric pH monitoring.

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux accounts for approximately 75 percent of esophageal pathology. Heartburn, or acid regurgitation, is very common. Even when excessive, these symptoms can be caused by achalasia, diffuse spasm, esophageal carcinoma, pyloric stenosis, cholelithiasis, gastritis, gastric or duodenal ulcer, and coronary artery disease. Gastroesophageal reflux can present with atypical symptoms, such as nausea, vomiting, postprandial fullness, chest pain, choking, chronic cough, wheezing, or hoarseness. Bronchiolitis, recurrent pneumonia, idiopathic pulmonary fibrosis, and asthma can be due primarily to gastroesophageal reflux disease. An alternative definition for gastroesophageal reflux disease is the presence of endoscopic esophagitis. Using this criterion assumes that all patients who have esophagitis have excessive regurgitation of gastric juice into their esophagus (Fig. 23-3). This is true in 90 percent of patients, but in 10 percent the esophagitis has other causes.

A third approach to define gastroesophageal reflux disease is to measure the basic pathophysiologic abnormality of the disease, i.e., increased exposure of the esophagus to gastric juice.

Etiology There are three known causes of increased esophageal exposure to gastric juice in patients with gastroesophageal reflux disease: a mechanically incompetent LES, inefficient esophageal clearance of refluxed gastric juice, and abnormalities of the gastric reservoir that augment physiologic reflux.

The Lower Esophageal Sphincter Failure of the LES is caused by inadequate pressure or overall length or abnormal position. Failure of all three sphincter components inevitably leads to increased esophageal exposure to gastric juice.

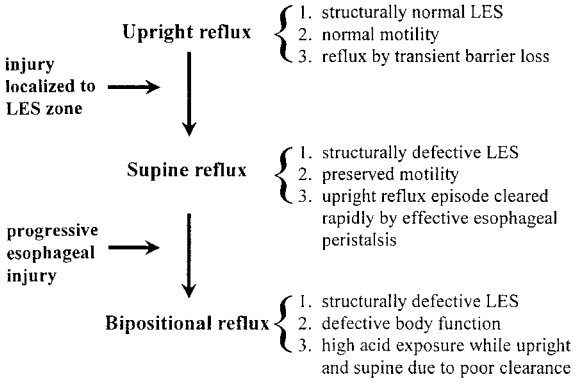

FIGURE 23-3 Proposed mechanisms of the progression of gastroesophageal reflux disease.

The most common cause of a mechanically defective LES is inadequate sphincter pressure. Sphincter pressure depends on the length and tension properties of the sphincter's smooth muscle. An adequate abdominal length is important in preventing reflux caused by increases in intraabdominal pressure. Reflux can occur whenever an increase in gastric pressure exceeds the sphincter pressure that is necessary to provide competency for the overall length of sphincter present.

Esophageal Clearance A second portion of the antireflux mechanism in human beings is effective esophageal clearance. Ineffectual clearance is more apt to be seen in association with a mechanically defective sphincter, where it augments the esophageal exposure to gastric juice by prolonging the duration of each reflux episode.

Four factors important in esophageal clearance are gravity, esophageal motor activity, salivation, and anchoring of the distal esophagus in the abdomen. The bulk of refluxed gastric juice is cleared from the esophagus by primary peristaltic waves initiated by a pharyngeal swallow. Manometry of the esophageal body can detect failure of esophageal clearance by analysis of the pressure amplitude and speed of wave progression through the esophagus.

Salivation contributes to esophageal clearance by neutralizing the minute amount of acid that is left following a peristaltic wave. Saliva production also may be increased by the presence of acid in the lower esophagus. This is referred to as *water brash.*

The presence of a hiatal hernia also can contribute to an esophageal propulsion defect due to loss of anchorage of the esophagus in the abdomen. The presence of a hiatal hernia contributes to the pathogenesis of gastroesophageal reflux disease.

Gastric Reservoir Abnormalities of the gastric reservoir that increase esophageal exposure to gastric juice include gastric dilatation, increased intragastric pressure, persistent gastric reservoir, and increased gastric acid secretion. The effect of gastric dilatation is to shorten the overall length of the LES, resulting in a decrease in the sphincter resistance to reflux.

Increased intragastric pressure occurs from the outlet obstruction of a scarred pylorus or duodenum, a vagotomy, and in the diabetic patient with gastroparesis. A persistent gastric reservoir results from delay of gastric emptying and increases the exposure of the esophagus to gastric juice by accentuating physiologic reflux. It is caused by gastric atony, advanced diabetes, diffuse neuromuscular disorders, anticholinergic medications, and postviral infections, vagotomy, antropyloric dysfunction, and duodenal dysmotility. Gastric hypersecretion can increase esophageal exposure to gastric acid juice by reflux of concentrated gastric acid.

Complications of Gastroesophageal Reflux Complications due to repetitive reflux are esophagitis, stricture, Barrett's esophagus, and progressive pulmonary fibrosis due to repetitive aspiration. The mechanical defect of the sphincter is primary and not the result of inflammation or tissue damage. Unrestricted reflux of gastric juice into the esophagus leads to mucosal injury with progressive deterioration of esophageal contractility and regurgitation into the pharynx with aspiration. The presence and severity of reflux complications are related to the presence of a mechanically defective sphincter and an increased esophageal exposure to both acid and alkalinity. Gastroesophageal reflux disease is significantly worse in patients with acid/alkaline reflux as compared with those with only acid reflux. Duodenal-gastric reflux and the acid secretory capacity of the stomach interrelate by altering the pH and enzymatic activity of the refluxed gastric juice to modulate the injurious effects of enzymes on the esophageal mucosa.

The disparity in injury caused by acid and bile alone as opposed to gross esophagitis caused by pepsin and trypsin explains the poor correlation between the symptoms of heartburn and endoscopic esophagitis. The reflux of acid gastric juice contaminated with duodenal contents could break the esophageal mucosal barrier, causing severe heartburn. Changing the pH of refluxed duodenogastric juice from acid to alkaline by the administration of histamine H_2 blockers

may intensify the mucosal injury while giving the patient a sense of security by alleviating the symptom of heartburn.

When esophageal injury occurs, a luminal stricture and/or Barrett's esophagus can develop by replacement of repetitively destroyed squamous mucosa with columnar epithelium. Endoscopically, the Barrett's changes can be associated with esophagitis, stricture, Barrett's ulceration, or dysplasia. Barrett's epithelium may become dysplastic and progress to adenocarcinoma with an incidence between 0.5 and 10 percent.

Esophageal stricture occurs at the site of maximal inflammatory injury, i.e., the columnar-squamous epithelial interface. As the inflammation extends higher, the stricture moves progressively up the esophagus. In patients with normal acid exposure, the stricture may be due to a drug-induced chemical injury resulting from the lodgment of a capsule or tablet in the distal esophagus. Long, stringlike strictures as a result of repetitive caustic injury from a capsule or tablet are often resistant to dilatation. Refluxed gastric juice can reach the pharynx with pharyngeal tracheal aspiration, causing cough, choking, hoarseness, and recurrent pneumonia. In patients with increased esophageal acid exposure, if the pH is below 4 for 1 percent of the time in the cervical esophagus, there is a high probability that the respiratory symptoms have been caused by aspiration.

Medical Therapy

Gastroesophageal reflux disease is such a common condition that most patients with mild symptoms carry out self-medication. Patients should be advised to elevate the head of the bed, avoid tight clothing, eat small frequent meals, avoid eating their nighttime meal soon before retiring, lose weight, and avoid alcohol, coffee, chocolate, and peppermints.

Alginic acid reacts with sodium bicarbonate in saliva to form a viscous solution that protects the esophagus against the noxious gastric contents. Medications to promote gastric emptying, such as metoclopramide, domperidone, and cisapride, have been of little value in severe disease.

In patients with persistent symptoms, the mainstay of medical therapy is acid suppression. High doses of proton pump inhibitors, such as omeprazole, can reduce gastric acidity by 80–90 percent. With severe esophagitis, healing may occur in only half of patients. Within 6 months of discontinuation of any form of medical therapy for gastroesophageal reflux disease, 80 percent of patients have a recurrence of symptoms.

Patients whose symptoms persist despite simple antacid therapy should undergo endoscopy to determine if the complications of re-

flux disease such as esophagitis, stricture, or Barrett's esophagus are present. All are then placed on histamine H_2 or omeprazole therapy. If their symptoms disappear completely after 12 weeks of therapy, the medication should be discontinued and the patient observed. If their symptoms recur within 4 weeks, they should be studied with manometry and 24-h foregut pH monitoring. Patients who on repeat endoscopy show persisting complications of the disease also should be studied. Depending on the results of the tests, further intensive medical therapy may be instituted, or the patient may be considered for surgical therapy if the criteria are met. Patients whose symptoms do not recur within 4 weeks and are free of complications of the disease should be monitored and treated intermittently when symptoms occur.

Indications for Antireflux Surgery

Before proceeding with an antireflux procedure, it is necessary to confirm that the patient's symptoms are caused by increased esophageal exposure to gastric juice secondary to a mechanically defective LES. This requires performing esophageal function studies, i.e., 24-h esophageal pH monitoring and esophageal manometry. Patients with increased esophageal acid exposure, a mechanically defective LES, and no complications of the disease should be given the option of surgery if they are drug dependent to control their symptoms.

If the patient responds symptomatically to medical therapy but endoscopic esophagitis persists, surgery should be performed. Without surgery, these patients can progress to develop a stricture or Barrett's esophagus.

Anatomic shortening of the esophagus can compromise the ability to do an adequate repair without tension and lead to an increased incidence of breakdown or thoracic displacement of the repair. When present, the motility of the esophageal body must be evaluated carefully, and if it is adequate, a gastroplasty should be performed. In patients who have absence of contractility or more than 50 percent interrupted or dropped contractions or a history of several failed previous antireflux procedures, esophageal resection should be considered as an alternative.

The surgeon should query the patient for specific complaints of epigastric pain, nausea, vomiting, and loss of appetite. These can be due to excessive duodenogastric reflux, which occurs in about one-third of patients with gastroesophageal reflux disease. In these patients, 24-h pH monitoring of the stomach may help to detect and quantitate duodenogastric reflux. If the symptoms of duodenogastric reflux persist after antireflux surgery, the administration of

sucralfate may relieve the persistent complaint of nausea and epigastric pain.

Approximately 30 percent of patients with proven gastroesophageal reflux on 24-h pH monitoring will have hypersecretion on gastric analysis. These factors may modify the proposed antireflux procedure in patients with active ulcer disease or documentation of previous ulceration by the addition of a highly selective vagotomy.

Delayed gastric emptying is found in approximately 40 percent of patients with gastroesophageal reflux disease. Only in patients with severe emptying disorders is there a need for an additional gastric procedure.

Principles of Surgical Therapy (Fig. 23-4) The primary goal of antireflux surgery is to safely reestablish the competency of the cardia. First, the operation should restore the pressure of the distal esophageal sphincter to a level twice resting gastric pressure. Second, the operation should place an adequate length of the distal esophageal sphincter in a positive-pressure environment of the abdomen. Third, the operation should allow the reconstructed cardia to relax on deglutition. Fourth, the fundoplication should not increase the resistance of the relaxed sphincter to a level that exceeds

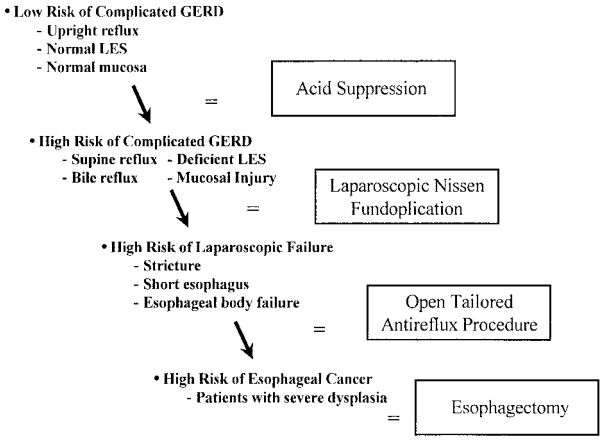

FIGURE 23-4 Conceptual schema of the ideal treatment at each stage of the spectrum of gastroesophageal reflux disease.

the peristaltic power of the body of the esophagus. Fifth, the operation should ensure that the fundoplication can be placed in the abdomen without undue tension and maintained there by approximating the crura of the diaphragm above the repair.

PRIMARY ANTIREFLUX REPAIRS

The most common antireflux procedure is the Nissen fundoplication using only the gastric fundus to envelope the esophagus in performing the fundoplication, sizing the fundoplication with a No. 60 French bougie, and limiting the length of the fundoplication to 1–2 cm.

In the presence of altered esophageal motility, where the propulsive force of the esophagus is not sufficient to overcome the outflow obstruction of a complete fundoplication, a partial fundoplication may be indicated (the Belsey Mark IV repair).

In patients with a short esophagus due to stricture, Barrett's esophagus, or a large hiatal hernia, a Collis gastroplasty is performed as an esophageal lengthening procedure. The gastroplasty will lengthen the tubular esophagus by constructing a gastric tube, allowing tension-free construction of a Belsey Mark IV or Nissen fundoplication around the gastric tube, with placement of the repair in the abdomen.

Indications for performing an antireflux procedure by transthoracic approach are a previous antireflux procedure, esophageal myotomy for achalasia or diffuse spasm, esophageal stricture or Barrett's esophagus, hiatal hernia that does not reduce below the diaphragm, associated pulmonary pathology, and an obese patient (Fig. 23-5).

Studies have shown that the Nissen fundoplication is an effective and durable antireflux repair in 91 percent of patients over 10 years. Laparoscopic Nissen fundoplication has been shown to relieve typical symptoms of gastroesophageal reflux in greater than 90 percent of patients. Overall, there is a 4.2 percent conversion rate to open surgery and a 0.5 percent rate of early reoperation. The incidence of dysphagia has decreased to 3–5 percent with increasing experience and attention to technical details. Patients with early, uncomplicated gastroesophageal reflux are the best candidates for a laparoscopic approach. It is recommended that the surgical approach to patients with gastroesophageal reflux disease be selective, i.e., that the specific antireflux procedure for any patient be based on the patient's existing esophageal function.

BARRETT'S ESOPHAGUS

The condition whereby the tubular esophagus is lined with columnar epithelium rather than squamous epithelium is an acquired abnormality that occurs in 7–10 percent of patients with gastroesophageal

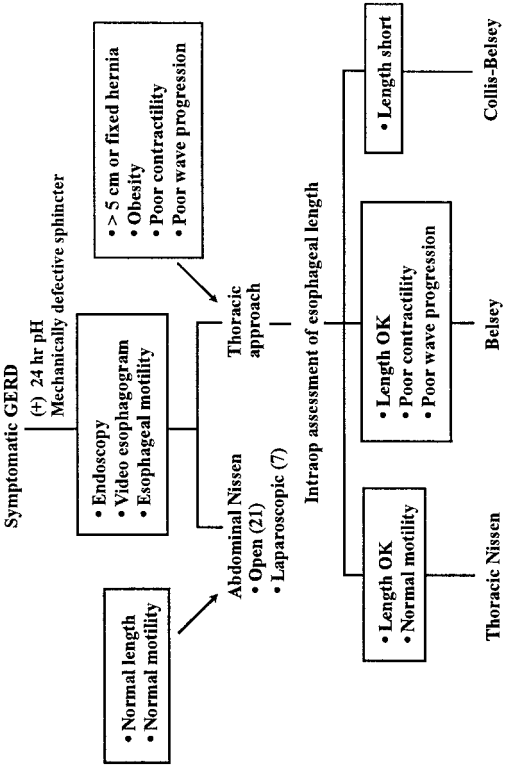

FIGURE 23-5 Algorithm of decision making for tailored antireflux surgery.

reflux disease and represents the end stage of the natural history of this disease.

The definition of Barrett's esophagus has evolved considerably over the past decade. Traditionally, Barrett's esophagus was identified by the presence of columnar mucosa extending at least 3 cm into the esophagus. Now, the diagnosis is made given any length of endoscopically identifiable columnar mucosa that proves on biopsy to show intestinal metaplasia. The hallmark of intestinal metaplasia is the presence of intestinal goblet cells.

Barrett's esophagus is associated with profound mechanical deficiency of the LES and marked esophageal acid exposure. The typical complications in Barrett's esophagus include ulceration in the columnar-lined segment, stricture formation, and a dysplasia-cancer sequence. It has the propensity to bleed, penetrate, or perforate. Risk of adenocarcinoma is variously estimated at 1 in 50 patient-years to 1 in 400 patient-years, a risk 40 times that of the general population. About one-third of all patients with Barrett's present with malignancy.

Patients whose symptoms are readily controlled by medication are suitable for medical therapy (histamine H_2 blockers and omeprazole). Healing of ulcers and stabilization of strictures are not readily achieved. Medical treatment does nothing to correct the underlying defective sphincter and does nothing to reduce the reflux of alkalized gastric juice or prevent aspiration. The symptomatic relief may allow tissue damage to progress unnoticed, so advancement of the disease continues to occur. For this reason, surgery may be appropriate earlier in the course of the disease.

Since Barrett's esophagus is a premalignant condition, there are strong theoretical grounds for reversing the underlying cause before malignancy develops by performing antireflux surgery. Regression of Barrett's epithelium after surgery has not been reported often. There is a growing body of evidence to attest to the ability of fundoplication to protect against dysplasia and invasive malignancy. When high-grade dysplasia is discovered at biopsy, an esophagectomy is recommended because 50 percent of such specimens will show early invasive carcinoma.

STRICTURE

The development of a stricture while on acid suppression therapy in a patient with a mechanically defective sphincter represents a failure of medical therapy and is an indication for a surgical antireflux procedure. Before surgery, a malignant etiology of the stricture should be excluded and the stricture progressively dilated up to a No. 60 French bougie. Three factors become important in the management of these patients: (1) the response to dilatation, (2) an assessment of esophageal length by endoscopy or barium swallow, and (3) adequacy of esophageal contractility on motility studies.

If the amplitude of esophageal contractions and the length of the esophagus are adequate, total fundoplication can be performed. In a patient with adequate esophageal length in whom dysphagia persists or esophageal contractility is compromised, partial fundoplication should be done. If the esophagus is shortened by the disease process, a gastroplasty and partial fundoplication should be performed.

ATYPICAL REFLUX SYMPTOMS

Chronic respiratory symptoms such as chronic cough, recurrent pneumonia, episodes of nocturnal choking, waking up with gastric content in the mouth, or soilage of the bed pillow also may indicate the need for surgical therapy. The chest radiograph in patients suffering from gastroesophageal reflux often shows signs of pleural thickening, bronchiectasis, and chronic interstitial pulmonary fibrosis. If 24-h pH monitoring confirms the presence of increased esophageal acid exposure and manometry shows a mechanical defect of the LES and normal esophageal body motility, an antireflux procedure can be done with an expected good result.

Chest pain may be an atypical symptom of gastroesophageal reflux and is often confused with coronary artery disease. Fifty percent of patients in whom a cardiac etiology of the chest pain has been excluded will have increased esophageal acid exposure as a cause of the episode of pain. An antireflux procedure provides relief of the chest pain with greater constancy than will occur with medical therapy.

Dysphagia, regurgitation, and/or chest pain on eating can be related to the presence of a large paraesophageal hernia, intrathoracic stomach, or a small hiatal hernia with a narrow diaphragmatic hiatus. The surgical repair of the hernia usually includes an antireflux procedure because of the potential of destroying the competency of the cardia during the surgical dissection.

REOPERATION FOR FAILED ANTIREFLUX REPAIRS

Placement of the wrap around the stomach is the most frequent cause for failure after open procedures, whereas herniation of the repair into the chest is the most frequent cause of failure after a laparoscopic procedure. This is probably due, in both instances, to an unrecognized short esophagus. Partial or complete breakdown of the wrap or construction of a too tight or too long wrap occurs with both open and closed procedures. Ten percent of these patients had an antireflux procedure for a misdiagnosed underlying esophageal motor disorder.

The preferred surgical approach to a patient who has had a previously failed antireflux procedure is through a left thoracotomy with a peripheral circumferential incision in the diaphragm to provide for simultaneous exposure of the upper abdomen and safe dissection of the previous repair from both abdominal and thoracic sides of the diaphragm. When dysphagia is associated with poor motility and multiple previous repairs, esophageal resection and replacement should be considered.

MOTILITY DISORDERS OF THE PHARYNX AND ESOPHAGUS

Clinical Manifestations Dysphagia is the primary symptom of esophageal motor disorders. To apply surgical therapy to the problem of dysphagia, the surgeon needs to know the precise functional abnormality causing the symptom. This usually entails a complete esophageal motility evaluation in addition to contrast studies and endoscopy.

Disorders of the pharyngoesophageal phase of swallowing result from a discoordination of the neuromuscular events involved in chewing, initiation of swallowing, and propulsion of the material from the oropharynx into the cervical esophagus.

Pharyngoesophageal swallowing disorders usually result from cerebrovascular accidents, brain stem tumors, poliomyelitis, multiple sclerosis, Parkinson's disease, pseudobulbar palsy, peripheral neuropathy, or operative damage to the cranial nerves. Muscular diseases such as radiation-induced myopathy, dermatomyositis, myotonic dystrophy, and myasthenia gravis are less common causes. Extrinsic compression by thyromegaly, cervical lymphadenopathy, or hyperostosis of the cervical spine can cause pharyngoesophageal dysphagia.

Video- and cineradiography are currently the most objective tests to evaluate oropharyngeal bolus transport, pharyngeal compression, relaxation of the pharyngoesophageal segment, and the dynamics of airway protection during swallowing.

In patients with Zenker's diverticulum, it has been difficult to consistently demonstrate a motility abnormality. Perhaps the diverticulum develops as a consequence of the repetitive stress of bolus transport through a noncompliant muscle of the pharyngoesophageal segment. A cricopharyngeal bar is a result of a noncompliant pharyngoesophageal segment and can be improved by a cricopharyngeal myotomy.

Zenker's Diverticulum

Zenker's pharyngoesophageal diverticula have occurred in 0.1 percent of 20,000 routine barium examinations, classically in elderly white males, and they tend to enlarge progressively with time. Presenting symptoms include dysphagia associated with the spontaneous regurgitation of undigested, bland material, often interrupting eating or drinking. The dysphagia can be severe enough to cause debilitation and severe weight loss. Chronic aspiration and repetitive respiratory infection are common associated complaints.

The diagnosis is established by a barium swallow. Endoscopy is potentially dangerous, owing to obstruction of the true esophageal lumen and the attendant risk of diverticular perforation.

The low morbidity and mortality of a cricopharyngeal and upper esophageal myotomy has encouraged a liberal approach toward its use for almost any problem in the oropharyngeal phase of swallowing. This attitude has resulted in an overall success rate of only 64 percent.

The myotomy can be performed under local or general anesthesia through an incision along the anterior border of the left sternocleidomastoid muscle. The pharynx and cervical esophagus are exposed by retracting the sternocleidomastoid muscle and carotid sheath laterally and the trachea and larynx medially. The diverticulum is carefully freed from the overlying areolar tissue to expose its neck just below the inferior pharyngeal constrictor and above the cricopharyngeus muscle. Placement of a nasogastric tube into the cricopharyngeal sphincter helps in localization of the structures. The myotomy is extended cephalad, dividing 1–2 cm of inferior constrictor muscle and caudally dividing the cricopharyngeal muscle and the cervical esophagus for a length of 4–5 cm.

If the diverticulum is present after a myotomy, it may be inverted to the prevertebral fascia using a permanent suture. If the diverticulum is excessively large, a diverticulectomy should be performed. Recurrence of a Zenker's diverticulum is seen late, presumably because of persistence of the underlying loss of compliance of the cervical esophagus when a myotomy is not performed.

MOTILITY DISORDERS OF THE ESOPHAGEAL BODY AND LOWER ESOPHAGEAL SPHINCTER

With standard esophageal manometry, specific primary esophageal motility disorders have been recognized. These include achalasia, diffuse esophageal spasm, the so-called nutcracker esophagus, and the hypertensive LES. Twenty-four-hour monitoring of esophageal motor activity has shown that there are significant differences in the classification of esophageal motor disorders when based on standard manometry or ambulatory monitoring.

ACHALASIA

The best known and understood primary disorder of the esophagus is achalasia, a primary disorder of the LES. Abnormal esophageal peristalsis develops as a result of the increased resistance provided

by the nonrelaxing LES. Observations in patients with pseudoachalasia due to tumor, a tight stricture, or a too tight antireflux procedure indicate that dysfunction of the esophageal body can be caused by the increased outflow obstruction. That esophageal peristalsis can return in patients with classic achalasia following dilatation or myotomy provides further support for a primary disease of the LES.

The pathogenesis of achalasia is presumed to be a neurogenic degeneration. In patients with the disease, degenerative changes have been shown in the vagus nerve and in the ganglia in the Auerbach plexus of the esophagus itself. Degeneration results in hypertension of the LES, elevation of intraluminal esophageal pressure, and a subsequent loss of peristalsis in the body of the esophagus. As the disease progresses, the esophagus becomes massively dilated and tortuous.

DIFFUSE AND SEGMENTAL ESOPHAGEAL SPASM

This esophageal motor disorder is characterized clinically by substernal chest pain and/or dysphagia. Diffuse esophageal spasm is primarily a disease of the esophageal body and is a rare condition occurring about five times less frequently than achalasia.

Hypertrophy of the muscular layer of the esophageal wall and degeneration of the esophageal branches of the vagus nerve have been observed. The classic manometric finding is simultaneous and repetitive esophageal contractions of abnormally high amplitude or long duration. The esophagus retains a degree of peristaltic performance in excess of that seen in achalasia. The LES usually shows normal resting pressure and relaxation of deglutition. In patients with advanced disease, the tertiary contractions appear helical and are termed "corkscrew" esophagus.

NUTCRACKER ESOPHAGUS

The disorder termed "nutcracker"' or "supersqueezer" esophagus is the most frequent of the primary esophageal motility disorders. It is a manometric abnormality characterized by peristaltic esophageal contractions with peak amplitudes greater than 2 standard deviations above the normal values in individual laboratories. Esophageal myotomy is a therapeutic option for patients with dysphagia and diffuse esophageal spasm but is of questionable value in patients with chest pain thought secondary to nutcracker esophagus.

HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER

This disorder is characterized by an elevated basal pressure of the LES with normal relaxation and normal propulsion in the esophageal body. About half of these patients have associated

motility disorders of the esophageal body, particularly hypertensive peristalsis and simultaneous contractions. Myotomy of the LES may be indicated in patients not responding to medical therapy or dilatation.

NONSPECIFIC ESOPHAGEAL MOTOR DISORDERS

Many patients complaining of dysphagia or chest pain of noncardiac origin demonstrate a number of contraction patterns on esophageal manometry that are clearly out of the normal range but do not meet the criteria of a primary esophageal motility disorder. Surgery plays no role in the treatment of these disorders unless there is an associated diverticulum. Progression from a nonspecific esophageal motility disorder to classic diffuse esophageal spasm has been demonstrated. Twenty-four-hour esophageal pH and motility monitoring has shown that an increased esophageal exposure to gastric juice is common in patients diagnosed as having a nonspecific esophageal motility disorder.

DIVERTICULA OF THE ESOPHAGEAL BODY

An esophageal diverticulum most commonly occurs with nonspecific motility disorders but can occur with all the primary motility disorders. The motility disorder is usually diagnosed before development of the diverticulum.

Epiphrenic diverticula arise from the terminal third of the thoracic esophagus. They are classically "pulsion" diverticula and have been associated with diffuse spasm, achalasia, or nonspecific motor abnormalities in the body of the esophagus.

When associated with esophageal motility disorders, esophageal myotomy from the distal extent of the diverticulum to the stomach is indicated; otherwise, one can expect a high incidence of suture-line rupture. When a large diverticulum is associated with a hiatal hernia, the diverticulum is excised, a myotomy is performed, and the hernia is repaired because of the high incidence of postoperative reflux when it is omitted.

Midesophageal or traction diverticula were noted frequently in patients who had mediastinal lymph node involvement with tuberculosis. It is now believed that some diverticula in the midesophagus also may be caused by motility abnormalities.

Most midesophageal diverticula are asymptomatic and may be ignored. Patients with symptoms of dysphagia, regurgitation, chest pain, or aspiration in whom a diverticulum is discovered should be investigated thoroughly for an esophageal motor abnormality and treated appropriately.

The indication for surgical intervention is the degree of symptomatic disability. If a motor abnormality is documented, a myotomy should be performed.

OPERATIONS

Long Esophageal Myotomy for Motor Disorders of the Esophageal Body A long esophageal myotomy is indicated for dysphagia caused by any motor disorder characterized by segmental or generalized simultaneous contractions when symptoms are not relieved by medical therapy. Such disorders include diffuse and segmental esophageal spasm, vigorous achalasia, and nonspecific motility disorders associated with a mid- or epiphrenic esophageal diverticulum. Twenty-four-hour ambulatory studies aid in the identification of patients who might benefit from a surgical myotomy. The symptom of chest pain alone is not an indication for a surgical procedure.

Most surgeons extend the myotomy distally across the LES to reduce outflow resistance. Consequently, some form of antireflux protection is needed to avoid gastroesophageal reflux if there has been extensive dissection of the cardia. A partial fundoplication will not add resistance to interfere with the ability of the myotomized esophagus to empty.

A myotomy is performed through all muscle layers extending distally over the stomach 1–2 cm below the gastroesophageal junction and proximal on the esophagus over the distance of the manometric abnormality. The muscle layer is dissected from the mucosa laterally for a distance of 1 cm. The gastric fundic flap is sutured to the margins of the myotomy over the distal 4 cm and replaced into the abdomen. This maintains separation of the muscle and acts as a partial fundoplication to prevent reflux.

If an epiphrenic diverticulum is present, it is excised by dividing the neck and closing the muscle. The myotomy is then performed on the opposite esophageal wall. If a midesophageal diverticulum is present, the myotomy is made so that it includes the muscle around the neck, and the diverticulum is inverted and suspended by attaching it to the paravertebral fascia of the thoracic vertebra.

Postoperative motility studies show that myotomy reduces the amplitude of esophageal contractions to near zero, eliminating both simultaneous and peristaltic waves. A delicate balance exists between success and failure of a long esophageal myotomy, and this emphasizes the importance of preoperative motility studies.

Myotomy of the Lower Esophageal Sphincter Secondary to reflux disease, achalasia is the most common functional disorder of the esophagus to require surgical intervention. Relief can be achieved by an uncontrolled instrumental rupture of the sphincter muscle or by a controlled surgical myotomy. Surgical myotomy is associated with low morbidity and gives better long-term results. In practice, most patients are dilated. An inherent risk of pneumatic dilatation is rupture of the esophagus (as high as 15 percent).

In performing a surgical myotomy of the LES, there are four important principles: (1) minimal dissection of the cardia, (2) adequate distal myotomy to reduce outflow resistance, (3) prevention of postoperative reflux, and (4) prevention of rehealing of the myotomy site.

A modified Heller myotomy is performed through all muscle layers, extending distally over the stomach to 1–2 cm below the junction and proximally on the esophagus for 4–5 cm. The cardia is reconstructed by suturing the gastric fundic flap to the margins of the myotomy to prevent rehealing of the myotomy site and to provide reflux protection in the area of the divided sphincter.

If simultaneous esophageal contractions are associated with the sphincter abnormality, the so-called vigorous achalasia and then the myotomy should extend over the distance of the motility abnormality, as mapped by the preoperative motility study. When an antireflux procedure is added to the myotomy, it should be a partial fundoplication. A 360-degree fundoplication is associated with progressive retention of swallowed food, regurgitation, and aspiration. It has been shown that video-assisted endosurgical myotomy can be accomplished safely either laparoscopically or thoracoscopically.

Esophageal Resection for End-Stage Motor Disorders of the Esophagus Patients with dysphagia and long-standing benign disease whose esophageal function has been destroyed by disease or multiple surgical procedures are best managed by esophagectomy. Weak contractions, failure of the distal esophageal sphincter to relax, and loss of the secondary peristaltic reflex signal end-stage motor disease.

CANCER OF THE ESOPHAGUS

Squamous carcinoma accounts for most esophageal carcinomas. Its incidence is highly variable, ranging from approximately 20 per 100,000 in the United States and Britain to 540 per 100,000 in the Guriev District of Kazakhstan. Environmental factors such as food additives (nitroso compounds) and deficiencies (zinc and molybdenum) have been suggested. In Western societies, smoking and alcohol consumption are strongly linked with squamous carcinoma.

Adenocarcinoma of the esophagus, once an unusual malignancy, is diagnosed with increasing frequency and accounts for over 50 percent of the esophageal cancer in some Western countries. The most important etiologic factor in the development of primary adenocarcinoma of the esophagus is a metaplastic columnar-lined, or Barrett's, esophagus, which occurs as a complication in approximately 10 percent of patients with gastroesophageal reflux

disease. This risk is similar to the risk for developing cancer of the lung in a person with a 20 pack-year history of smoking. There is no reliable evidence that medical therapy or an antireflux procedure removes the risk of neoplastic transformation; malignancy in Barrett's esophagus is curable if detected at an early stage.

Clinical Manifestations Esophageal cancer is a disease of advancing age, with dysphagia and weight loss the most common symptoms. Extension of the primary tumor can cause stridor, coughing, choking, aspiration pneumonia, severe bleeding, or vocal cord paralysis. Systemic metastases may cause jaundice or bone pain.

Dysphagia usually presents late in the natural history of the disease, when more than 60 percent of the esophageal circumference is infiltrated with cancer. Thus the disease is usually far advanced at the time of diagnosis, and greater than 40 percent of patients will have evidence of distant metastases.

Staging (Table 23-1) The stage of the disease is determined by the depth of penetration of the primary tumor and the presence of

TABLE 23-1
STAGING OF CANCER OF THE ESOPHAGUS AND CARDIA: MODIFIED WNM CRITERIA

Stage	Classification			No. of Patients	%5-Year Survival	P Value
0	W_0	N_0	M_0	38	88.2	} 0.0002
I	W_0	N_1	M_0	59	50.3	
	W_1	N_1	M_0			
II	W_1	N_1	M_0	95	22.5	} 0.0005
	W_2	N_0	M_0			
III	W_2	N_1	M_0	138	10.7	} 0.02
	W_1	N_2	M_0			
	W_0	N_2	M_0			} 0.0001
IV	Any W	Any N	M_1	33	0	
				408		

SOURCE: From Ellis FH, Heatley GJ, Krosna MJ, Williamson WA, Balogh K: Esophagogastrectomy for carcinoma of the esophagus and cardia; A comparison of findings and results after standard resection in three consecutive 8-year time intervals, using improved staging criteria. *J Thorac Cardiovasc Surg* 14:836, 1997, p 836, with permission.

lymph node and distant organ metastases. Classification is based on imaging techniques. Computed tomographic (CT) scans only confirm clinical findings when extensive disease is present. Magnetic resonance imaging (MRI) has so far not been shown to be superior. Preoperative staging shows only minor differences in long-term survival among various stages of the disease. Only metastasis to lymph nodes and tumor penetration of the esophageal wall have a significant and independent influence on prognosis.

Tumor size, cell type, degree of cellular differentiation, and location of the tumor within the esophagus have no effect on survival of early lesions. Resectable esophageal tumors, which meet the criteria of no wall penetration and/or less than four regional lymph node metastases, could be defined as potentially curable.

The important goal of clinical staging of esophageal carcinoma is to determine cure or palliation. Making the selection for cure or palliation identifies the mission of the operation. It emphasizes the use of durable reconstruction in patients operated on for cure and identifies patients for multimodal therapy if surgical cure is not possible.

Clinical Approach *Patient Selection* The selection of surgical therapy for patients with carcinoma of the esophagus depends on the anatomic stage of the disease, the swallowing capacity of the patient, and the location of the primary tumor (Fig. 23-6).

Primary malignant tumors of the cervical esophagus are more common in females and drain directly into the paratracheal and deep cervical or internal jugular lymph nodes with minimal flow in a longitudinal direction. Lesions not fixed to the spine, not invading major vessels, and not having fixed cervical lymph node metastases should be resected.

Low cervical lesions that reach the level of the thoracic inlet are usually unresectable because of early invasion of the great vessels and trachea. The length of the esophagus below the cricopharyngeus is insufficient to allow intubation or construction of a proximal anastomosis for a bypass procedure.

Tumors that arise within the middle or upper third of the thoracic esophagus lie too close to the trachea and aorta to allow an en bloc resection. Only tumors that have not penetrated through the esophageal wall and have not metastasized to the regional lymph nodes are potentially curable.

Tumors of the lower esophagus and cardia are usually adenocarcinomas. Squamous cell carcinoma of the lower esophagus, however, does occur. Both tumors are amenable to en bloc resection. The longitudinal lymph flow in the esophagus can result in skip areas with small foci of tumor above the primary lesion, un-

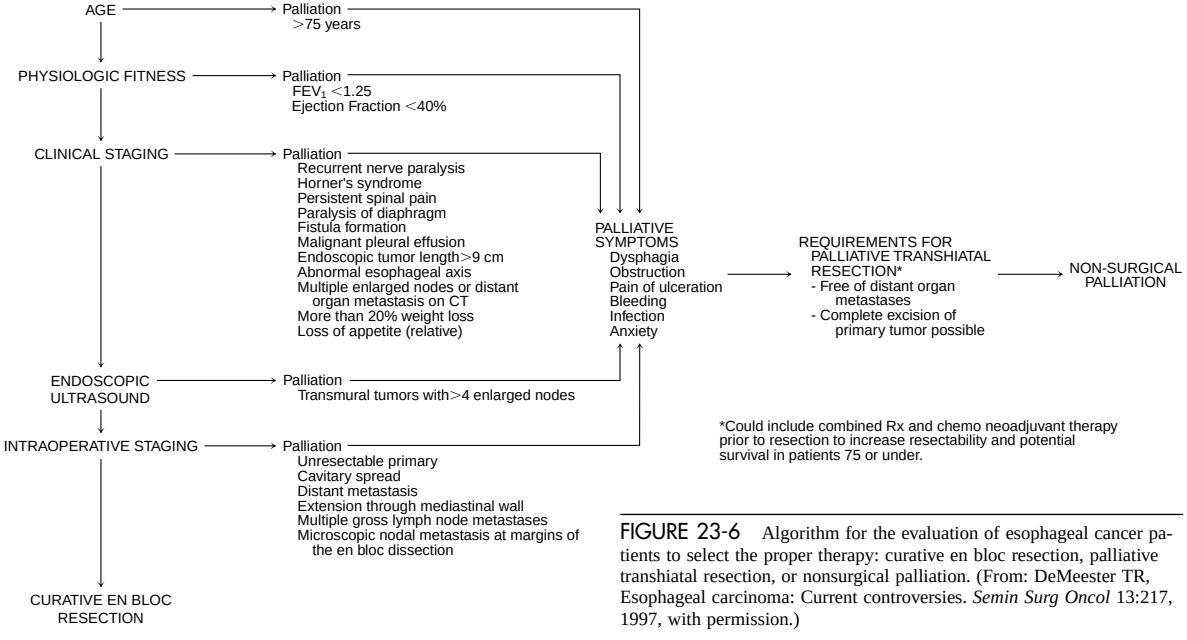

FIGURE 23-6 Algorithm for the evaluation of esophageal cancer patients to select the proper therapy: curative en bloc resection, palliative transhiatal resection, or nonsurgical palliation. (From: DeMeester TR, Esophageal carcinoma: Current controversies. *Semin Surg Oncol* 13:217, 1997, with permission.)

derscoring the importance of a wide resection of esophageal tumors. A curative resection requires a cervical division of the esophagus and a greater than 50 percent proximal gastrectomy. This compromises the length of the stomach and esophagus remaining to reestablish gastrointestinal continuity and necessitates a colon interposition.

An en bloc resection for cure of carcinoma of the esophagus is unwise in patients older than 75 years because of the additional operative risk in face of a short life expectancy.

Physiologic Status Patients undergoing esophageal resection should have sufficient cardiopulmonary reserve to tolerate the operation. The forced expiratory volume in 1 s (FEV_1) should be 2 L or more; an FEV_1 of less than 1.25 L carries a 40 percent risk of death from respiratory insufficiency within 4 years. Echocardiography and thallium imaging provide accurate information on wall motion, ejection fraction, and myocardial blood flow. A resting ejection fraction of less than 40 percent is an ominous sign.

Clinical Staging Clinical factors that indicate an advanced stage of carcinoma are recurrent nerve paralysis, Horner syndrome, spinal pain, paralysis of the diaphragm, fistula formation, and malignant pleural effusion. Factors that make surgical cure unlikely include a tumor greater than 8 cm in length, abnormal axis of the esophagus on a barium radiograph, enlarged lymph nodes on CT, a weight loss of greater than 20 percent, and loss of appetite. Staging depends on the length of the tumor measured with endoscopy and the degree of wall penetration and lymph node metastasis seen with endoscopic ultrasound. Finding a small tumor should encourage an aggressive approach, and the smaller the tumor, the more aggressive the approach should be.

Intraoperative Staging Intraoperative staging is designed for intraoperative selection of favorable candidates for a curative en bloc resection. Patients with a tumor that penetrates through the esophageal wall or multiple or distant lymph node metastases have a poor survival.

Curative en bloc dissection is abandoned if intraoperative staging reveals an unresectable primary tumor, cavitary spread of the tumor, distant organ metastasis, extension of the tumor through the mediastinal pleura, multiple gross lymph node metastases, or microscopic evidence of lymph node involvement at the margins of the en bloc resection. If the tumor does not extend through the esophageal wall and there are fewer than six lymph nodes positive, the 5-year survival is 75 percent (Fig. 23-7).

FIGURE 23-7 Algorithm of intraoperative decision making for cancer of the lower esophagus and cardia.

Management of Patients Excluded from Curative Resection If the patient is physiologically fit, a simple esophageal resection and reconstruction with esophagogastrostomy offers the best palliation. If an obstructing tumor cannot be resected because of invasion of the trachea, aorta, or heart, or when the patient's general condition precludes an operative procedure, a number of techniques, including bouginage, intubation, laser ablation, and electrical coagulation, are available and can be used alone or in combination.

Surgical Treatment

The nutritional status of the patient is of paramount importance for the outcome of an esophageal resection. A feeding jejunostomy tube provides the most reliable and safest method for nutritional support in patients who cannot consume an oral diet and have a functionally normal small bowel. The jejunostomy is performed as a separate procedure to allow for preoperative nutritional support. Otherwise, the jejunostomy tube is placed at the time of esophageal resection.

Cervical Esophageal Cancer Tumors treated with radiation therapy initially tend to recur locally as well as systemically. Patients who undergo surgical therapy have few local recurrences of the tumor provided total excision was possible, but they succumb to metastatic disease. Improvements in the techniques of immediate esophageal reconstruction have reduced the complications of the surgical treatment of this disease and have encouraged a more aggressive surgical approach. Palliation is better achieved in patients who underwent esophagectomy with immediate gastric pull-up than in those who underwent primary radiation therapy or chemotherapy.

A total laryngectomy in combination with esophagectomy is necessary, and simultaneous en bloc bilateral neck lymph node dissection is done, sparing the jugular veins on both sides.

The thoracic esophagus is removed by blunt dissection through cervical and upper abdominal incisions, and gastrointestinal continuity is reestablished by pulling the stomach up through the esophageal bed.

Tumors of the Thoracic Esophagus and Cardia A combined transthoracic and transhiatal approach is used to remove tumors in the middle or upper third of the thoracic esophagus because of their tendency to adhere to hilar structures. Gastrointestinal continuity is reestablished by pulling up the previously prepared stomach through the posterior mediastinum and anastomosing it to the esophagus in the neck.

To remove tumors in the lower third of the thoracic esophagus and cardia, an en bloc resection for cure or a transhiatal removal for palliation is preferred. The en bloc resection is done through three incisions: right posterolateral thoracotomy with en bloc dissection of the distal esophagus, mobilization of the esophagus, closure of the thoracotomy, and repositioning of the patient in the recumbent position; an upper midline abdominal incision and en bloc dissection of the stomach and associated lymph nodes; and a left neck incision, transhiatal removal of the previously en bloc dissected distal esophagus and mobilized proximal esophagus, and left colon interposition. If an incurable situation is identified, a palliative resection is performed in a manner similar to that described for tumors of the middle and upper thoracic esophagus. A standard left thoracotomy, or an Ivor Lewis approach, is not advocated because of the proven need to resect long lengths of the esophagus to eradicate submucosal spread, the higher morbidity of a thoracic anastomotic leak, and the high incidence of esophagitis secondary to reflux following an intrathoracic anastomosis. Some surgeons advocate that if the morbidity of the procedure is acceptable, aggressive surgical attempts at cure with an en bloc dissection are justified.

Alternative Therapies

Primary treatment with radiation therapy does not produce results comparable with those obtained with surgery. Its use is restricted to patients who are not candidates for surgery. There is a reluctance to treat patients with advanced disease.

The proposal to use adjuvant chemotherapy in the treatment of esophageal cancer began when it became evident that most patients develop postoperative systemic metastases without local recurrence. Systemic chemotherapy may be helpful if the cells are sensitive to the agent. On the other hand, chemotherapy may be a hindrance because of its immunosuppressive properties. Randomized, prospective studies with squamous cell carcinoma have shown no survival benefit with preoperative chemotherapy over surgery alone. A complete response to chemotherapy occurred only in 6 percent of patients. With the exception of the potential to improve resectability of tumors located above the carina, the benefits of preoperative chemotherapy are questionable.

Preoperative combination chemoradiotherapy using cisplatin and 5-fluorouracil in combination with radiotherapy has been reported to be beneficial in both adenocarcinoma and squamous cell carcinoma of the esophagus. Of all the randomized, prospective studies, only one showed any survival benefit with preoperative chemoradiotherapy over surgery alone.

Current data support giving chemoradiotherapy as a matter of routine in a limited number of clinical settings including (1) preoperatively to reduce tumor size in a young person with surgically incurable squamous cell carcinoma above the carina and (2) chemotherapy as salvage therapy for recurrent systemic disease after surgical resection (Fig. 23-8).

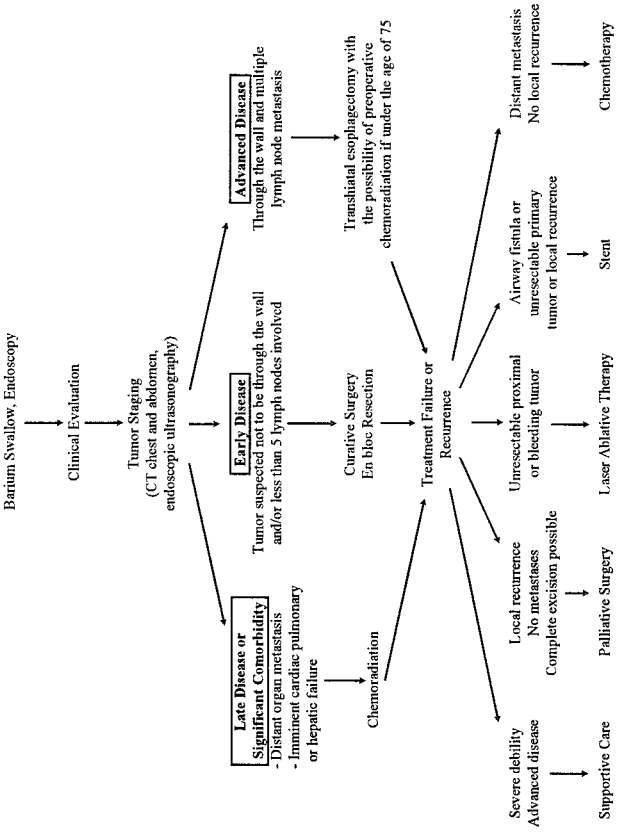

FIGURE 23-8 Suggested global algorithm for the management of carcinoma of the esophagus.

SARCOMAS

Sarcomas and carcinosarcomas are rare neoplasms. They present with the symptom of dysphagia, which does not differ from the dysphagia associated with the more common epithelial carcinoma. A barium swallow usually shows a large polypoid intraluminal esophageal mass. The smooth polypoid nature of the lesion is distinctive enough to suggest the presence of a sarcoma rather than the more common ulcerating, stenosing carcinoma. Esophagoscopy commonly shows an intraluminal necrotic mass. Accurate diagnosis by endoscopic biopsy is difficult because of surface necrosis.

Polypoid sarcomas of the esophagus remain superficial to the muscularis propria and are less likely to metastasize to regional lymph nodes. Thus the presence of a large polypoid tumor should not deter the surgeon from resecting the lesion. Sarcomatous lesions of the esophagus can be divided into epidermoid carcinomas with spindle cell features such as carcinosarcoma or true sarcomas such as leiomyosarcoma, fibrosarcoma, and rhabdomyosarcoma.

Surgical resection is the treatment of choice, since radiation therapy has little success. Surgical resection is responsible for the majority of the reported 5-year survivals.

BENIGN TUMORS AND CYSTS OF THE ESOPHAGUS

Benign tumors and cysts of the esophagus are relatively uncommon and are divided into those within the muscular wall and those within the lumen of the esophagus. The intramural lesions are either solid tumors or cysts; the most common are leiomyomas. Fibromas, myomas, fibromyomas, and lipomyomas, lipomas, neurofibromas, hemangiomas, osteochondromas, granular cell myoblastomas, and glomus tumors are all quite rare.

Intraluminal lesions are polypoid or pedunculated growths that originate in the submucosa, develop into the lumen, and are covered with normal stratified squamous epithelium. These tumors have a rich vascular supply; myxoma, myxofibroma, fibroma, and fibrolipoma are examples. Pedunculated intraluminal tumors should be removed.

Leiomyomas

Leiomyomas constitute more than 50 percent of benign esophageal tumors. The average age at presentation is 38 years. Leiomyomas are twice as common in males than in females. Because they

originate in smooth muscle, 90 percent are located in the lower two-thirds of the esophagus.

Typically, leiomyomas are oval and remain intramural, and the overlying mucosa is freely movable and normal in appearance. Dysphagia and pain are the most common complaints. Bleeding related to the tumor is so rare that when hematemesis or melena occurs in a patient with an esophageal leiomyoma, other causes should be investigated.

A barium swallow is the most useful method to demonstrate a leiomyoma of the esophagus. The tumor appears as a smooth, semilunar or crescent-shaped filling defect, sharply demarcated, and covered and surrounded by normal mucosa. The mass should not be biopsied because of an increased chance of mucosal perforation at the time of surgical enucleation.

Leiomyomas should be removed surgically; the majority can be removed by simple enucleation. Large lesions or those involving the gastroesophageal junction may require esophageal resection.

Esophageal Cysts

Cysts may be congenital or acquired. Congenital cysts are lined wholly or partly by columnar ciliated epithelium of the respiratory type, by glandular epithelium of the gastric type, by squamous epithelium, or by transitional epithelium. Acquired retention cysts also do occur, probably from obstruction of the excretory ducts of the esophageal glands.

Enteric and bronchogenic cysts are the most common and arise as a result of developmental abnormalities during the formation and differentiation of the lower respiratory tract, esophagus, and stomach from the foregut.

Cysts vary in size and are usually located intramurally in the middle of the lower third of the esophagus. Their symptoms are similar to those of a leiomyoma. Surgical excision is the preferred treatment, with most able to be enucleated without damage to the mucosa.

ESOPHAGEAL PERFORATION

Perforation of the esophagus constitutes a true emergency. It most commonly occurs following diagnostic or therapeutic procedures. Spontaneous perforation, referred to as *Boerhaave's syndrome*, is the etiologic cause for only 15 percent of such patients, foreign bodies for 14 percent, and other trauma 10 percent. Pain is a striking and consistent symptom. If subcutaneous emphysema is present, the diagnosis is almost certain.

Spontaneous rupture of the esophagus has a poor survival because of the delay in recognition and treatment. Air or an effusion in the pleural space shown on the chest radiograph is often misdiagnosed as a pneumothorax or pancreatitis. If the chest radiograph is normal, the diagnosis is often confused with a myocardial infarction or dissecting aneurysm.

Spontaneous rupture usually occurs in the left pleural cavity or just above the gastroesophageal junction. During vomiting, high peaks of intragastric pressure can be recorded, frequently exceeding 200 mmHg. When this pressure exceeds 150 mmHg, rupture of the esophagus is apt to occur. When a hiatal hernia is present and the sphincter remains exposed to abdominal pressure, the lesion produced is usually a Mallory-Weiss mucosal tear, and bleeding rather than perforation is the problem.

Diagnosis Abnormalities on the chest radiograph can be variable and should not be depended on to make the diagnosis. The presence of mediastinal emphysema, a strong indicator of perforation, takes at least 1 h to be demonstrated, and mediastinal widening secondary to edema may not occur for several hours. In cervical perforation, cervical emphysema is common and mediastinal emphysema rare; the converse is true for thoracic perforations. A pleural effusion secondary to inflammation of the mediastinum occurs late.

The diagnosis is confirmed with a contrast esophagram; water-soluble Gastrografin is preferred. There is a 10 percent false-negative rate. When the patient is upright, the passage of water-soluble contrast material can be too rapid to demonstrate a small perforation. The studies should be done with the patient in the right lateral decubitus position to fill the whole length of the esophagus, allowing the actual site of perforation to be shown.

Management The key to optimal management is early diagnosis. The most favorable outcome is obtained following primary closure of the perforation within 24 h, resulting in 80–92 percent survival. The most common location for the injury is the left lateral wall of the esophagus just above the gastroesophageal junction. The edges of the injury are trimmed and closed. The closure is reinforced with the use of a pleural patch or construction of a Nissen fundoplication.

After 24 h, survival decreases to less than 50 percent. If the delay approaches 24 h and the tissues are inflamed, division of the cardia and resection of the diseased portion of the esophagus are recommended. The remainder of the esophagus is mobilized, and as much normal esophagus as possible is saved and is brought out as an end-cervical esophagostomy. The contaminated mediastinum

is drained, and a feeding jejunostomy tube is inserted. The recovery from sepsis is often immediate, dramatic, and reflected by a marked change in the patient's course in 24 h.

Nonoperative management of the esophageal perforation has been advocated in selected patients. Conservative management should not be used in patients who have free perforations into the pleural space. Cameron proposed three criteria for the nonoperative management of esophageal perforation: the barium swallow must show the perforation to be contained and drain well back into the esophagus, mild symptoms should be present, and there should be minimal evidence of clinical sepsis.

CAUSTIC INJURY

Accidental caustic injuries occur mainly in children. In adults and teenagers, the swallowing of caustic liquids is usually deliberate during suicide attempts.

Pathology Caustic substances cause both an acute and chronic injury. Alkalies dissolve tissue and, therefore, penetrate more deeply; acids cause a coagulative necrosis that limits their penetration. There is a correlation between the depth of lesion and the concentration of sodium hydroxide solution. Esophageal contractions are weakest at the striated–smooth muscle interface. Clearance from this area may be somewhat slower, so caustic substances are in contact longer with the mucosa and affect this level more than in the lower portions.

The lesions caused by lye injury occur in three phases. In the acute necrotic phase, lasting 1–4 days after injury, there is a coagulation and an intense inflammatory reaction. In the ulceration and granulation phase, starting 3–5 days after injury, the superficial necrotic tissue sloughs, leaving an ulcerated, acutely inflamed base, and granulation tissue fills the defect. Third is the phase of cicatrization and scarring, which begins the third week following injury. The previously formed connective tissue begins to contract, resulting in narrowing of the esophagus. During this period, efforts must be made to reduce stricture formation.

Clinical Manifestations The clinical picture of an esophageal burn is determined by the degree and extent of the lesion. Early complaints consist of pain in the mouth and substernal region, hypersalivation, pain on swallowing, and dysphagia. Fever and bleeding can occur, and frequently the patient vomits. During the scarring phase, the complaint of dysphagia reappears and is due to

fibrosis and narrowing of the esophagus. If dysphagia does not develop within 8 months, it is unlikely that a stricture will occur.

Early esophagoscopy is advocated to establish the presence of an esophageal injury. The scope should not be introduced beyond the proximal esophageal lesion in order to lessen the possibility of perforation. Radiographic examination is important in later follow-up to identify strictures.

Treatment The immediate treatment consists of limiting the burn by swallowing neutralizing agents within the first hour. Lye or other alkali can be neutralized with half-strength vinegar, lemon juice, or orange juice. Acid can be neutralized with milk, egg white, or antacids. Emetics are contraindicated because vomiting renews the contact of the caustic substance with the esophagus and can contribute to perforation if vomiting is too forceful. Hypovolemia is corrected, and broad-spectrum antibiotics are administered to lessen the inflammatory reaction and prevent infectious complications. A feeding jejunostomy tube is inserted to provide nutrition. Oral feeding can be started when the dysphagia of the initial phase has regressed. Dilatations can be started the first day after the injury with the aim of preserving the esophageal lumen. This approach is controversial in that dilatations can traumatize the esophagus. The use of steroids to limit fibrosis is debatable.

The presence of extensive necrosis of the esophagus frequently leads to perforation and is best managed by resection. When there is extensive gastric involvement, the esophagus is nearly always necrotic or severely burned, and total gastrectomy and near-total esophagectomy are necessary.

Some authors have advocated the use of an intraluminal esophageal stent in patients who are found to have evidence of esophagogastric necrosis; a biopsy of the posterior gastric wall should be performed to exclude occult injury. Esophagoscopy should be done if strictures are present, and dilatation should be initiated. Antegrade and retrograde dilatations with a Tucker bougie have been satisfactory. The length of time the surgeon should persist with dilatation before consideration of esophageal resection is problematic. If during the course of treatment an adequate lumen cannot be established or maintained, operative intervention should be considered.

Currently, the stomach, jejunum, and colon are the organs used to replace the esophagus, either through the posterior mediastinum or the retrosternal route. Free jejunal grafts based on the superior thyroid artery have provided excellent results. Minor errors of judgment or technique may lead to serious or even fatal complications.

The site of the upper anastomosis depends on the extent of the pharyngeal and cervical esophageal damage encountered. Recovery

is long and may require several endoscopic dilatations and often reoperations. Sleeve resections of short strictures are not successful because the anastomosis is carried out in a diseased area.

The management of a bypassed damaged esophagus after injury is problematic. If the esophagus is left in place, ulceration from gastroesophageal reflux or the development of carcinoma must be considered. However, the extensive dissection necessary to remove the esophagus has a significant morbidity. Leaving the esophagus in place preserves the function of the vagus nerves and, in turn, the function of the stomach. Most experienced surgeons recommend that the esophagus be removed unless the operative risk is unduly high.

DIAPHRAGMATIC HERNIAS

With the advent of clinical radiography, it became evident that a diaphragmatic hernia was a relatively common abnormality and was not always accompanied by symptoms. Three types of esophageal hiatal hernias were identified: the sliding hernia, the paraesophageal hernia, and the combined or mixed hernia. The end stage of a hernia occurs when the whole stomach migrates up into the chest by rotating 180 degrees, with the cardia and pylorus as fixed points. In this situation, the abnormality is usually referred to as an *intrathoracic stomach.*

Incidence and Etiology The true incidence of a hiatal hernia in the overall population is difficult to determine. Sliding hiatal hernia is seven times more frequent than a paraesophageal hernia. Structural deterioration of the phrenicoesophageal membrane over time may explain the higher incidence of hiatal hernias in the older age group. The phrenicoesophageal membrane yields to stretching in the cranial direction due to the persistent intraabdominal pressure and the tug of esophageal shortening on swallowing. The persistent posterior fixation of the cardia to the preaortic fascia and the median arcuate ligament is the only essential difference between a sliding and paraesophageal hernia.

Clinical Manifestations The clinical presentation of a paraesophageal hiatal hernia differs from that of a sliding hernia. There is usually a higher prevalence of symptoms of dysphagia and postprandial fullness with paraesophageal hernias, but the typical symptoms of heartburn and regurgitation are dominant in sliding hiatal hernia. Both are caused by an underlying mechanical deficiency of the cardia.

About one-third of patients with a paraesophageal hernia complain of hematemesis due to the recurrent bleeding from ulceration of the gastric mucosa in the herniated portion of the stomach. Respiratory complications are frequently associated with a paraesophageal hernia and may consist of recurrent pneumonia from aspiration. With time, the stomach migrates into the chest and can cause intermittent obstruction due to the rotation. The presence of a paraesophageal hernia can be life-threatening and lead to excessive bleeding or volvulus with acute gastric obstruction or infarction.

The symptoms of sliding hiatal hernias are usually due to functional abnormalities associated with gastroesophageal reflux and include heartburn, regurgitation, and dysphagia. These patients have a mechanically defective LES.

There are a group of patients with sliding hiatal hernias not associated with reflux disease who have dysphagia due to an obstruction of the swallowed bolus by diaphragmatic impingement on the herniated stomach. These patients usually have a mechanically competent sphincter, but the impingement of the diaphragm on the stomach can result in propelling the contents of the supradiaphragmatic stomach into the esophagus and pharynx, resulting in pharyngeal regurgitation and aspiration. This abnormality is confused with typical gastroesophageal reflux disease. Surgical reduction of the hernia results in relief.

Diagnosis A radiograph of the chest with the patient in the upright position can diagnose a hiatal hernia if it shows an air-fluid level behind the cardiac shadow. The paraesophageal hiatal hernia is a permanent herniation of the stomach; a barium swallow provides the diagnosis in virtually every case.

Fiberoptic esophagoscopy is very useful in the diagnosis and classification of a hiatal hernia because of the ability to retroflex the scope. A sliding hiatal hernia can be identified by noting a gastric pouch lined with rugal folds extending above the impression caused by the crura of the diaphragm. A paraesophageal hernia is identified on retroversion of the scope by noting a separate orifice adjacent to the gastroesophageal junction into which gastric rugal folds ascend.

Pathophysiology It has been assumed that a sliding hernia is associated with an incompetent distal esophageal sphincter, whereas a paraesophageal hiatal hernia constitutes a pure anatomic entity and is not associated with an incompetent cardia. Accordingly, surgical therapy has been directed toward restoration of the physiology of the cardia in patients with a sliding hernia and simply

reducing the stomach into the abdominal cavity and closing the crura for a paraesophageal hernia.

Physiologic testing with 24-h esophageal pH monitoring has shown that paraesophageal hiatal hernia can be associated with pathologic gastroesophageal reflux. Physiologic studies have shown that the competency of the cardia depends on an interrelationship of distal esophageal sphincter pressure, its length exposed to the positive-pressure environment of the abdomen, and its overall length. A deficiency in any one of these manometric characteristics of the sphincter is associated with incompetency of the cardia regardless of whether the hernia is present. Patients with a paraesophageal hernia who have incompetent cardias have been shown to have a distal esophageal sphincter with normal pressure but a shortened overall sphincter length and its displacement outside the positive-pressure environment of the abdomen.

Therapy In a sliding hernia, even though the sphincter appears to be within the chest on a radiographic barium study, it still can be exposed to abdominal pressure because of the surrounding hernia sac that functions as an extension of the abdominal cavity. A high insertion of the phrenicoesophageal membrane into the esophagus gives adequate length of the distal esophageal sphincter exposed to abdominal pressure. A low insertion gives inadequate length.

In summary, the cause for a mechanical incompetency of the cardia is similar regardless of the type of hernia and is identical in patients who have an incompetent cardia and no hiatal hernia. The presence of a paraesophageal hiatal hernia is an indication for surgical repair. The life-threatening complications of bleeding, infarction, and perforation recommend surgical correction even in the elderly with a shorter life expectancy. Patients with a paraesophageal hernia treated medically may die from the complications of strangulation, perforation, and exsanguinating hemorrhage secondary to acute dilatation of the herniated intrathoracic stomach without warning. Patients with a paraesophageal hernia should have elective repair of their hernia regardless of the severity of their symptoms or the size of the hernia. If surgery is delayed and repair is done on an emergency basis, there is a 19 percent operative mortality, compared with less than 1 percent for an elective repair.

Based on pathophysiologic studies, the repair of a paraesophageal hernia should include an antireflux procedure. This is particularly necessary when the operation is performed on an urgent basis without preoperative studies.

MISCELLANEOUS ESOPHAGEAL LESIONS

Plummer-Vinson Syndrome

This uncommon clinical syndrome is characterized by dysphagia associated with atrophic oral mucosa, spoon-shaped fingers with brittle nails, and chronic anemia. It characteristically occurs in middle-aged edentulous women. Iron-deficiency anemia is a common finding. Not all patients exhibit the classic syndrome, some lacking anemia, dysphagia, and an esophageal web.

Videoradiographic study and endoscopy have demonstrated a fibrous web just below the cricopharyngeus muscle as the cause of dysphagia. Treatment consists of dilatation of the web and iron therapy to correct the nutritional deficiency.

Clinical observation suggests that the esophageal web may be a drug-induced lesion. Since these patients have an iron-deficient anemia, it would be logical for physicians to prescribe ferrous sulfate, a drug known to cause esophageal injury. Malignant lesions of the oral mucosa, hypopharynx, and esophagus have been noted to occur in up to 10 percent of patients when followed long term.

Schatzki's Ring

Schatzki's ring is a thin submucosal circumferential ring in the lower esophagus at the squamocolumnar junction, often associated with a hiatal hernia. Its significance and pathogenesis are unclear. Various explanations of its origin have been put forward: It is a pleat of mucosa formed by infolding of redundant esophageal mucosa due to shortening of the esophagus; it is congenital; or it is an early stricture resulting from inflammation of the esophageal mucosa caused by chronic reflux.

Schatzki's ring is a distinct clinical entity having different symptoms. Twenty-four-hour esophageal pH monitoring showed that patients with a Schatzki's ring have a lower incidence of reflux than hiatal hernia controls. They also have better LES function.

Clinical symptoms associated with Schatzki's ring are episodes of short-lasting dysphagia during hurried ingestion of solid foods. Its treatment has varied from dilatation alone, dilatation with antireflux measures, an antireflux procedure alone, incision, and even excision of the ring.

Symptoms in patients with a ring are caused more by the presence of the ring than by gastroesophageal reflux. Furthermore, most patients with a ring but without proven reflux respond to one dilatation, whereas most patients with proven reflux require

repeated dilatation. The majority of Schatzki's ring patients without proven reflux have a history of ingestion of drugs known to be damaging to the esophageal mucosa.

Schatzki's ring is probably an acquired lesion that can lead to stenosis from chemical-induced injury by pill lodgment in the distal esophagus or by reflux-induced injury to the lower esophageal mucosa.

The best form of treatment of a symptomatic Schatzki's ring in patients who do not have reflux consists of esophageal dilatation for relief of the obstructive symptoms. In patients with a ring who have proven reflux and a mechanically defective sphincter, an antireflux procedure is necessary to obtain relief and avoid repeated dilatation.

Mallory-Weiss Syndrome

This syndrome is characterized by acute upper gastrointestinal bleeding following repeated vomiting. The mechanism is similar to spontaneous esophageal perforation, i.e., an acute increase in intraabdominal pressure against a closed glottis in a patient with a hiatal hernia.

Mallory-Weiss tears are characterized by arterial bleeding that may be massive. The diagnosis requires a high index of suspicion in the patient who develops upper gastrointestinal bleeding following prolonged vomiting or retching. Endoscopy confirms the suspicion by identifying one or more longitudinal fissures in the mucosa of the herniated stomach.

In the majority of patients the bleeding will stop spontaneously with nonoperative management. Only occasionally will surgery be required to stop blood loss. The procedure consists of laparotomy and high gastrostomy with oversewing of the linear tear.

Scleroderma

Scleroderma is a systemic disease wherein esophageal abnormalities occur in approximately 80 percent of patients. Small-vessel inflammation appears to be an initiating event, with subsequent perivascular deposition of normal collagen that may lead to vascular compromise. In the gastrointestinal tract, the predominant feature is smooth muscle atrophy. Whether the atrophy in the esophageal musculature is a primary effect or occurs secondary to the neurogenic disorder is unknown. The results of pharmacologic and hormonal manipulation suggest that scleroderma is a primary neurogenic disorder. In advanced disease, manifested by smooth muscle atrophy and collagen deposition, poor esophageal pump and a poor valve result.

The diagnosis of scleroderma can be made manometrically by the observation of normal peristalsis in the proximal striated esophagus

with absent peristalsis in the distal smooth muscle portion. The LES pressure is progressively weakened as the disease advances. Gastroesophageal reflux commonly occurs in patients with scleroderma because they have both hypotensive sphincters and poor esophageal clearance. This can lead to severe esophagitis and stricture formation.

Collis gastroplasty in combination with a Belsey antireflux repair is the usual surgical procedure for this problem. Surgery reduces esophageal acid exposure, but poor clearance of the esophagus persists. Consequently, only 50 percent of the patients have a good to excellent result. If the esophagitis is severe or there has been a previous failed antireflux procedure and the disease is associated with delayed gastric emptying, a gastric resection with Roux-en-Y esophagojejunostomy provides the best option.

Acquired Fistula

The esophagus lies in immediate contact with the membranous portion of the trachea and left bronchus, predisposing to the formation of fistulas to these structures. Most acquired esophageal fistulas communicate with the tracheobronchial tree and are secondary to esophageal or pulmonary malignancy. Clinically, these fistulas are characterized by paroxysmal coughing following the ingestion of liquids followed by recurrent or chronic pulmonary infections.

Spontaneous closure is rare owing to the presence of malignancy or a recurrent infectious process. Surgical treatment of benign fistulas consists of division of the fistulous tract, resection of irreversibly damaged lung tissue, and closure of the esophageal defect. To prevent recurrence, a pleural flap should be interposed. Treatment of malignant fistulas is difficult and can be done best by using a specially designed esophageal endoprosthesis that bridges and occludes the fistula, allowing the patient to eat.

TECHNIQUES OF ESOPHAGEAL RECONSTRUCTION

Options for esophageal substitution include gastric advancement, colon interposition, and either jejunal free transfer or advancement into the chest. Rarely, combinations of these grafts will be the only possible option. The indications for esophageal resection and substitution include malignant and end-stage benign disease. The latter includes reflux or drug-induced stricture formation that cannot be dilated without damage to the esophagus, a dilated and tortuous esophagus secondary to severe motility disorders, lye strictures, and multiple previous antireflux procedures.

Partial Esophageal Resection Low-lying benign lesions, with preserved proximal esophageal function, are best treated with interposition of a segment of proximal jejunum into the chest and primary anastomosis. Because the anastomosis is within the chest, a thoracotomy is necessary.

The jejunum is a dynamic graft and contributes to bolus transport, whereas the stomach and colon function more as a conduit. Replacement of the cervical portion of the esophagus while preserving the distal portion is occasionally indicated in cervical esophageal or head and neck malignancy and following the ingestion of lye. Free transfer of a portion of jejunum to the neck has become a viable option and is successful most of the time.

Reconstruction Following Total Esophagectomy No pretense should be made that the intrathoracic stomach or colon functions as well as the native esophagus after an esophagogastrectomy. The choice between these organs will be influenced by several factors, such as the adequacy of their blood supply and the length of resected esophagus that they are capable of bridging. If the stomach is involved with pathology, the length available for esophageal replacement may not be adequate. Diverticular disease, unrecognized carcinoma, or colitis prohibits the use of the colon. The blood supply of the colon is more affected by vascular disease than the stomach and may prevent its use. The colon provides the longest graft. The stomach usually can reach to the neck if the amount of lesser curve resected does not interfere with the blood supply to the fundus. Gastric interposition has the advantage that only one anastomosis is required. There is greater potential for aspiration of gastric juice or structuring of the cervical anastomosis from chronic reflux when stomach is used for replacement.

Patients following esophagogastrectomy may have discomfort during or shortly after eating, resulting from the loss of the gastric reservoir. These symptoms are less common when the colon is used as an esophageal substitute, probably because the distal third of the stomach is retained in the abdomen, and interposed colon provides an additional reservoir function.

Dysphagia after reestablishing gastrointestinal continuity with the stomach following esophagogastrectomy is reported to occur in 50 percent of patients, two-thirds of whom require postoperative dilatation. By contrast, dysphagia is uncommon and the need for dilatation is rare following colon interposition. The high incidence of dysphagia with use of the stomach is probably related to the esophagogastric anastomosis in the neck and the difficulty this imposes to passage of the swallowed bolus.

Another consequence of the transposition of the stomach into the chest is the development of postoperative duodenogastric reflux. Adding a pyloroplasty may worsen this problem. Following gastric advancement, the pylorus lies at the level of the esophageal hiatus, and a distinct pressure differential develops between the intrathoracic gastric and intraabdominal duodenal lumens. Unless the pyloric valve is extremely efficient, the pressure differential will encourage reflux of duodenal contents into the stomach. Duodenogastric reflux is less likely to occur following colonic interposition because there is sufficient intraabdominal colon to be compressed by the abdominal pressure, and the pylorus and duodenum remain in their normal intraabdominal position.

Although there is general acceptance of the concept that the esophagogastric anastomosis in the neck results in less postoperative esophagitis and stricture than one at the lower level, reflux esophagitis following cervical anastomosis does occur, albeit at a slower rate than when the anastomosis is at a lower level. Most patients undergo cervical esophagogastrostomy for malignancy; thus the long-term sequelae of an esophagogastric anastomosis in the neck is not of concern. Patients who have had a cervical esophagogastrostomy for benign disease, however, may develop problems associated with the anastomosis in the fourth or fifth postoperative year, severe enough to require anastomotic revision. This is less likely in patients who have had a colon interposition for esophageal replacement. Consequently, in patients who have a benign process or a potentially curable carcinoma of the esophagus or cardia, a colon interposition is used to obviate the late problems associated with a cervical esophagogastrostomy. Colon interposition for esophageal substitution is a more complex procedure than gastric advancement, with the potential for greater perioperative morbidity, particularly in inexperienced hands.

Composite Reconstruction Occasionally, a combination of colon, jejunum, and stomach is the only reconstructive option available. This situation may arise because of previous gastric or colonic resection, recurrence of dysphagia after a previous esophageal resection, or following postoperative complications such as ischemia of an esophageal substitute. Although not ideal, combinations of colon, jejunum, and stomach used to restore gastrointestinal continuity function surprisingly well. This recognition may allow alimentary reconstruction in an otherwise impossible situation.

For a more detailed discussion, see Peters JH, DeMeester TR: Esophagus and Diaphragmatic Hernia, chap. 23, in *Principles of Surgery,* 7th ed.

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CHAPTER

24

STOMACH

ANATOMY

Functional Relationships The *fundus* is located in the upper abdomen; it is thin walled and freely distensible and stores and partially digests food. Capacity is 1.5–2.0 L. The cardia is immediately adjacent to the gastroesophageal (GE) junction. The fundus is to the left of and superior to the cardia. The body extends from the fundus to the incisura. The *antrum* is the thick-walled, distal portion of the stomach; it mixes and grinds food and then releases it slowly through the pyloric sphincter. The *pancreas* is dorsal (inflammation delays gastric emptying, masses cause satiety). The *liver* is to the right and ventral, whereas the *spleen* is directly to the left and lateral. Enlargement of either also interferes with gastric capacity. Likewise, gastric disease (e.g., peptic ulceration) may affect adjacent organs. The *biliary tree* runs posterior to the duodenum.

Blood Supply and Lymphatics There are four major nutrient arteries (e.g., right/left gastric, right/left gastroepiploic) and an extensive submucosal arteriole plexus. See Fig. 24-1 for complete details. Short gastric veins arise from splenic veins and connect the fundus and spleen. The stomach can survive on only one major artery. Lymphatic drainage follows the vascular supply.

Innervation The major autonomic supply is vagal. The hepatic branch arises from the left anterior vagus and the celiac branch from the right posterior vagus. Each main vagus terminates in a *nerve of Laterjet*, which gives off small branches to the lesser curvature (secretory innervation to parietal cells). The distal-most branches are the "crow's feet," innervating the motor activity of the antrum. Splanchnic (sympathetic) branches follow arteries and modulate blood flow and muscular function.

Morphology External serosa, outer longitudinal, middle circular, inner oblique smooth muscle, then submucosa, muscularis mucosa,

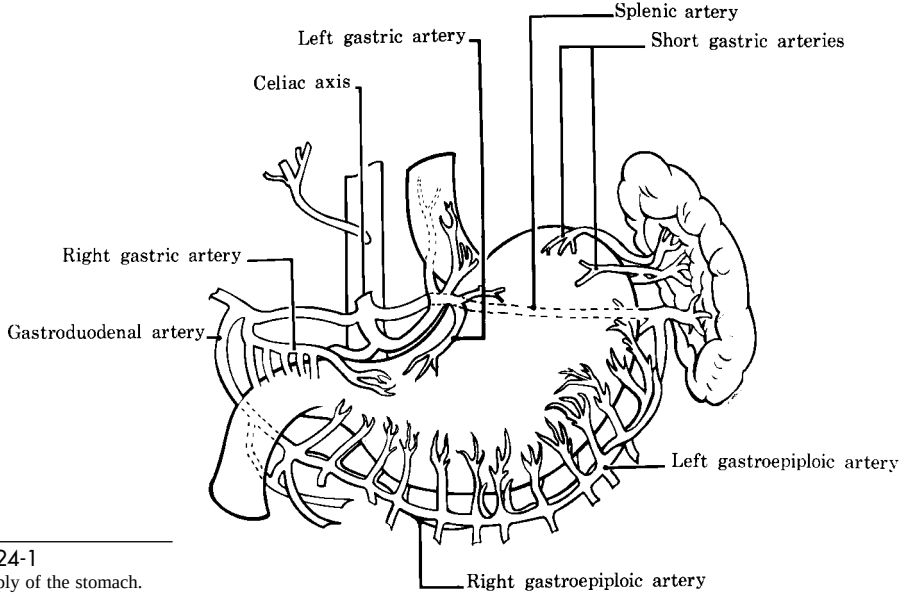

FIGURE 24-1
Blood supply of the stomach.

and mucosa. Small submucosal arterioles feed a rich mucosal capillary network.

Fundic Mucosa (Proximal Two-Thirds) Composed of deep glands that open into pits. Glands have surface epithelial (protect surface with mucus, alkaline secretions), mucous neck (line glands), progenitor (at base of gland), chief (secrete pepsinogen), parietal (secrete HCl), and endocrine cells (serotonin).

Antral Mucosa (Distal One-Third) Surface epithelial, mucous neck, and G cells (produce gastrin).

Sphincters *Lower esophageal sphincter* (LES) constitutes the distal 5 cm of esophagus-stomach junction. Relaxes with swallowing and then contracts to prevent reflux of gastric contents. *Pyloric sphincter* minimizes duodenogastric reflux and meters movement of food into duodenum, rejecting particles larger than 2 mm.

PHYSIOLOGY

Storage The stomach stores food for up to 4 h. *Receptive relaxation* is muscular relaxation with ingestion. Solid food settles on the greater curvature; liquids pass freely along the lesser curvature. The antrum grinds and recirculates food. The pylorus regulates emptying.

Digestion Salivary amylase acts on starches, only in center of gastric bolus (remains alkaline). Peptic digestion reduces the size of meat particles. Gastric lipase assists with early fat digestion. Most digestion, however, occurs in the small intestine.

Gastric Acid Secretion Interdigestive acid production is 2–5 mEq/h (BAO = basal acid output). The sight and smell of food stimulate acid and pepsinogen secretion (cephalic phase). Response is vagally mediated, and this also enhances the action of gastrin. *Gastrin* is elaborated by G cells in response to gastric distention and vagal stimulation. Gastrin, in turn, stimulates acid secretion from parietal cells. Luminal acid then suppresses gastrin secretion (negative feedback). Acidification of the duodenum causes *secretin* release, which inhibits gastrin and acid production and stimulates pancreatic bicarbonate release. Duodenum and upper jejunum also secrete small amounts of gastrin.

Parietal Cell Function Parietal cells secrete HCl. This occurs via H^+/K^+ exchange pump, which requires ATP. Acetylcholine (vagal

release), gastrin, and histamine stimulate and cimetidine, ranitidine, and famotidine (H_2 blockers), omeprazole (H^+/K^+-ATPase inhibitor), and prostaglandins (Cytotec) inhibit acid secretion. Vagotomy profoundly diminishes response to gastrin and histamine; however, anticholinergics only partially inhibit the response.

Surface Cell Function Impervious to H^+. Secrete protective layer of mucus and bicarbonate.

Gastric Emptying Meal anticipation causes vagal gastrin release, acid secretion, and together with ingestion, receptive relaxation, antral contractions, and relaxation of the pylorus. Liquids empty continuously, at a rate dependent on osmolarity. Solids are reduced to millimeter-sized particles and then traverse the pylorus. Osmolality of chyme is diluted by recirculation (trituration), preventing dumping. Fats empty slowest. The *gastric pacemaker* is on the greater curvature; action potentials travel toward the pylorus. Gastric emptying may be assessed with saline instillation, barium radiographs, or bimodal radiolabeled meals. With instillation of 750 mL of saline, less than 400 mL should be left by 30 min.

Sphincters Proximally is the LES, a high pressure zone at the GE junction. The LES relaxes with esophageal peristalsis. Distally is the true pyloric sphincter, which functions as above.

Other Gastric Function *Intrinsic factor,* produced by parietal cells, is essential for ileal vitamin B_{12} absorption. Gastric acid helps maintain foregut sterility. Gastric mucosa may participate in immunosurveillance and disposal of toxic substances. The stomach also rapidly warms (or cools) ingested contents. Gastric acid facilitates duodenal iron absorption.

DIAGNOSIS OF GASTRIC DISEASE

Symptoms

Anorexia Lack of appetite, frequently associated with physiologic stress. Common cause of weight loss with GI neoplasms.

Nausea and Vomiting See Chap. 22.

Pain Gastric mucosa devoid of pain endings. Gastritis, neoplasms, distention, and even gastric ulcers are relatively painless. Duodenal disease (i.e., ulceration) has characteristic pain patterns: gnawing

midepigastric pain that is relieved when acid is buffered (meals, antacids) and worse with unopposed acid (early morning). Gastric ulcers have subtle, diffuse pain during or after meals unless perforated; then the pain is generalized.

Reflux Gastric contents into esophagus. May cause (1) heartburn, (2) expectoration of chyme, and (3) cough from aspiration. Caused by loss of LES pressure zone. Vagal tone, intraabdominal pressure, drugs, and GI hormones may influence LES pressure. May be surgically corrected by Nissen fundoplication.

Signs

Bleeding *Hematemesis* is the vomiting of blood. *Coffee-ground emesis* reflects slow bleeding (acid-hematin); bright-red emesis implies rapid bleeding (varix, ulcer, tears, severe gastritis). Stools are usually black (melena) but may be red with rapid bleeds. Neoplasms can cause slow, chronic blood loss.

Weight Loss Neoplasia and gastric ulcer usually cause weight loss. Duodenal ulcer is associated with weight *gain;* food neutralizes acid, relieving duodenal ulcer pain.

Gastric Distention Produces autonomic-mediated pallor, tachypnea, bradycardia, and hypotension. Diagnosed by inspection/percussion; remedied by nasogastric aspiration.

Tenderness Duodenal ulcers may have associated deep midepigastric tenderness. Gastric ulcers and neoplasms are usually nontender. Perforated ulcers cause generalized peritonitis with abdominal rigidity.

Masses Distal gastric neoplasms may show anterior, movable masses. Pancreatic masses are fixed; liver masses descend with inspiration. Virchow's node is left supraclavicular metastasis.

Diagnostic Studies

Radiography Barium studies miss some duodenal lesions and most superficial gastric erosions; however, endoscopy is preferred for mucosal lesions, especially bleeding.

Endoscopy Essential for hemorrhage, gastric ulceration, and most duodenal ulcerations. Lesions may be biopsied for histology

as well as for *H. pylori*. Therapeutic techniques may be used for control of duodenal bleeding (e.g., electrocautery, epinephrine injection).

Gastric Analysis Saline lavages before/after a histalogue (2μg/kg) or pentagastrin (6μg/kg) dose. Maximal acid output (MAO) is 10–15 mEq/h; BAO is 2–3 mEq/h. Duodenal ulcer patients may have higher values; gastric ulcer patients may have lower values. However, significant overlap exists. Zollinger-Ellison (ZE) syndrome shows a high BAO ($>$ 50 mEq/h) with the BAO/MAO ratio at 0.6.

Other Conditions

Acid-reducing procedures may lead to anemia, and there is a question of gastric remnant cancer due to the resulting achlorhydria. Diarrhea may be due to dumping or postvagotomy syndrome.

ACID-PEPTIC DISEASE

Classification

Includes erosive gastritis and peptic ulcer. Reflux affects esophagus (see Chap. 23). True ulcers extend through the mucosa into the submucosa, in contrast with gastritis. Ulcers usually are chronic and include an inflammatory reaction.

PEPTIC ULCER

Duodenal ulcers are usually within 1–2 cm of the pylorus. They are often associated with acid hypersecretion. Gastric ulcers are as follows: Type I (most common)—proximal antrum or corpus (often acid hyposecretion); Type II—secondary to duodenal ulcer with pyloric stenosis; Type III—prepyloric/pyloric channel ulcer, similar etiology to duodenal ulceration.

Pathogenesis Three basic etiologies: acid hypersecretion, *H. pylori*, and nonsteroidal anti-inflammatory drugs (NSAIDs). *H. pylori* is found in 95 percent of duodenal ulcer disease and 80 percent of gastric ulcer disease. Eradicating *H. pylori* almost eliminates peptic ulcer disease. *H. pylori* may decrease acid resistance of mucous layer. Cause and effect, however, are difficult to prove. NSAIDs suppress prostaglandin synthesis and weaken the mucosal barrier. Between 10 and 30 percent of chronic NSAID users may develop peptic ulcer disease. Zollinger-Ellison (ZE) syndrome occurs in 0.1–1.0 percent of all peptic ulcer disease patients, and in about 20

percent of these patients, there is associated multiple endocrine neoplasia Type I (MEN-I).

Duodenal Ulcer Pathogenesis Overall, patients with duodenal ulcers secrete more acid compared with controls due to an increase in parietal cells, chief cells, or trophic factors (gastrin). *H. pylori* increases gastrin output and causes duodenitis. Some patients also have motility disorders, with rapid gastric emptying of liquids, exposing the duodenum to more acid than normal. The most prevalent physiologic abnormality may be decreased duodenal bicarbonate secretion.

Gastric Ulcer Pathogenesis Overall, basic defect is in gastric mucosal defense against acid-pepsin. Acid output is normal to nearly undetectable. Contrast with duodenal ulcer disease (some acid is required). Most basic abnormality may be reflux of duodenal contents. May be pyloric dysfunction; also caused by smoking. Reflux of bile acids, lysolethicin, and pancreatic secretions has a negative effect and damages the mucosa. Aspirin has a similar effect.

Clinical Manifestations and Diagnosis

Pain is the most common feature, gnawing or sharp midepigastric pain. Duodenal ulcer pain develops many hours after a meal when the bulb is empty. Relieved by food and alkali. In contrast, gastric ulcer pain is exacerbated with eating. Pain is usually chronic and recurrent. Other symptoms include nausea, weight loss, and mild tenderness. The peak incidence of gastric ulcers is at 50–65 years; most duodenal ulcers occur in the fourth decade.

Most diagnoses are by upper endoscopy or an upper GI series. In young patients, treatment is often based on symptoms alone, without diagnostic imaging. In elderly patients, imaging must be used because of the risk of malignancy. A double-contrast GI series detects 90 percent of gastric and duodenal ulcers, similar to endoscopy. Endoscopy is needed for all gastric ulcers because of the risk of malignancy. Endoscopy also provides material for *H. pylori* testing.

Complications

There are three main complications: bleeding, perforation, and obstruction. They usually follow previous symptoms. Between 15 and 20 percent of peptic ulcer disease develops gross bleeding. Patients

present with melena (duodenal and gastric ulcers) or hematemesis (gastric ulcers). Bleeding peptic ulcer disease is only one-third of all massive upper GI bleeding. Between 5 and 10 percent of peptic ulcers will perforate, which produces peritonitis, fever, leukocytosis, ileus, and marked abdominal pain. Pneumoperitoneum occurs in 75 percent. Occasionally, perforations seal or lead to abscess, or they may track to right lower quadrant. Obstruction occurs in less than 5 percent, most often in chronic duodenal ulcer disease. Vomiting can cause contraction alkalosis. Diagnosis is by GI series, endoscopy, and the saline load test.

ZOLLINGER-ELLISON SYNDROME

Symptoms include hypergastrinemia and severe peptic ulceration from a gastrinoma. Ulcers may be more distal and multiple. BAO is markedly elevated (BAO/MAO ratio > 0.6); the gastrin level may be greater than 1000 pg/mL. Equivocal gastrin levels may be stimulated with intravenous calcium or secretin administration. Gastrinomas are neoplasms, and they are overwhelmingly malignant ($>$ 90 percent) but slow growing; 50 percent have nodal or liver metastases at the time of diagnosis.

Treatment of Peptic Ulcer Disease

Medical Therapy (Table 24-1) Nonoperative treatment aims at (1) neutralizing gastric acid, (2) inhibiting secretion, and (3) protecting the gastric mucosa from injury. Antacids work by buffering gastric acid. H_2-receptor antagonists block receptors on parietal cells. Most potent are the substituted benzimidazoles, which block H^+/K^+-ATPase (omeprazole) and which work even in gastrinoma patients. Gastric mucosa can be protected with PgE_2 analogues (e.g., Misoprostol, Cytotec) that increase mucosal blood flow and bicarbonate and mucus production. Sucralfate binds to proteins in ulcer craters, promoting healing. Bismuth coats exposed protein and has activity against *H. pylori* (requires combined therapy).

H. pylori eradication is via combined therapy: (1) bismuth-tetracycline-metronidazole or (2) omeprazole plus two of clarithromycin, amoxicillin, and metronidazole. Eradication of *H. pylori* is very effective in preventing ulcer recurrence.

Operative Therapy, Duodenal Ulcer Disease Today, surgery is most often performed for complications of peptic ulcer disease or emergently, due to effectiveness of medical treatment. Indications are bleeding, obstruction, perforation, or intractability. Today, for duodenal ulcer disease, medically refractory pain is most often treated with highly selective vagotomy, reducing infectious complications and side effects.

TABLE 24-1
DRUGS FOR THE TREATMENT OF GASTRITIS AND PEPTIC ULCER

Class	Example	Mode of Action
Antacids	Aluminum hydroxide	Acid neutralization
H_2-receptor antagonists	Ranitidine	Secretory inhibition
Anticholinergics	Pirezepine	Secretory inhibition
Substituted benzimidazoles	Omeprazole	H^+/K^+-ATPase inhibition
Prostaglandins	Misoprostol	Cytoprotection
Sulfated disaccharides	Sucralfate	Protective coating
Colloidal bismuth	Bismuthate	Protective coating, eradicates *H. pylori*
Antibiotics	Metronidazole, tetracycline	Eradicates *H. pylori*

SOURCE: Modified from Stabile BE, Passaro E Jr: *Curr Probl Surg* 21:1, 1984, with permisssion.

Bleeding is main cause of death from duodenal ulcer disease. Upper endoscopy is essential for diagnosis and initial treatment (cautery, epinephrine injection). Follow this with H_2 blockers. Operation is indicated for a 6-unit bleed after initial control. Operative approach is via a pyloromyotomy, with undersewing of the bleeding ulcer base, incorporating the gastroduodenal artery.

After control, highly selective vagotomy can be performed or, in a poor-risk patient, vagotomy and pyloroplasty.

Perforation can be treated with simple closure and omental patch (Graham patch) in the poor-risk patient. Before *H. pylori* treatment, 80 percent recurred. In better-risk patients, a definitive procedure is preferred. Obstruction most often is treated with vagotomy and antrectomy, removing the scarred pyloris.

Operative Therapy, Gastric Ulcer Disease Medical therapy for gastric ulcer disease is not as effective as for duodenal ulcer disease. Surgery for gastric ulcer disease is needed earlier than for duodenal ulcer disease due to the higher incidence of malignancy. Gastric ulcer disease that recurs after medical therapy or that fails to heal needs operative intervention. Prepyloric gastric ulcers are treated as duodenal ulcers. Standard Type I gastric ulcers are treated with distal gastrectomy, including the ulcer. Vagotomy is not required.

Operative Therapy, Zollinger-Ellison Syndrome Since imaging studies are becoming more accurate, surgery is indicated for patients without metastatic disease. In patients with metastatic disease, omeprazole is very effective. Intraoperative ultrasound is useful for localized duodenal and pancreatic lesions, which should be resected.

Acute Erosive Gastritis

Acute erosive gastritis is the most common cause of upper GI bleeding. It accompanies severe, stressful illnesses.

Pathogenesis Includes acid secretion, back-diffusion of H^+ ions, decreased gastric mucosal blood flow, decreased mucus and alkaline secretion, and submucosal buffers. May be initiated by a disruption in the H^+ barrier. Aspirin, NSAIDs, alcohol, and bile salts may contribute.

Diagnosis Painless upper GI bleeding implies acute erosive gastritis. Endoscopy is critical; barium studies are not useful.

Therapy Directed at (1) repletion of losses from bleeding, (2) gastric rest with lavage of retained blood and clots (80 percent will stop bleeding spontaneously), and (3) neutralizing gastric acid with H_2 blockers and antacid pH titration to greater than 5. Omeprazole is as effective as antacids. Sucralfate may decrease pulmonary infections (decreased gastric bacterial colonization). Other adjuncts

include transendoscopic cautery, pitressin, and intraarterial embolization. Persistent bleeding (> 4–6 units, massive exsanguination) may be treated initially endoscopically with cautery or arteriographically, but persistence requires operation with gastrotomy and oversewing of bleeding sites accompanied by vagotomy and pyloroplasty. Gastrectomy may be needed if all other therapies fail.

GASTRIC NEOPLASMS

Malignant Tumors

GASTRIC CANCER

Over 90 percent of gastric tumors are malignant. Adenocarcinoma comprises 95 percent, lymphoma 4 percent, and leiomyosarcoma 1 percent. The highest incidence is in Chile, Japan, and Iceland. The United States has had a rapid decline in rate.

Etiology Foods high in nitrates (smoked foods) increase risk. Pernicious anemia and achlorhydria predispose. *H. pylori* may increase the risk sixfold. Other risk factions include smoking, gastric ulcer, and previous partial gastrectomy.

Pathologic Features Types include (1) superficial spreading (most favorable prognosis; does not penetrate through muscularis mucosae; no ulceration; early detection has 75 percent 10-year survival; detected only by endoscopy/screening) and infiltrating carcinoma, which may include (2) polypoid, (3) ulcerative, or (4) scirrhous (linitis plastica), which involves extensive wall infiltration without ulceration, giving a "leather-bottle" appearance to the upper GI series. Spread may be via lymphatics, hematogenous, by peritoneal seeding, or by direct extension. Fifty percent or more patients have tumor spread at the time of diagnosis.

Signs and Symptoms Anorexia, weight loss (> 95 percent). Symptoms usually occur late. Slow bleeding leads to hemorrhage. Nausea, vomiting, and dysphagia are common. Pain is infrequent and late. Examination reveals a mass (50 percent), but tenderness is rare. Hepatomegaly (liver metastasis), ovarian involvement (Krukenberg tumor), and pelvic seeding (Blumer's shelf) may be detected. Advanced malignancy may show an involved left supraclavicular node (Virchow's node).

Diagnosis and Staging Upper endoscopy with biopsy is essential. A GI series often is complementary. CT scanning is used for

preoperative staging. The TNM staging is shown in Table 24-2. Early gastric cancer is confined to the mucosa/submucosa. First found in Japan. Most are well differentiated. There is an excellent 5-year survival when disease is confined to the mucosa (99 percent) or submucosa (93 percent).

Treatment Primarily surgical. Subtotal gastrectomy, even if palliative, is useful except in most severe circumstances. Include 50–85 percent of stomach, gastrocolic omentum, nodes and mesentery, and proximal duodenum. Margins must be free of tumor. Reestablish continuity via gastrojejunostomy. Adjuvant therapy, especially for recurrence, is poor. Overall 5-year survival is less than 10 percent. Early diagnosis can lead to increased survival (Japan).

TABLE 24-2
TNM STAGING OF GASTRIC CANCER

Tis	Tumor limited to the mucosa without penetration through the basement membrane into the lamina propria.
T1	Tumor limited to the mucosa or mucosa and submucosa.
T2	Tumor extending into the muscularis propria and may extend into but not through the serosa.
T3	Tumor penetrates the serosa without invading contiguous structures.
T4	Tumor invading adjacent structures.
N0	No metatases to regional lymph nodes.
N1	Involvement of perigastric lymph nodes within 3 cm of the primary tumor along the lesser or greater curvature.
N2	Involvement of regional lymph nodes more than 3 cm from the primary tumor, which are removable at operation, including those located along the left gastric, splenic, celiac, and common hepatic arteries.
N3	Involvement of other intraabdominal lymph nodes such as the para-aortic, hepatoduodenal, retropancreatic, and mesenteric nodes.
M0	No distant metastases.
M1	Distant metastases present.

OTHER GASTRIC MALIGNANCIES

Lymphoma/Lymphosarcoma May be isolated to stomach or from widespread disease. Thickened rugal folds. Anorexia, weight loss, and early satiety are common. Diagnosis is made by biopsy. May be treated by radiation therapy alone (preferred) or radiation with resection for bleeding and obstruction. Survival may approach 85 percent at 5 years.

Leiomyosarcoma Least common. Smooth muscle malignancy. Hemorrhage common. Resection is preferred treatment. Distal spread occurs late, and survival is favorable. Prognosis is related to tumor grade, size, and margins.

Benign Gastric Neoplasms *Polyps* Most common benign tumors of stomach. (1) Adenomatous polyps occur with pernicious anemia, Peutz-Jeghers syndrome, and Gardner's syndrome. These do have a malignant potential and should be biopsied via endoscopy with a snare. Malignant polyps are treated as gastric adenocarcinoma. (2) Inflammatory polyps are sessile and asymptomatic and may be seen with hypertrophic gastritis (Ménétrier's disease) or multiple inflammatory gastric polyps. They must be biopsied endoscopically but do not require formal resection.

Leiomyomas Common smooth muscle benign neoplasms. At more than 4 cm they ulcerate and may have massive hemorrhage, requiring emergency operation with formal resection. Smaller lesions may be wedged or shelled out.

Miscellaneous Lesions Submucosal lipomas are detected radiographically and are of little consequence. Ectopic pancreas may present as a mucosal dimple.

OTHER GASTRIC PATHOLOGY

Hypertrophic Gastritis (Ménétrier's Disease) Rare gastric epithelial inflammation with massive gastric folds and eventually multiple polyps. There is submucosal edema with inflammatory cells and glandular hypertrophy. Plasma proteins may be lost through this epithelium. Rarely, kwashiorkor may develop. Initially managed nutritionally. Must follow serially to assess for development of cancer.

Mallory-Weiss Tear Gastric mucosal disruption at esophagogastric junction after violent retching. Massive bleeding in only 10 percent. Bleeding stops spontaneously in 80–90 percent. Confirm by endoscopy. Operation uncommonly indicated. Massive hemorrhage

may require operation with high gastrotomy and deep oversewing without acid reduction.

MISCELLANEOUS CONDITIONS

Acute gastric dilatation is followed by vasovagal symptoms. Usually occurs intra- or postoperatively. *Gastric volvulus* is uncommon and associated with paraesophageal hiatal hernia. Gangrene and perforation will develop. Therefore, even asymptomatic paraesophageal hernias should have operative repair. *Foreign bodies* occur in children, and sharp objects should be retrieved endoscopically. *Bezoars* are nondigestible conglomerates that occur in postgastrectomy patients or with ingestion of hair or persimmons. Treatment is with papain or endoscopic fragmentation. *Atrophic gastritis*, or *pernicious anemia*, shows parietal cell loss, achlorhydria, and loss of intrinsic factor and, subsequently, B_{12} depletion. There is a high risk for malignancy. *Corrosive gastritis* may be caused by caustic ingestion (alkali cause esophageal strictures), and strong acid may lead to gastric perforation. Dieulafoy's lesion is a bleeding mucosal end artery with mucosal erosion.

SURGERY OF THE STOMACH

Antiulcer surgery is aimed at reducing acid secretion via vagotomy, antrectomy, and/or removing a parietal cell mass. Following resection, reconstruction is required.

Vagotomy

Eliminates cholinergic stimulus to parietal cells. BAO and MAO are reduced by 80 and 50 percent, respectively. Gastrin levels increase. May be truncal vagotomy (next to esophagus), selective (just after celiac/hepatic branches), or highly selective (parietal cell branches). Truncal vagotomy alters motility by denervating antral pump ("crow's feet"). Requires concomitant emptying procedure (pyloroplasty or gastrojejunostomy). Avoid pyloroplasty if there is significant scarring. Highly selective vagotomy denervates parietal cells and preserves the gastric emptying mechanism; pyloroplasty is not necessary.

Resection

Required for malignant disease. Subtotal gastrectomy now uncommon for ulcer disease. Removes antrum and major portion of parietal cells. Reconstruction is described below. Antrectomy with

vagotomy has the lowest recurrence if surgery is needed for ulcer disease.

Reconstruction

Following resection, the gastric remnant must be anastomosed to the small intestine. Either a gastroduodenostomy is done (to the stump of the duodenum, distal to resection, Billroth I) or a gastrojejunostomy is done (to the proximal jejunum, immediately distal to the ligament of Treitz, Billroth II). Gastroduodenostomy is preferred if technically possible. For total gastrectomy, a roux-en-Y esophagojejunostomy is needed to prevent alkaline reflux.

CHOICE OF OPERATION

First, consider the disease process; then look at morbidly, recurrence, and side effects. Table 24-3 provides a summary for duodenal ulcer disease. These data, however, do not reflect the factor of *H. pylori* eradication. Laparoscopic approaches to gastric surgery are evolving and are currently only applied in elective settings.

Postgastrectomy Syndromes

Procedures that destroy or bypass the pylorus or sever the vagal trunks may cause a wide range of disturbances. About 20 percent of patients have transient symptoms, 5 percent have permanent, nondisabling symptoms, but 1 percent may become "gastric cripples." Therefore, lesser, pyloric-sparing procedures (i.e., parietal cell vagotomy) are being used more frequently.

Dumping Syndrome Related to ingestion of carbohydrates after pyloric ablation and their rapid movement into the small intestine.

TABLE 24-3
MORTALITY, SIDE EFFECTS, AND RECURRENCE RATES FOR THE THREE MOST COMMON ACID-REDUCING OPERATIONS

Operation	Mortality (%)	Side Effects (%)	Recurrence (%)
Vagotomy and antrectomy	2	5	1
Vagotomy and drainage	1	5	10
Highly selective vagotomy	0.2	1	10

Characterized by light-headedness, palpitations, cramps, and diarrhea. Frequent small meals with few carbohydrates help. Octreotide is used in refractory cases.

Small-Capacity Syndrome Associated with extensive resections. Early satiety.

Postvagotomy Diarrhea May cause explosive diarrhea unrelated to meals, and gallstones. Occurs most often with truncal vagotomy (up to 30 percent), least with parietal cell vagotomy. Pathogenesis unclear; may be bile salts.

Bile Gastritis Erosive gastritis with reflux of bile through incompetent or bypassed pylorus. Low-grade pain, nausea, bilious vomiting. Roux-en-Y diversion may give relief. Only significant in 2 percent.

Afferent-Loop Syndrome Severe postprandial pain relieved by massive bilious vomiting. From obstruction at junction of afferent limb and gastric remnant. Treated by conversion to roux-en-Y.

Gastric Stump Carcinoma May develop in up to 3 percent of gastrectomy patients.

TREATMENT OF MORBID OBESITY

Morbid obesity constitutes weight 100 lb over ideal body weight. Ultimately hypertension, non-insulin-dependent diabetes mellitus, arthritis, gallstones, and cardiopulmonary dysfunction develop. Almost always refractory to medical therapy. Previously, jejunoileal bypass was successful, but complications (e.g., malabsorption, liver disease, renal calculi, gallstones) have led to its abandonment. Currently, operations aim to limit daily intake to about 800 kcal. Gastric bypass with a roux-en-Y jejunal limb to a 30–60-mL gastric pouch has been successful. Alternatively, gastric partitioning (vertical banded gastroplasty) is also used. Results show average of 50–67 percent loss of excess weight at 1.5 years.

For a more detailed discussion, see Ashley SW, Evoy D, and Daly JM: Stomach, chap. 24 in *Principles of Surgery,* 7th ed.

CHAPTER

25

SMALL INTESTINE

ANATOMY

The duodenum is 20 cm long, the jejunum is 100–110 cm long, and the ileum is 150–160 cm long. The jejunoileum extends from the *ligament of Treitz* (the peritoneal fold at the duodenojejunal junction) to the ileocecal valve. The jejunum is larger and thicker than the ileum and has only one to two vascular arcades versus four to five in the ileum. The small bowel is tethered by the *mesentery*, which carries the vascular and lymphatic supply. The mesentery travels obliquely from the left of L2 to the right of the S1 joint; it is normally very mobile. The blood supply to the jejunum and ileum is via the superior mesenteric artery, which also supplies the proximal transverse colon. Vascular arcades in the mesentery provide collateral supply. Venous drainage parallels the arterial supply, leading to the superior mesenteric vein, which joins the splenic vein behind the pancreas to form the portal vein. Lymphatic drainage is from the bowel wall (lacteals), through the mesenteric nodes, to the superior mesenteric nodes, into the cisterna chyli, and finally to the thoracic duct. Mucosal folds form circumferential transverse *plicae circulares*. Innervation is parasympathetic (vagus, celiac ganglia) and affects secretion and motility. Sympathetics come from the splanchnic nerves via the celiac plexus, affect secretion and bowel and vascular motility, and carry pain afferents.

Histology

Serosa This is the outermost, visceral peritoneum that encircles the jejunum, covering the duodenum only anteriorly.

Muscularis This consists of a thin outer longitudinal layer and a thicker inner circular smooth muscle layer. *Auerbach's plexus* lies between the layers.

Submucosa This is a layer of fibroelastic connective tissue with vessels, nerves (*Meissner's plexus*), and lymphatics. *Strongest component of bowel wall.*

Mucosa This contains transverse folds with fingerlike villi. Cells of villi have microvilli (brush border) and glycocalyx fuzz, which increase surface area. Villi are largest in the duodenum. The mucosa is composed of three distinct layers.

Muscularis Mucosae This is the deepest mucosal layer, a thin sheet of muscle.

Lamina Propria This is a continuous connective tissue layer between the muscularis mucosae and the epithelium. It contains plasma cells, lymphocytes, eosinophils, macrophages, fibroblasts, and smooth muscle and serves to support the epithelium and act as an immunogenic barrier.

Epithelium This is the one layer of cells covering the villi and lining the crypts of Lieberkuhn. The crypts contain goblet cells (mucous), enterochromaffin cells (endocrine), Paneth cells (zymogen granules), and basal undifferentiated cells. New cells march up the crypt onto the villus, taking 3–7 days. Villi have endocrine, goblet, and absorptive cells covered by microvilli, which are covered by glycocalyx fuzz. Absorptive cells contain digestive enzymes and some specific absorption receptors (Fig. 25-1).

PHYSIOLOGY

Motility

Pace-setter potentials originate in the duodenum, initiate contractions, and propel food through the small bowel via *segmentation* (short segment contraction with to and fro mixing) and *peristalsis* (aboral migration of contraction wave and food bolus). The *migrating myoelectric complex* (MMC) sweeps the entire bowel during fasting. This is all under neurohumoral control, stimulated by *motilin.* Vagal cholinergics are excitatory; vagal peptidergics are inhibitory. Gastrin, cholecystokinin, and motilin stimulate muscular activity; secretin and glucagon inhibit it.

Digestion and Absorption

Fat Pancreatic lipase hydrolyzes triglycerides; components combine with bile salts to form micelles. A micelle then traverses the cell membrane passively by diffusion and then disaggregates, releasing bile salts back into the lumen and fatty acids and monoglycerides into the cell. The cell then re-forms the triglycerides and

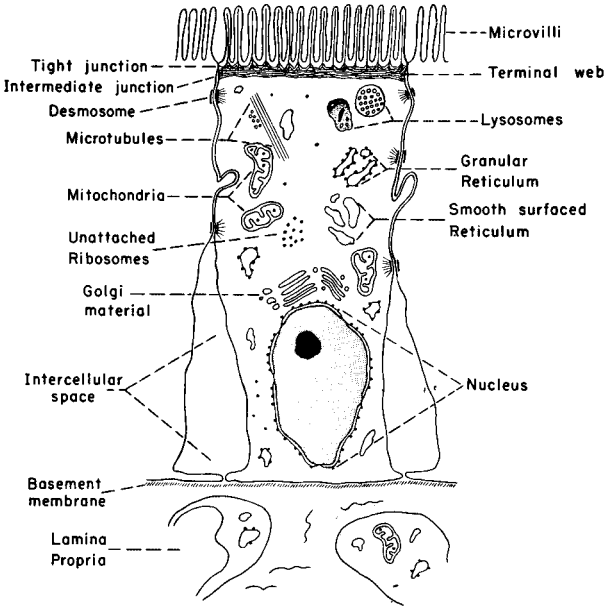

FIGURE 25-1 Schematic diagram of an intestinal absorptive cell. (From Trier JS et al, in Sleisenger MH, Fordtran JS (eds): *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management.* Philadelphia, Saunders, 1983, chap. 48, with permission.)

combines these with cholesterol, phospholipids, and apoproteins to form chylomicrons, which exit cells and enter the lacteals. Small fatty acids can enter capillaries to the portal vein directly. Bile salts are resorbed into the enterohepatic circulation in distal ileum. Of a 5-g bile salt pool, 0.5 g is lost daily; the pool recirculates six times in 24 h.

Protein Gastric acid denatures proteins, and pepsin begins proteolysis. Pancreatic proteases (trypsinogen, activated by enterokinase to trypsin, and endopeptidases, exopeptidases) further digest proteins, yielding amino acids and two to six residue peptides. Active transport brings di- and tripeptides into absorptive cells.

Carbohydrate Pancreatic amylase rapidly digests carbohydrates in the duodenum. Brush border enzymes complete the digestion into hexoses, which are specifically transported into epithelial cells.

Water and Electrolytes Water, bile, and gastric, salivary, and intestinal fluids contribute up to 8–10 L/day of water, most of which is absorbed. Water is osmotically and hydrostatically absorbed or may diffuse passively. Sodium and chloride are absorbed by coupling to organic solutes or by active transport. Bicarbonate is absorbed by sodium-hydrogen exchange. Calcium is absorbed via active transport in the duodenum and jejunum, facilitated by parathormone (PTH) and vitamin D. Potassium is absorbed by passive diffusion.

Endocrine Function

Small bowel mucosa releases a wealth of hormones into blood (endocrine), via local discharge (paracrine), or as neurotransmitters.

Secretin This is a 27-amino acid peptide released from small bowel mucosa by acidification or contact with fat. Secretin stimulates pancreatic water and bicarbonate release, which neutralizes gastric acid. It also stimulates bile flow and inhibits gastrin release, gastric acid, and motility.

Cholecystokinin This is released by mucosa in response to amino acids and fatty acids. Cholecystokinin causes gallbladder contraction with relaxation of the sphincter of Oddi and pancreatic enzyme secretion. It also is trophic for bowel mucosa and pancreas and stimulates motility and the release of insulin.

Other Peptides *Gastric inhibitory peptide* (GIP) is released by glucose and fat and stimulates insulin release. It also enhances the oral versus intravenous response to glucose load. Others released by the small bowel include *vasoactive intestinal peptide* (VIP), *enteroglucagon*, *motilin* (intestinal smooth muscle contraction), *bombesin*, *somatostatin* (paracrine inhibitory peptide), *neurotensin*, and *peptide YY* (PYY).

Immune Function

The mucosa prevents pathogen entrance. It is a major source of immunoglobulin, produced by plasma cells in the lamina propria. M cells overlying lymphocytes in Peyer's patches exposed to anti-

gens migrate to regional nodes, to the bloodstream, and then return to redistribute in the lamina propria to elaborate specific antibody.

INFLAMMATORY DISEASES

Crohn's Disease

Crohn's disease is a chronic inflammatory disease of the small or large intestine with acute exacerbations and spontaneous remissions. The true etiologic agent is unknown. Symptoms include intermittent, sometimes disabling diarrhea associated with meals, weight loss, and abdominal pain. This is the most common surgical disease of the small intestine. The risk is increased 30 times in siblings and 13 times in first-degree relatives.

Pathology The disease consists of mucosal and submucosal inflammation with aphthous ulcers. It progresses to transmural involvement with intense mononuclear cell infiltration and linear ulcers that, when severe, may coalesce resulting in *cobblestone mucosa.* The wall thickens and becomes edematous. Noncaseating granulomas appear late in the bowel wall and nodes. The mesentery becomes thick and short. Fat wraps from the mesenteric to the antimesenteric border. Scarring and fibrosis occur, narrowing the lumen. Typically, involved areas are not contiguous (skip lesions). Involved loops become adherent, matted, and may have internal fistulas.

Clinical Manifestations

In young adults, the symptoms include abdominal pain (intermittent, crampy), diarrhea (85 percent), and weight loss. The small bowel alone is affected in 30 percent, ileocolitis is seen in 55 percent, and the colon only is affected in 15 percent. The disease *may involve any enteric mucosa, including the mouth and anus.* Anal fissures, fistulas, and perianal abscesses are common. Extraabdominal manifestations include arthritis, uveitis, iritis, hepatitis, erythema nodosum, and pyoderma gangrenosum. Stools rarely contain pus, mucus, or blood (as in ulcerative colitis). Fever is seen in one-third of patients. In addition, patients may present with pain, intestinal obstruction, abscess, or a fistula to bowel, bladder, or skin. Free perforation is rare.

Diagnosis Small bowel barium follow-through shows nodular contour, luminal narrowing, linear ulcers, sinuses and clefts, and cobblestoning. Enteroclysis (double-contrast small bowel x-ray) is

more sensitive. Barium enema may be useful. *Acute ileitis* is inflammation of the terminal ileum, which can mimic appendicitis but is self-limited and does not lead to Crohn's disease.

Treatment Nonsurgical treatment consists of combinations of anti-inflammatory, antineoplastic, and antibiotic agents such as sulfasalazine (Azulfidine), corticosteroids (for acute exacerbations), azathioprine, 6-mercaptopurine, cyclosporine, and metronidazole. Patients with obstructive symptoms are treated with bowel rest, hyperalimentation, nasogastric decompression, and pulsed steroids. Surgery is reserved for complete obstruction (rare) or for chronic high-grade partial obstruction (more common). Appendectomy (alone) is to be avoided with active appendiceal or cecal disease but should be performed otherwise. Operation is indicated for such complications as obstruction, pain, abscess, fistula, perforation, bleeding, perianal disease, growth retardation, refractory disease, or complications of nonsurgical therapy. More than 70 percent of all Crohn's patients ultimately require surgery. Intraoperatively, only grossly involved intestine should be removed; *wide resections are to be avoided.* Stomas are rarely needed for small bowel Crohn's disease. Bypass with exclusion is *not* used.

Prognosis Surgical therapy is *not* curative. Recurrence at 5, 10, 15, and 25 years is 29, 52, 64, and 84 percent, respectively, after surgery. The disease burns out with advancing age, especially age greater than 50 years. Ileal Crohn's disease increases the risk of adenocarcinoma more than 60-fold.

Tuberculous Enteritis

This entity is rare in Western countries. It is seen mostly as a secondary infection in pulmonary tuberculosis patients. The ileocecal region is involved most often, usually with caseating granulomas. The disease may produce a hypertrophic reaction with luminal stenosis, ulceration, or both. Ulceration produces diarrhea and pain alternating with constipation. Treatment is with combination chemotherapy. Surgery is reserved for perforation, obstruction, or hemorrhage.

Typhoid Enteritis

This disease is caused by *Salmonella typhosa,* with ulceration of Peyer's patches, splenomegaly, and mesenteric adenopathy. It is rare in Western patients. Treatment is Bactrim or amoxicillin. Patients may have gross hemorrhage, and ileal perforation is seen in 2 percent.

NEOPLASMS

Primary small bowel neoplasms are very rare. The colon is affected 40 times more than the small intestine. Symptoms are often vague: epigastric pain, nausea, vomiting, colic, diarrhea, bleeding (usually occult). The most common reasons for operation are obstruction, bleeding, and pain. Benign tumors cause intussusception in adults; malignant tumors directly obstruct the bowel. Diagnosis is difficult. Endoscopy is useful for duodenal and proximal jejunal lesions; the rest of the bowel requires small bowel barium radiographs.

Benign Neoplasms

Benign neoplasms are either of epithelial or connective tissue origin. Most often they are adenomas, leiomyomas, or lipomas (Table 25-1). Often these cause no symptoms unless they cause obstruction by intussusception; they also may bleed (one-third are occult). Surgery is indicated if the diagnosis is made or suspected. Most often simple segmental resection is used.

TABLE 25-1
TYPES AND RELATIVE FREQUENCY OF SMALL BOWEL BENIGN NEOPLASMS

Neoplasms	Percentage
Leiomyomas	17
Lipomas	16
Adenomas	14
Polyps	14
Polyposis, Peutz-Jeghers	3
Hemangiomas	10
Fibromas	10
Neurogenic tumors	5
Fibromyomas	5
Myxomas	2
Lymphangiomas	2
Fibroadenomas	1
Others	1

ADENOMA

These consist of true adenomas, villous adenomas, or Brunner's gland adenomas (hyperplastic duodenal glandular proliferation without malignant potential); 20 percent are seen in the duodenum. Most are asymptomatic. Villous adenomas have 35–55 percent malignant potential.

LEIOMYOMA

These are benign, single smooth muscle lesions. Most commonly present with bleeding.

PEUTZ-JEGHERS SYNDROME

This syndrome consists of mucocutaneous melanotic pigmentation (circumoral, buccal, palms, soles, perianal) and gastrointestinal polyps. It occurs by simple dominant inheritance. Polyps are multiple jejunal, ileal, and rectal and are hamartomas. They may cause intussusception or bleeding. Curative resection usually is not possible. Surgery is indicated for obstruction or bleeding.

Malignant Neoplasms

Metastatic lesions (ovarian, colonic, gastric, breast, lung primary) are the most common. Primary malignancies include adenocarcinomas, carcinoids, sarcomas, and lymphomas. Patients have diarrhea with mucus/tenesmus, obstruction, and chronic blood loss. Usually there is an insidious presentation. Treatment is wide resection, including nodes. Duodenal lesions require pancreaticoduodenectomy. Palliative resections are done for relief of symptoms/obstruction. Overall survival is poor (average 20 percent 5-year survival). Periampullary carcinoma may have up to 40 percent 5-year survival.

ADENOCARCINOMA

Approximately 50 percent of small bowel malignancies are adenocarcinomas. They are seen mostly in the duodenum and proximal jejunum; 50 percent of duodenal carcinomas involve the ampulla and are associated with intermittent jaundice. Jejunal lesions are associated with obstruction.

SARCOMAS

Sarcomas comprise 20 percent of small bowel malignancies; leiomyosarcomas are most common. They may bleed or obstruct.

LYMPHOMA

Lymphomas comprise 10–15 percent of small bowel malignancies. They are most common in the ileum. They may be primary small bowel neoplasms or part of systemic disease.

CARCINOIDS

Carcinoids arise from enterochromaffin (Kulchitsky) cells. They occur as often as adenocarcinomas of the small bowel. Their malignant potential is variable. They secrete serotonin and substance P. Carcinoid syndrome (i.e., flushing, bronchospasm, diarrhea, vasomotor collapse, hepatomegaly, and right-sided heart valvular disease) occurs in less than 5 percent. (Hepatic metastasis is likely present before the syndrome occurs.) Carcinoids arise in the appendix (46 percent), ileum (28 percent), and rectum (17 percent). Appendiceal tumors metastasize 3 percent of the time as compared with ileal carcinoids (35 percent metastatic rate). Of those less than 1 cm in diameter (75 percent of gastrointestinal carcinoids), only 2 percent metastasize. Gross appearance is a yellow or tan, round, hard submucosal nodule. Often asymptomatic, but can cause abdominal pain, obstruction, diarrhea, and weight loss; carcinoid syndrome is rare.

Diagnosis A small bowel series, mesenteric arteriograms, and computed tomographic scans are useful. Urine examination for 5-hydroxyindoleacetic acid (5-HIAA) with or without pentagastrin stimulation is used for diagnosis of syndrome.

Malignant carcinoid syndrome is rare, occurring in only 6–9 percent of carcinoid patients. It is seen most often with small bowel disease and hepatic metastasis. Symptoms include hepatomegaly, diarrhea, flushing, right-sided heart valvular disease, and asthma. Symptoms are due to serotonin, substance P, and possibly bradykinin and prostaglandins E and F.

Treatment Primary carcinoids less than 1 cm in size are treated by segmental small bowel resection. Larger lesions or lesions with involved nodes require wide bowel excision with inclusion of mesentery. Appendiceal carcinoids less than 2 cm in size require only simple appendectomy; if carcinoids are more than 2 cm in size, the patient should have a right hemicolectomy. Carcinoid syndrome may be treated by curative or palliative resection or with long-acting somatostatin.

Prognosis Overall survival rate is 54 percent, with 75 percent for local disease, 59 percent for regional spread, and 19 percent for

distal spread. Because of the indolent nature of the disease, debulking and palliative resections are used.

DIVERTICULAR DISEASE

Congenital diverticula are *true,* composed of all layers; acquired diverticula are *false,* because only mucosa and submucosa protrude through a muscular defect. *Meckel's* and *duodenal diverticula* are the most common diverticula of the small bowel.

Duodenal Diverticula (Fig. 25-1)

Incidence is 10–20 percent in autopsy series; 90 percent are asymptomatic; and less than 5 percent require operative intervention. Between 67 and 75 percent are found in the periampullary region on the medial wall. Manifestations may be obstruction, perforation, or bleeding. Those associated with the ampulla may produce cholangitis, pancreatitis, and recurrent choledocholithiasis from stasis or choledochal sphincter dysfunction. Surgical therapy is diverticulectomy or extended sphincteroplasty for those involving the ampulla.

Jejunal and Ileal Diverticula

These are less common than those in the duodenum. Multiple false diverticula may occur and lead to jejunal pseudo-obstruction and dyskinesia.

Meckel's Diverticulum

This is the most common *true* diverticulum of the gastrointestinal tract. It is congenital, from incomplete closure of the omphalomesenteric or vitelline duct. Usually it is located 2–3 ft from ileocecal valve and is 1–12 cm long. It may have heterotropic gastric mucosa or pancreatic tissue. Overall, it is seen in 2 percent of population. Complications include intestinal obstruction (via volvulus or intussusception), bleeding (gastric mucosa produces acid, ulcer is in adjacent ileum), or acute diverticulitis. Meckel's diverticulum in a hernia is a *Littre hernia.* Diagnosis is via enteroclysis or technetium-99m pertechnetate scan. Complications of Meckel's are often confused with acute appendicitis. Asymptomatic Meckel's diverticulum found incidentally at surgery should *not* be removed.

MISCELLANEOUS PROBLEMS

Small Bowel Ulcerations

Most of these ulcerations are due to drugs (enteric-coated potassium or corticosteroids), vascular disorders, Crohn's disease,

syphillis, typhoid fever, tuberculosis, lymphoma, gastrinoma, or Meckel's diverticulum. Nonspecific ulcers may be found in the terminal ileum. Treatment is for complications, pain, obstruction, bleeding, and perforation.

Fistulas

Most often fistulas are due to surgical trauma; less than 2 percent are associated with Crohn's disease. Complications include sepsis, fluid and electrolyte imbalances, skin breakdown, and malnutrition. Overall, intestinal fistulas have more than 20 percent mortality, even with total parenteral nutrition (TPN). The key to successful management is fluid, electrolyte, and nutritional maintenance with control of sepsis. Proximal fistulas have higher output ($>$ 500 mL/day) and more severe complications. A gastrointestinal series is essential to identify the anatomic location of the fistula. Treatment includes drainage of the fistula or cavity, TPN, bowel rest, and skin protection. Somatostatin may be helpful. Factors that prevent spontaneous closure are high output, distal obstruction, marked disruption in intestinal integrity, inflammation (undrained abscess, active granulomatous disease), a foreign body in the tract, cancer, radiated tissue, a short tract ($<$ 2.5 cm), or epithelialization of the tract. Fewer than 30 percent close spontaneously, and most that do close, do so in about 3 weeks.

Pneumatosis Cystoides Intestinalis

This is an uncommon condition manifested by multiple gas-filled cysts (submucosal, subserosal) in the gastrointestinal tract. It is most often associated with other conditions, and usually it does not require surgical therapy.

Blind Loop Syndrome

Bacterial overgrowth in a stagnant area of small bowel produces diarrhea, steatorrhea, anemia, weight loss, abdominal pain, vitamin deficiencies (especially B_{12}), and neurologic disorders. This is usually secondary to strictures, fistulas, blind pouches (postoperative), or diverticula.

Short Bowel Syndrome

After massive, often emergent small bowel resection (volvulus, mesenteric vascular occlusion, Crohn's disease), short bowel syndrome may arise. Hallmarks are diarrhea, fluid and electrolyte deficiencies, and malnutrition. Usually up to 70 percent resection can

be tolerated if the terminal ileum and ileocecal valve are preserved. Loss of the terminal ileum leads to abnormalities of vitamin B_{12} and bile salt absorption. Jejunal resection is better tolerated than ileal resection. After resection, adaptation occurs: Villi lengthen, and cell number and renewal increase, thus increasing the absorptive surface. Luminal feeding (especially glutamine), pancreaticobiliary secretions, and certain hormones (cholecystokinin, secretin, neurotensin, PYY) appear to be trophic and necessary for adaptation. Adaptation does not occur with TPN alone.

Treatment Treatment includes prevention with conservative resection of marginally viable bowel and "second look" operations to reassess such intestine; early on, treatment is corrective for fluid and electrolyte losses and TPN. Early enteral nutrition is essential. Elemental diets or polymeric diets are useful. Milk products should be avoided. Fat-soluble vitamin supplementation is often needed. Vitamin B_{12} injections may be used. Histamine H_2 blockers may diminish diarrhea from rapid transit. Certain amino acids (glutamine) may specifically aid in adaptation.

Intestinal Bypass

Jejunoileostomy for the treatment of morbid obesity has been almost completely abandoned. Long-term complications include liver failure, death, cirrhosis, hyperoxaluria, renal calculi, avitaminoses, blind loop syndrome, pancreatitis, and gallstones, among many others. Morbid obesity is now treated with gastric partitioning or gastric bypass. Supermorbidly obese patients can be treated initially with intestinal bypass. A previously constructed jejunoileal bypass should be taken down, and intestinal continuity should be restored if significant metabolic imbalances or hepatic failure exists. There is some early evidence that partial ileal bypass (200 cm) may be useful in refractory hyperlipidemia.

For a more detailed discussion, see Evers BM, Townsend CM Jr, Thompson JC: Small Intestine, chap. 25 in *Principles of Surgery,* 7th ed.

CHAPTER

26

COLON, RECTUM, AND ANUS

ANATOMY

Colon

Structure The colon is 90–150 cm. Its diameter varies. The cecum is the widest part (7.5–8.5 cm), and the sigmoid colon is the narrowest (2.5 cm). In cases of distal obstruction, the cecum is the part most likely to rupture (Laplace's law: $T = P \times R$). The layers of the colonic wall include mucosa, submucosa, circular muscle, longitudinal muscle that coalesces into three separate teniae coli, and serosa. The mechanical strength of the colonic wall derives from the submucosa, the layer with the highest collagen content. The ascending colon and descending colon usually are fixed to the retroperitoneum, whereas the cecum, transverse colon, and sigmoid colon usually are intraperitoneal and mobile. The omentum is attached to the transverse colon.

Arterial Supply The superior mesenteric artery supplies the ascending colon and transverse colon through its ileocolic artery, right colic artery (present in only 15 percent of patients), and middle colic artery. The inferior mesenteric artery supplies the descending colon and sigmoid colon through its left colic branch and sigmoidal branches.

Venous Drainage The inferior mesenteric vein drains the descending colon, sigmoid colon, and upper part of the rectum and enters the splenic vein. The rest of the venous drainage of the colon follows the arterial pattern and joins the superior mesenteric vein.

Lymphatic Drainage Lymphatic drainage originates in the submucosa and follows the arterial supply.

Nerve Supply The sympathetic nerves usually inhibit peristalsis, and the parasympathetic nerves stimulate it. The sympathetic supply to the colon is derived from the thoracolumbar segments. The parasympathetic supply to the ascending colon and transverse colon

is derived from the posterior vagus nerve and to the descending colon and sigmoid colon from the S2–S4 sacral roots.

Rectum and Anus

Structure The teniae coli end at the distal sigmoid colon, and the longitudinal muscle layer of the rectal wall is continuous. The rectum is 12–15 cm long, extending from the sigmoid colon to the anal canal. The anterior peritoneal reflection is 5–9 cm from the anal verge and usually is larger in males. In its upper part, the rectum is covered with peritoneum anteriorly, and in its lower part, it is extraperitoneal. There are three lateral curves in the rectum that form the valves of Houston. The rectum is surrounded by extensions of the pelvic fascia, which have to be divided during surgical dissection.

The pelvic floor is formed by the levator ani muscle. The anal canal is about 4 cm long, extending from the pelvic floor to the anal verge. The dentate line is the mucocutaneous junction, about 1.5 cm from the anal verge. The anal canal is surrounded by the anal sphincter, which has an internal and external component. The internal sphincter is a continuation of the circular smooth muscle of the rectum, is an involuntary muscle, and is normally contracted at rest. The external sphincter is a voluntary striated muscle and is a caudad extension of the levator ani.

Arterial Supply The upper part of the rectum is supplied by the superior rectal artery, which is the terminal branch of the inferior mesenteric artery. The lower part of the rectum is supplied by the middle rectal and inferior rectal arteries, which are branches of the internal iliac arteries.

Venous Drainage This corresponds to the arterial supply, with the upper part of the rectum draining into the inferior mesenteric vein and the lower part into the caval system through the internal iliac veins. The two parts are connected by a rich network of collaterals, and therefore, low rectal and anal canal tumor can metastasize to both the portal and systemic venous systems.

Lymphatic Drainage This follows the arterial supply. The upper rectum drains into the inferior mesenteric lymph nodes. The lower rectum may drain into the inferior mesenteric system or the iliac lymph nodes. Below the dentate line the drainage is to the inguinal lymph nodes.

Nerve Supply The sympathetic innervation of the rectum as well as the bladder and the genital system is from the hypogastric nerves

originating in the thoracolumbar segments. The parasympathetic supply is from the nervi erigentes (S2–S4 sacral roots). Injury to these nerves during surgical dissection can cause bladder and sexual dysfunction. The sympathetic system usually controls ejaculation, and the parasympathetic controls erection.

PHYSIOLOGY

Normal Colonic Function

The colon absorbs water, sodium, chloride, and short-chain fatty acids and secretes potassium and bicarbonate. It helps in maintaining fluid balance and avoiding dehydration. This capacity is lost in patients with an ileostomy, who are more prone to dehydration.

Colonic Motility This is complex and not fully understood. Three patterns of colonic contraction are observed on radiologic studies: retrograde movements, segmental contractions, and mass movements. The latter cause propagation of colonic contents toward the anus. Colonic motility is influenced by emotions, hormones, and the amount of bulk in the diet.

Colonic Flora Bacteria account for one-third of the weight of the feces. There are 10^{11} to 10^{12} bacteria per gram of feces. *Bacteroides* species, an anaerobe, is the most common. *Escherichia coli* and other enterobacteria are the common aerobes, 10^{8} to 10^{10} organisms per gram. Colonic bacteria are important in the production of vitamin K. Suppression of the normal flora with broad-spectrum antibiotics may lead to overgrowth of pathogens, specifically *Clostridium difficile.*

Colonic Gas Ninety-nine percent of colonic gas is nitrogen, oxygen, carbon dioxide, hydrogen, and methane. The gas in the bowel is derived from swallowed air, bacterial fermentation of carbohydrates and protein in the bowel lumen, and diffusion to the bowel lumen from the blood. The average daily flatus volume is 600 cc. Hydrogen and methane are combustible, and accordingly, electrosurgery should not be performed on unprepared bowel. Complaints of excessive bowel gas may be improved by diet modifications.

DISORDERS OF COLONIC MOTILITY

Irritable Bowel Syndrome This is the most common cause of chronic abdominal pain. It is manifest by alternating constipation and diarrhea, pain, and bloating. Workup for organic causes of pain

is negative. Treatment includes reassurance, diet modifications, and antispasmodic medications.

Constipation This usually is defined as less than three bowel movements per week while on a high-residue diet. Causes include neoplasms, metabolic and endocrine disorders (hypothyroidism), neurologic diseases (Parkinson's disease), medications (narcotics, antidepressants), a low-fiber diet, colonic inertia with slow transit, and anomalies of the pelvic floor. A recent onset of constipation is an indication to study the colon for neoplasms. Slow colonic transit is evaluated by ingestion of radiopaque markers that are followed throughout the gastrointestinal (GI) tract with serial abdominal radiographs. Pelvic floor anomalies are evaluated by anal manometry and defecography (see below). In patients with colonic inertia documented by transit time study and normal pelvic floor function who do not respond to conservative treatment, surgical treatment with abdominal colectomy and ileorectal anastomosis should be considered.

Normal Function of the Anorectum

The rectum functions mainly as a reservoir and holds up to 1200 cc of liquid. The anal sphincter has an external component that provides the voluntary squeeze pressure and an internal component that provides the resting pressure. *Continence* is defined as controlled elimination of rectal contents. Defecation has the following stages:

1. Movement of feces into the rectum
2. Rectal-anal inhibitory reflex in which distention of the rectum causes relaxation of the internal anal sphincter
3. Voluntary relaxation of the external anal sphincter
4. Voluntary increase of intraabdominal pressure by the diaphragm and abdominal wall muscles, causing evacuation of feces through the anal canal

Dysfunction of the Anorectum

Incontinence This is defined as an inability to control rectal evacuation. The cause may be mechanical (such as damage to the sphincter during birth trauma) or neurogenic (diabetic neuropathy, multiple sclerosis). Evaluation of incontinence includes

1. Digital examination to assess the anatomy of the anal sphincter
2. Anal manometry assessing resting pressure, squeeze pressure, and sensation

3. Pudendal nerve terminal motor latency, which assesses velocity of conduction in the pudendal nerve
4. External sphincter electromyography
5. Endorectal ultrasound to assess integrity of the anal sphincter

Surgical correction of mechanical incontinence is aimed at restoring the circular integrity of the sphincter mechanism. In patients with extensive injury to the sphincter muscle and nerves, precluding sphincter repair, reconstruction may be done by encircling the rectum with a flap of gracilis or gluteus maximus muscle. Modest success is reported.

Obstructed Defecation This refers to deficient relaxation of the anal sphincter, specifically the puborectalis, on attempting defecation. Diagnosis is established by defecography, in which barium with stool consistency is installed in the rectum, and defecation attempts are documented on cinefluoroscopy.

DIAGNOSTIC TESTS IN COLON AND RECTAL DISEASE

The rectal examination is mandatory. The examining finger reaches about 8 cm above the dentate line and can detect distal rectal cancers and polyps, palpate prostatic nodules, detect neoplastic and inflammatory lesions in the cul-de-sac, assess the tone and integrity of the anal sphincter, and obtain stool for occult blood testing.

Tests for Occult Blood These are based on the peroxidase activity of blood, which creates a blue color reaction with guaiac gum by adding hydrogen peroxide. The false-positive rate is high because of other catalysts in the diet that produce the same reaction, as well as bleeding from other trivial sources in the GI tract not related to malignancy. Cancer also may bleed intermittently; occult blood tests might be negative in patients with malignancy. Despite this, occult blood testing of the stool is considered a standard test and has been proved to decrease mortality from colon cancer.

Carcinoembryonic Antigen (CEA) This glycoprotein is present in colorectal cancer and serves as biochemical marker for the malignancy. Its serum level is elevated in advanced and metastatic disease but usually is normal with localized disease. It also is elevated in other malignancies (e.g., breast, pancreas) and in ulcerative colitis, cirrhosis, and renal failure. It is nonspecific and not sensitive enough for screening purposes. Its main clinical use is for follow-up after operation. Serial elevations suggest recurrent or metastatic disease.

Endoscopic Tests *Rigid Proctosigmoidoscopy* The rigid sigmoidoscope is 25 cm long and 2 cm in diameter with an attached light source. The examination usually reaches 15 cm. Beyond this level it may cause significant discomfort to the patient. This is a good, simple, and inexpensive tool to fully assess the rectum, obtain biopsies, and remove small polyps. It can be done easily in an office setting. The preparation for the test is by administration of two Fleet enemas. A suction device is necessary.

Flexible Sigmoidoscopy The instrument is 60 cm long and uses fiberoptic or video technology. The examination usually reaches the middle descending colon and will detect up to 50 percent of large bowel malignancies. It is the standard screening tool for large bowel neoplasms in average-risk patients over age 50.

Colonoscopy The test allows visualization of the large bowel and the terminal ileum. The original technology was fiberoptic, but this has been largely replaced by video technology, which allows higher-resolution images, convenience for the examiner, and improved participation of the assistant staff. It is the most accurate tool in detecting colonic neoplasms, and it allows biopsy, removal of polyps, as well as control of large bowel bleeding; it usually is preferable to barium enema. The test requires good bowel preparation, similar to that of colon resection, and usually is done with intravenous sedation ("conscious sedation") on an outpatient basis. Complications, which are uncommon, include perforation and bleeding.

Imaging Techniques *Contrast Studies* The standard test is an air contrast ("double contrast") barium enema (BE), which has good sensitivity in detecting malignancies and polyps larger than 1 cm. The older "full column" barium enema is used less commonly because of lower sensitivity. Barium should be avoided in acutely ill patients, in whom peritonitis or perforation is a concern, as well as in patients who are likely to need colonoscopy or computed tomographic (CT) scan of the abdomen, because the presence of barium in the bowel interferes with these tests. Water-soluble contrast material (Hypaque, Gastrografin) is preferable in these situations.

Computed Tomographic (CT) Scan This is an excellent tool in assessing infectious processes like diverticulitis and abscesses. And it is a standard test in assessing liver metastases from colon cancer.

Magnetic Resonance Imaging (MRI) Unlike the CT scan, in MRI there is no need for intravenous contrast material, and the test can

be used safely in patients with renal failure and in those with allergy to contrast material.

Endorectal Ultrasound This is performed by inserting an ultrasound probe into the rectum. It is sensitive and accurate in assessing the depth of invasion of rectal cancer and lymph node involvement. It also is useful in assessing the anatomy of the anal sphincter and a perianal infectious process.

DIVERTICULAR DISEASE

Colonic diverticula are false, since their wall does not contain a muscle layer. The incidence of diverticulosis increases with age and is estimated to be 75 percent in Americans over age 80. Diverticulosis is attributed to the Western diet, which is low in dietary fiber. A possible mechanism of diverticular formation is increased intraluminal pressure causing herniation of the submucosa through weak areas in the colonic wall, usually at a site where an arteriole penetrates the wall. The part of the large bowel most affected is the sigmoid colon. Diverticulosis has the potential for complications but by itself is usually not associated with symptoms and could barely be considered a pathologic finding.

Diverticulitis

Diverticulitis is an inflammation starting in a diverticulum and affecting the tissues around the bowel wall; usually it is associated with perforation in the wall of the diverticulum. The part of the colon most often affected is the sigmoid ("left-sided appendicitis"). Patients with acute diverticulitis present with left lower quadrant pain, change in bowel habits, fever, localized tenderness, left lower quadrant mass, possible distention as a result of partial obstruction or ileus, pelvic tenderness on rectal examination, and leukocytosis. Diagnosis can be verified by CT scan of the abdomen showing inflammatory changes in the pericolic and mesenteric fat or with a water-soluble contrast study showing an extramucosal mass effect. If an abscess is seen on CT scan, percutaneous drainage under CT guidance can be done. Barium studies are undesirable in the acute stage of the disease.

Treatment Uncomplicated diverticulitis often can be treated on an outpatient basis with a clear liquid diet and broad-spectrum antibiotics by mouth (a combination of metronidazole and ciprofloxacin is safe and effective). Sicker patients should be hospitalized

and treated with intravenous antibiotics and bowel rest. Most patients respond to conservative treatment within 48 h.

In patients with recurrent attacks of diverticulitis or those who do not respond to medical treatment, surgery may be indicated. When surgery is performed electively with adequate antibiotic and mechanical bowel preparation, a primary anastomosis is constructed after resecting the involved segment.

In patients who present with free perforation and peritonitis, urgent surgery is necessary for sepsis control, which obviously does not allow for mechanical cleansing of the bowel. The involved segment of the colon, usually the sigmoid colon, is resected, the distal segment is closed as a blind pouch, and the proximal bowel is brought to the skin level as an end-colostomy (Hartmann's procedure). In experienced hands and with good-risk patients, primary anastomosis without a colostomy may still be considered. In patients who present originally with diverticular abscess, CT-guided percutaneous drainage may provide control of the acute sepsis and enable elective colon resection later.

Diverticulitis can cause fistulization between the sigmoid colon and adjacent organs, including the urinary bladder, vagina, and small bowel. A colovesical fistula will manifest with pneumaturia and recurrent urinary tract infections. Surgical treatment is resection of the involved colonic segment.

Bleeding from Diverticular Disease and Angiodysplasia

Because of the proximity of the diverticula to the colonic arterioles, erosion in the wall of the diverticulum may involve the arterial wall. The bleeding is painless, often massive, and may cause hypovolemic shock.

This primarily affects older patients. The two most common causes are diverticulosis and angiodysplasia. With angiography readily available, angiodysplastic lesions of the colon and the rest of the GI tract are frequently diagnosed. These lesions are acquired, occur in elderly people, and more commonly are localized in the right colon. An angiogram will show the site of the bleeding and the presence of an early filling vein resulting from arterial venous shunting within the lesion. Larger lesions can be detected colonoscopically.

Massive lower GI bleeding is defined as bleeding from a source distal to the ligament of Treitz that exceeds 3 units of blood in 24 h. Inflammatory bowel disease, ischemic colitis, and tumors may cause lower GI bleeding, but this rarely is massive or life threatening. With significant rectal bleeding, it is important to rule out a gas-

troduodenal source by placement of a nasogastric (NG) tube or, preferably, by esophagogastroduodenoscopy. Initial management includes volume resuscitation, correcting coagulopathy if present, and attempts to identify the source of bleeding. Diagnostic tests include proctoscopy to rule out an anorectal source, a tagged red blood cell scan, mesenteric angiography, and colonoscopy. The tests supplement each other, and the choice of the specific test depends on the clinical circumstances and the expertise of the examiner.

Between 75 and 90 percent of lower GI bleeding will stop without surgery. In the remaining patients, surgery is necessary to control bleeding. If the source of bleeding is definitely identified, segmental resection is performed. Otherwise, after ruling out bleeding from the small bowel and rectum, abdominal colectomy with ileostomy or with ileorectal anastomosis is performed.

INFECTIONS

Infectious Colitides

Bacterial Colitis Causative organisms include *Campylobacter,* pathogenic *E. coli, Salmonella,* and *Shigella.* The clinical presentation is that of acute diarrheal disease, sometimes bloody. Diagnosis is obtained by stool cultures and stool analysis for leukocytes. Most organisms are sensitive to aminoquinolines (e.g., ciprofloxacin).

Pseudomembranous Colitis This occurs in patients who received broad-spectrum antibiotics (e.g., clindamycin, semisynthetic penicillins, cephalosporins). Alteration of the normal colonic flora results in overgrowth of *C. difficile,* an anaerobe that produces an exotoxin that injures the colonic mucosa. This syndrome can occur up to 6 weeks after antibiotic therapy. The clinical spectrum varies from mild self-limited diarrhea to severe transmural inflammation, toxic colon, and perforation. Leukocytosis is out of proportion to the other clinical findings. Diagnosis is established by checking the stool for the toxin and endoscopy that may show the typical yellowish pseudomembranes. Treatment includes stopping the antibiotics, if possible, and metronidazole PO or IV. Vancomycin is an alternative treatment but is avoided, if possible, because of the risk of emergence of vancomycin-resistant *Enterococcus.* Patients with toxic colon or perforation may need resection. The recurrence rate after conclusion of treatment is about 20 percent.

Amebic Colitis The infection is caused by the protozoan *Entamoeba histolytica,* usually involves the colon, and may spread

secondarily to the liver as an amebic abscess. Most patients are asymptomatic carriers. Active disease manifests with multiple small ulcers throughout the colon but mainly in the cecum.

The clinical presentation is that of bloody diarrhea that may imitate ulcerative colitis. Complications include toxic colon, perforation, and development of cecal ameboma that may imitate cancer. Diagnosis is established by stool analysis of a fresh specimen. Treatment is metronidazole and Iodoquinol.

Cytomegalovirus (CMV) Colitis This occurs mainly in acquired immune-deficiency syndrome (AIDS) patients. Ten percent of these patients will develop CMV colitis with mucosal ulceration, diarrhea, hemorrhage, fever, and weight loss. Endoscopic biopsy may be diagnostic. The treatment is ganciclovir.

Infections of the Anorectal Region

ABSCESS AND FISTULA

Fistulas are the result of abscesses draining to the surface. Most abscesses originate in the anal glands, at the level of the dentate line. From there they may spread to different anatomic locations: the intersphincteric plane between the internal and external sphincters, the perianal space adjacent to the anus, the ischiorectal space between the rectum and the ischial tuberosity, or the supralevator space above the levator ani.

The main symptom is severe throbbing anal pain, typically keeping the patient awake at night. The examination reveals swelling and tenderness in the perianal area. If the abscess is intersphincteric, it may be detected only by rectal examination and may not be visible on the outside. The treatment is surgical drainage. Antibiotics are added to patients with extensive infection, have a high fever, or are immunocompromised. An intersphincteric abscess is drained through the anal canal by dividing the overlying mucosa and internal sphincter.

Fifty percent of patients treated by drainage will be cured. The other 50 percent will develop an additional abscess or a perianal fistula connecting the anal canal, usually at the level of the dentate line, to the perianal skin. Treatment of fistula is by fistulotomy, laying the tract open. If the fistula tract incorporates a significant part of the sphincter, fistulotomy may result in incontinence. An alternative treatment may be encircling the involved tissue with heavy silk thread or a rubber band (seton), which provides drainage and stimulates scarring. The seton can be removed later or allowed to gradually cut through the tissue it incorporates while scar formation is progressing, and a gap in the sphincter continuity is avoided.

PILONIDAL DISEASE

This is a sinus or abscess cavity in the sacrococcygeal area resulting from ingrowth of hair. It is most common in the second and third decades of life, with a male predominance. The primary opening is usually at the intergluteal crease in the midline, about 5 cm above the anus. The acute presentation is that of a painful abscess. After it resolves, a chronically infected and draining sinus remain. Identifying the typical midline pits makes the diagnosis. Surgical treatment includes unroofing and drainage of the sinus, but the primary openings have to be excised to prevent recurrence.

HIDRADENITIS SUPPURATIVA

This infection affects the apocrine sweat gland in the perianal region, with superficial sinuses and abscesses involving the dermis and subcutaneous tissue. Treatment is by wide drainage of the infected sinuses.

NECROTIZING PERINEAL INFECTIONS (FOURNIER'S GANGRENE)

This often occurs in compromised hosts (e.g., AIDS patients, diabetics, or those on chemotherapy), but sometimes without an obvious underlying illness, trivial infections of the perianal region or to the lower urogenital tract may develop into an aggressive, life-threatening soft tissue infection. The presenting picture is that of severe perineal pain, swelling, fever, leukocytosis, and gangrene of the soft tissue of the perineum. The infection usually is polymicrobial and synergistic. Treatment includes broad-spectrum antibiotics, aggressive debridement to the level of viable tissue, which may include excision of the scrotal skin, and sometimes a diverting colostomy.

SEXUALLY TRANSMITTED DISEASES OF THE ANORECTUM

These usually are transmitted by anal intercourse and are more common in male homosexuals. Infected vaginal discharge can transfer the disease to the anal area in females. Diagnosis is obtained by specific cultures and serologic tests, and treatment is with the appropriate antimicrobial agents. Conditions include gonococcal proctitis, anorectal syphilis, chlamydial proctitis, herpes proctitis, and anal warts.

Anal warts, or condylomata acuminata, are caused by human papillomavirus (HPV). HPV infections are the most common sexually transmitted diseases in Western countries. The lesions may be external, on the perineal skin, or internal, within the anal canal.

Diagnosis is made by the characteristic appearance and by histologic examination of removed specimens. Treatment is by surgical

excision and fulguration or by application of a variety of local preparations. The recurrence rate is high in all techniques used because of residual virus in the tissue, although surgical excision has the highest success rate. Certain serotypes of the papillomavirus are associated with malignant degeneration to squamous cell carcinoma, and accordingly, lifelong follow-up is recommended. Since a sexual contact can transmit more than one type of infection at a time, these patients also should be tested for infection with the human immunodeficiency virus (HIV), hepatitis B, hepatitis C, syphilis, gonorrhea, and chlamydia.

INFLAMMATORY BOWEL DISEASE

This includes two major entities, ulcerative colitis (UC) and Crohn's disease (CD). The two conditions are closely related and are attributed to a defect in immune regulation in the GI tract that leads to uncontrolled immune reaction to different antigens. Ulcerative colitis usually is confined to the large bowel, involving the mucosa (termed *mucosal colitis*), whereas Crohn's disease may affect any part of the GI tract, from the mouth to the anus, and usually involves the full thickness of the bowel wall. The clinical pictures overlap, and in 15 percent of patients the colitis is indeterminate. Symptoms usually are related to inflammation of the bowel and include diarrhea, rectal bleeding, tenesmus, abdominal pain, fever, and weight loss. Other organs may be affected, including the musculoskeletal system (spondylitis, arthritis), the skin (erythema nodosum, pyoderma gangrenosum), the eye (iritis), the hematopoietic system (anemia, thrombocytosis, hypercoagulable state), the kidneys (nephrolithiasis), and the biliary tract (sclerosing cholangitis, cholelithiasis).

Differences between the two entities include the fact that CD may affect any part of the GI tract, and in most patients the small bowel is involved, often in a noncontinuous distribution ("skipped" segments), whereas UC is usually continuous from the rectum proximally and usually involves the colon only and at the most the very distal part of the ileum ("backwash" ileitis); fistulas are rare in UC and common in CD; strictures are common in CD and rare in UC; perianal disease (fistulas, abscesses, fissures) are common in CD and uncommon in UC; and the malignant potential is higher in UC than in CD.

The clinical presentation depends on the extent of involvement, severity of the inflammation, and chronicity. The most acute presentation is that of toxic colon (not necessarily "megacolon") requiring aggressive medical management and often necessitating colectomy.

A milder form of ulcerative colitis may involve the distal large bowel, the rectum, or the rectum and the sigmoid colon. It is called *ulcerative proctitis* or *ulcerative proctosigmoiditis.* Ninety percent of these patients respond to medical treatment and never go on to develop *pancolitis.*

Medical Treatment of Inflammatory Bowel Disease

This is similar for ulcerative colitis and Crohn's disease, suggesting a like etiology. Sulfasalazine, the former mainstay of therapy, has been largely replaced by 5-aminosalicylic acid (5-ASA) preparations (Asacol, Pentasa), which have much fewer side effects and are better tolerated by patients. These are maintenance medications for stable ulcerative colitis and Crohn's colitis.

In acutely ill patients on initial presentation or in previously diagnosed patients with a flare-up, the acute stage is controlled with steroids, usually prednisone, in doses of 20–80 mg/day, with quick tapering of the dose on clinical response. The most severely ill patients may require hospitalization, intravenous fluids, bowel rest, and intravenous steroids. If there is no response to medical treatment within a few days, operation is performed usually by abdominal colectomy.

The role of immunomodulators (previously called *immunosuppressants*), such as 6-mercaptopurin (6MP) and Imuran, is gradually increasing as their efficacy and safety become better established. They are used mainly for maintenance therapy and as steroid-sparing drugs in patients who remain significantly symptomatic while on 5-ASA preparations alone. Side effects include bone marrow suppression, pancreatitis, and the theoretical concern of inducing malignancies, especially lymphomas. In long-term use, 6MP is better tolerated than prednisone and has fewer side effects.

Success has been reported in the use of short courses of cyclosporin A given intravenously to control acute colitis not responsive to steroids. The use of antibiotics has been studied extensively. The only one with proved efficacy is metronidazole for perianal Crohn's disease and in controlling abscesses and fistulas. In 1998 the Food and Drug Administration (FDA) approved a new drug, infliximab, a chimeric monoclonal antibody to tumor necrosing factor (TNF), for use in Crohn's disease resistant to other treatment.

Ulcerative Colitis

Indications for Surgery Indications include active disease not responsive to medical therapy, uncontrolled bleeding, toxic colon

not responsive to aggressive medical treatment, and risk of malignancy. In patients with ulcerative colitis for more than 7 years, colonoscopic surveillance is recommended every 1–2 years with multiple random biopsies. A finding of mucosal dysplasia is an indication for operative removal of the large bowel.

Surgical Management Because inflammation is confined to the large bowel, resection of this organ is curative, unlike Crohn's disease, which cannot be eradicated surgically and has a high risk of recurrence after resection. For decades, the operation of choice was total proctocolectomy with ileostomy. In the last 20 years, a sphincter-sparing operation evolved, restorative proctocolectomy. This involves resection of the colon and upper rectum, removal of the mucosa of the remaining rectum, constructing an ileal reservoir (pouch) from the terminal ileum, and anastomosing the reservoir at the level of the dentate line. The operation removes all large bowel mucosa while preserving the sphincter mechanism and maintaining continence. Candidates for this operation are younger patients, usually under 50 years of age, with adequate sphincter function and in whom Crohn's disease has been ruled out. They are willing to accept problems associated with the pouch, including the potential for mild incontinence, multiple bowel movements a day, and the potential for recurrent episodes of pouch inflammation ("pouchitis").

Crohn's Disease

Unlike ulcerative colitis, surgery is not curative, and recurrence rates are high. Surgery is indicated only for complications that do not respond to conservative treatment. Surgical treatment of Crohn's disease usually involves resection of the diseased segment of the bowel. When the presentation is acute with localized perforation, abscess, or phlegmon, it is desirable to control the acute complications nonsurgically and perform the operation on a less urgent basis.

Ileocolonic Crohn's Disease This variant involves the ileocecal area. It may present with obstruction, internal fistulization, or abscess formation. It is desirable to drain the abscesses percutaneously before operative resection.

Colonic Crohn's Disease Presentation is similar to that of ulcerative colitis, including toxic colon. Surgical options include total proctocolectomy with ileostomy or, in patients with relative rectal sparing, an abdominal colectomy with ileorectal anastomosis. Restorative proctocolectomy should not be done.

Anorectal Crohn's Disease This may manifest with bleeding, tenesmus, multiple abscesses and fistula formation, and loss of the reservoir capacity of the rectum due to scarring, leading to frequent bowel movement. In 35 percent of patients with Crohn's disease, the anus is involved, and in 4 percent, anal involvement is the first manifestation of the disease. Surgery for complications such as abscess and fistula should be as conservative as possible, avoiding cutting any part of the anal sphincter because of the poor healing of wounds and the risk of incontinence.

NEOPLASTIC DISEASE

The two most significant neoplastic lesions of the large bowel are adenoma, or adenomatous polyp, and adenocarcinoma. It usually is accepted that the two are related, representing different stages of the same process, and that most cancers are derived from adenomatous polyps, hence the adenoma-carcinoma or polyp-cancer sequence. Carcinoma arising de novo from flat colonic mucosa is much less frequent. One major exception is the cancer arising from dysplastic mucosa in inflammatory bowel disease, in which there is no "polyp stage." Accordingly, discussions regarding etiology and screening refer to both adenomatous polyps and cancer.

Etiology

The exact etiology is not known, but it is recognized that neoplastic proliferation of the large bowel mucosa is related to alterations in the genetic code, either in the germ line or as an acquired somatic mutation.

Genetic Considerations It is estimated that 10–15 percent of colorectal cancer cases are familial.

Familial Adenomatous Polyposis (FAP) An autosomal dominant disorder, the diagnosis requires the presence of more than 100 polyps in the large bowel. The polyps are adenomatous, and the process leading to malignancy follows the adenoma-carcinoma sequence. Extracolonic manifestations include desmoid tumors in the abdomen, osteomata, and adenomata of the stomach and duodenum. All patients will develop cancer, usually by age 40, unless treated surgically. In the past these patients were treated with abdominal colectomy and ileorectal anastomosis, necessitating continuous surveillance of the rectal mucosa for the development of polyps and malignancy, or with total proctocolectomy with

ileostomy. These procedures have been largely replaced with restorative proctocolectomy.

Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) The criteria for this syndrome include

1. At least three relatives with colorectal cancer, two of which are first degree
2. Involvement of at least two generations
3. At least one patient diagnosed under the age of 50.

The syndrome is characterized by autosomal dominant inheritance, early age at the manifestation of malignancy, predominance of lesions in the proximal colon, and tendency for synchronous and metachronous lesions. Accordingly, it is recommended that patients be treated with subtotal colectomy. A few different DNA defects were identified in this syndrome. The cancer develops from adenomatous polyps through the typical adenoma-carcinoma progression. In a variant of the syndrome there is an increased incidence of endometrial, gastric, ovarian, and urinary malignancies.

Dietary Factors Epidemiologic studies indicate that diet has a role in the development of colon cancer. In third world countries where diets include less processed food and are higher in fiber and lower in fat, the incidence of colorectal cancer is lower. When people from these countries immigrate to the United States, they acquire a higher rate of colon cancer. Dietary recommendations include decreasing the fat content and increasing the fiber in the diet.

Chronic Inflammation Inflammatory bowel disease, especially chronic ulcerative colitis, is associated with an increased risk of colon cancer. Early age of onset, involvement of the whole colon, and more than 10 years of the illness indicate high risk for malignancies. For patients with pancolitis for 25 years, the risk of cancer is estimated to be 40 percent. Accordingly, surveillance colonoscopy is recommended in patients with pancolitis starting at 7–10 years from onset and performed once a year. Multiple biopsies are obtained, and a finding of dysplasia indicates a possible need for operation.

Screening for Polyps and Cancer

Screening is aimed at the general population with average risk of large bowel cancer. The goal is to detect a neoplastic process at an early stage, ideally at the polyp phase of the polyp-cancer sequence. Complex considerations regarding cost-effectiveness, reliability, sen-

sitivity, and specificity all affect the choice of the screening test. Current recommendations are that average-risk patients over age 50 will have yearly fecal occult blood testing and flexible sigmoidoscopy every 5 years. If the occult blood testing is positive, or if polyps are found on sigmoidoscopy, pancolonoscopy is indicated. In individuals with a history of polyps, previous large bowel cancer, family history of colon cancer, or ulcerative colitis for more than 10 years, periodic colonoscopy is recommended. The interval depends on the specific clinical situation and usually is every 5 years.

Polyps

There are three histologic types: hamartomas, hyperplastic polyps, and adenomas. The latter is a true neoplasm with the most clinical significance.

Hamartomas A hamartoma is a growth showing excessive proliferation of one type of tissue without true neoplastic changes.

Peutz-Jeghers Syndrome This is an autosomal dominant syndrome manifested with pigmentation of the mucocutaneous areas and hamartomous polyps of the small and large bowel composed of excessive amounts of muscularis mucosa. Progression of the polyps to malignancy has been described but is not common. There is a higher incidence of malignancy in other organs, including breast and ovary. Symptoms include bleeding and bowel obstruction secondary to intussusception.

Juvenile Polyps These usually occur in children but are seen in adults as well. They are hamartomas composed of dilated glands and abnormal lamina propria. Bleeding secondary to autoamputation or intussusception can occur.

Familial Juvenile Polyposis This is an autosomal dominant syndrome with multiple juvenile polyps throughout the colon. It can manifest with bleeding or obstruction, and there is increased risk of GI malignancies. The treatment is subtotal colectomy.

Hyperplastic Polyps These are very common, usually less than 5 mm in size, with histologic examination showing no maturation and hyperplasia without nuclear dysplasia. They are not considered premalignant.

Adenomatous Polyps These are the most significant polyps because of frequency and malignant potential. Some will develop to

cancer, a process that may take 5–15 years. Morphologically, these polyps are described as pedunculated (with a stalk) or sessile (flat). Histologically, they are classified as tubular, villous, or mixed tubulovillous depending on the dominant pattern. The bigger the polyp, and the more villous component it has, the more the malignant potential.

Most benign polyps are asymptomatic. Occasionally, large pedunculated polyps can manifest with bleeding or intussusception. As a general rule, adenomatous polyps should be removed because of their malignant potential. Most polyps can be removed by colonoscopic snaring, usually in one piece. Large or sessile polyps may necessitate piecemeal polypectomy, in one or more sessions. Occasionally, in patients who are good surgical risks with a long life expectancy, large or sessile polyps that cannot be completely or safely removed by colonoscopic snaring may require colectomy.

Malignant polyps are those in which neoplastic changes proceed deep to the muscularis mucosa. For these, polypectomy may still be a sufficient treatment if the following criteria are fulfilled:

1. The polyp is pedunculated.
2. The stalk is not involved, and the margins of resection are free.
3. There is no vascular, lymphatic, or neural invasion, and the lesion is not poorly differentiated.

Large Bowel Cancer

This is the most common cancer of the GI tract. In women it is second only to breast cancer as a cause of cancer-related death, and in men it is third after carcinoma of the lung and the prostate. It is estimated that in 1998, 131,000 Americans will be diagnosed with the disease (95,000 colon, 36,000 rectum), and 56,000 will die. Rectal cancer is slightly more common in men; colon cancer is more common in women. The cumulative risk of an American to develop colorectal cancer during his or her life span is approximately 6 percent. The disease is related to age and occurs most often after age 50; screening efforts are directed to that age group. Five-year survival in North America is 40–50 percent.

COLON CANCER

Clinical Manifestations The presence of symptoms and their severity depend on the location and extent of the tumor. Tumors in the right colon present with occult bleeding, undetected by the patient, and may manifest with symptoms of iron-deficiency anemia. Such a finding in an adult male or postmenopausal female is an indication for colonoscopy. Tumors in the left colon may present with

visible bleeding, change in bowel habits, and crampy abdominal pain secondary to partial obstruction. Large bowel cancer also may present for the first time with metastatic disease to the liver, ascites, and pulmonary metastases.

Acute Presentation A significant number of patients with large bowel malignancy will present acutely with perforation or obstruction. Untreated obstruction may lead to ischemia and perforation. Perforation also may occur primarily at the site of the tumor as a result of transmural growth and necrosis.

Diagnosis and Evaluation In patients with symptoms suggestive of colon cancer, endoscopy is the test of choice because of its sensitivity and ability to obtain tissue samples for histologic examination. Synchronous lesions exist in up to 5 percent of patients and should be ruled out before making a surgical plan of treatment. When endoscopy is not feasible, contrast studies of the colon are used. CT scan of the abdomen may be used to rule out liver metastases. Carcinoembryonic antigen (CEA) determination is done preoperatively as a baseline study. Its elevation suggests metastatic disease.

Surgical Treatment Large bowel surgery is classified as "clean contaminated." When the bowel is open during operation, there is always some contamination of the operative field with colonic contents, including bacteria. Mechanical cleansing of the bowel before surgery significantly decreases the bacterial count and the risk of postoperative infection. Commonly used regimens include polyethylene glycol (PEG) lavage of the bowel and sodium phosphate laxatives. Additional reduction of bacterial counts in the bowel lumen is accomplished by oral antibiotics the day before surgery. The standard regimens are neomycin with erythromycin or neomycin with metronidazole. It also is a standard practice to administer intravenously broad-spectrum antibiotics just before surgery. Routine use of antibiotics postoperatively is not justified.

Operative Technique The objective of surgical treatment is to remove the involved segment of the bowel with the corresponding mesentery and the lymphatic channels. Because the lymphatics follow the arterial supply, the extent of resection corresponds to the arterial distribution. Any operation begins with thorough abdominal exploration to rule out peritoneal or hepatic metastases, as well as additional abdominal pathology (such as cholelithiasis). The segment of the colon is removed with the corresponding mesentery. The anastomosis can be performed manually or by stapling devices.

It should be tension-free and with a good blood supply to the anastomosed edges. The common resections for colon cancer are right colectomy, extended right colectomy, transverse colectomy, left colectomy, and sigmoid colectomy. The resected specimen is inspected to assess surgical margins. A minimal margin of 5 cm on either side of the tumor is desirable (smaller margins are acceptable in surgery for rectal cancer).

Emergency Operation This is performed for obstruction, perforation, and rarely, bleeding. Diagnosis is confirmed by contrast studies, preferably with water-soluble contrast material and not barium. Because, by definition, the bowel is not prepared, there is a higher risk of anastomotic leak and infection. Resection of the involved segment is always desirable. The standard approach is to avoid primary anastomosis and perform a resection and a colostomy. However, in selected good-risk patients there is a place for intraoperative cleansing of the colon by lavage with primary anastomosis, avoiding colostomy and its associated morbidity, psychological distress, and the need to perform an additional operation for closure.

Staging and Prognosis Prognosis is related to the staging of the tumor. The Dukes staging system was favored because of its simplicity. The following is the Astler-Coller modification:

Dukes A: Tumor confined to the submucosa
Dukes B1: Tumor extending to the muscularis propria
Dukes B2: Tumor extending beyond the serosa of the bowel
Dukes C1: Lymph nodes are positive, with tumor not extending beyond bowel wall
Dukes C2: Lymph nodes are positive, with tumor extending beyond the bowel wall
Dukes D: Distant metastases

The uncorrected 5-year survival for Dukes A, B, and C is 85, 65, and 46 percent, respectively; the corresponding corrected values are 100, 78, and 54 percent. Other prognostic factors not incorporated in the Dukes system are the histologic differentiation of the tumor, presence of venous and perineural invasion, bowel perforation, elevated CEA level, and aneuploid nuclei.

Adjuvant Chemotherapy This is indicated for patients with Dukes C staging. The standard combination is 5-fluorouracil (5-FU) with levamisole or 5-FU with leucovorin. These regimens

reduce mortality from the cancer by approximately 30 percent. Their value when residual metastatic disease is present is limited, and the side effects may outweigh the benefits.

Long Term Follow-Up Patients are followed with periodic liver function tests, CEA measurements, and CT scans of the abdomen if the previous tests are abnormal. Seventy percent of recurrent cancers will manifest within 2 years and 90 percent within 4 years. There is an increased risk of metachronous lesions (i.e., a second primary large bowel neoplasm that presents later), and follow-up with colonoscopy is indicated 1 year after the original operation and then every 3–5 years. Early detection of hepatic metastases may be of value in patients with only a few lesions and no extrahepatic disease. They can be treated with hepatic resection with up to 30 percent 5-year survival.

RECTAL CANCER

Similar to colon cancer, this usually is adenocarcinoma and derived from adenomatous polyps after the polyp-cancer sequence. The surgical approach is influenced by the proximity of the anal sphincter, the desirability of preserving the sphincter, and the proximity of the pelvic sidewalls limiting the extent of the resection. Unlike the rest of the large bowel, the rectum can be accessed easily through the anus for diagnostic and therapeutic purposes. Consideration in treatment planning includes the stage of the primary tumor, its relationship to the sphincter, and the presence of lymphatic or distant metastases.

Diagnosis Evaluation of rectal cancer includes digital examination to determine its size and degree of fixation, rigid sigmoidoscopy to assess its morphology and distance from the dentate line, and transanal ultrasound as the most accurate tool to assess depth of invasion and lymph node status. Pelvic examination should be performed in females to rule out invasion of the posterior wall of the vagina. The urinary system is assessed for possible ureteral obstruction or invasion of the prostate in males. CT scan is performed to assess the presence of liver metastases, which is an argument against radical treatment.

Surgical Treatment of Rectal Cancer When resection is performed, adequate distal and lateral margins should be accomplished, including the lymphatic-bearing area or the mesentery. If this allows preservation of the anal sphincter, continuity is reestablished by anastomosis. This procedure is low anterior resection, during

which the peritoneal reflection is opened to dissect the extraperitoneal rectum. The procedure is technically demanding and can be aided by the use of end-to-end stapling devices. The lymphatic drainage of the rectum is in a cephalad direction. Accordingly, requirements for a distal margin in rectal cancer are less than those for colon cancer, and a 2-cm margin is considered sufficient.

In lower rectal lesions, when safe margins cannot be accomplished without impairing the anal sphincter, the resection involves the anus and the sphincter mechanism, with construction of an end colostomy. This operation is abdominal-perineal resection (APR).

In small, favorable distal rectal lesions, good cure rates can be accomplished by nonresective procedures such as transanal excision or transanal fulguration of the lesion. These may be supplemented with external-beam radiation. Another technique is that of endocavity radiation, applying a high dose of low-energy radiation directly to the lesion through a specially designed proctoscope.

Adjuvant Therapy for Rectal Cancer The overall 5-year survival rate for rectal cancer is less than 50 percent. Local recurrence rate in the pelvis is 20–30 percent and is associated with major morbidity and subsequent mortality. Local recurrence is high in rectal cancer because of the limited ability to perform wide resection within the confines of the pelvis. Multiple studies have assessed the role of adjuvant therapy in decreasing local recurrence and improving survival. The current trend is to administer chemoradiation preoperatively or postoperatively, with the chemotherapy component including 5-FU, which presumably acts as a radiosensitizer.

COMPLICATIONS OF SURGERY FOR COLON AND RECTAL CANCER

Complications can include bleeding, infection, cardiopulmonary complications such as myocardial infarction and pulmonary embolus (most of these patients should be on prophylactic low-dose heparin perioperatively), and wound complications. A specific problem related to rectal surgery is impairment of the urogenital innervation, sympathetic and parasympathetic, resulting in sexual dysfunction (impaired erection, retrograde ejaculation) or impaired bladder function.

A major complication in patients undergoing bowel resection is that of anastomotic leak. This is most common after low anterior resection when the anastomosis is extraperitoneal. Small leaks without sepsis can be managed conservatively. Larger ones resulting in sepsis may require proximal diverting colostomy or ileostomy

and pelvic drainage. If, during the original operation, a low anterior anastomosis is considered to have a high risk for leak, it can be protected by proximal diverting colostomy or ileostomy.

Other Colorectal Tumors

Lymphoma The incidence of large bowel lymphoma has increased as a result of the AIDS epidemic, with the GI tract being a common site for the non-Hodgkin's HIV-associated lymphomas. Treatment includes resection with chemotherapy and radiation.

Large Bowel Carcinoid These are neuroendocrine tumors, with 2 percent of GI carcinoids occurring in the colon and 15 percent in the rectum. The tumor is located in the submucosa, usually is asymptomatic, and rarely behaves in a malignant fashion when it is less than 1 cm in size. Lesions bigger than 2 cm can invade the muscularis propria and metastasize to lymph nodes. Surgical treatment is local excision for smaller lesions and bowel resection for larger ones.

Anal Neoplasms

TUMOR OF THE ANAL MARGINS

This involves tumors below the dentate line. It includes squamous cell carcinoma, basal cell carcinoma, Bowen's disease (intraepidermal squamous cell carcinoma), and extramammary Paget's disease (tumor arising in the intraepidermal portion of the apocrine sweat glands). Diagnosis is made by biopsy, and the treatment is local excision with free margins. Advanced cases may require abdominal-perineal resection.

ANAL CANAL CANCER

This involves the transitional zone of the anal canal, 6–12 mm above the dentate line. Tumors in the area are referred to as *squamous*, *basaloid*, *cloacogenic*, or *transitional*. Diagnosis is established by biopsy. Small early lesions can be treated by local excision. For more advanced lesions, treatment formerly was abdominal-perineal resection. Currently, the Nigro protocol of chemoradiation, which combines chemotherapy with 5-FU and mitomycin C with external-beam radiation, is being used. It accomplishes a cure rate comparable with that of abdominal-perineal resection and has replaced radical surgery as the treatment of choice. If the regimen fails and the tumor recurs locally, abdominal-perineal resection is performed.

MISCELLANEOUS LESIONS

Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

The syndrome is an ileus involving the proximal large bowel, usually to the level of the splenic flexure. The clinical presentation simulates mechanical obstruction. It usually is seen in acutely ill patients or after a major trauma. Water-soluble contrast study or colonoscopy should rule out mechanical obstruction. Colonoscopy also can be used to decompress the distended proximal colon and is successful in most patients. In patients in whom colonic distention progresses and the cecal diameter exceeds 12 cm with no response to conservative treatment, there is a risk of cecal perforation. Surgical decompression with cecostomy or colostomy is indicated.

Volvulus

Volvulus is a twisting of a segment of the colon over the mesenteric axis causing closed-loop obstruction that can lead to strangulation and gangrene. It accounts for less than 10 percent of large bowel obstruction in the United States.

SIGMOID VOLVULUS

This accounts for more than 90 percent of colonic volvulus, usually in chronically ill and elderly patients. The clinical presentation is that of abdominal pain, distention, and obstipation. Diagnosis is established by plain film revealing a distended sigmoid loop; it is verified by water-soluble contrast study. This shows a "bird's beak" deformity at the point of obstruction. Barium should not be used in these acutely ill patients. In patients with overt peritoneal signs, an operation is indicated. Otherwise, sigmoidoscopic or colonoscopic decompression is indicated and is successful in most patients. The recurrence rate is high, and elective surgical resection is indicated in patients who are reduced without surgery.

CECAL VOLVULUS

This occurs in younger patients and is related to an anatomically redundant cecum and right colon. The patient presents with abdominal pain, nausea, and vomiting. Plain abdominal x-rays reveal a distended cecum. The diagnosis may be verified with a water-soluble contrast study. Colonoscopy is used to reduce the volvulus nonoperatively. When this fails or in cases of overt peritoneal signs suggesting gangrene of the cecum, surgery is indicated. Surgical

treatment may be detorsion, cecopexy, tube cecostomy, or right colectomy.

TRANSVERSE COLON VOLVULUS

This is the least common type of colonic volvulus. Presentation, diagnosis, and treatment are similar to those of sigmoid colon volvulus.

Ischemic Colitis

This usually is a disease of the elderly. It occasionally is related to occlusion of a major mesenteric vessel (such as ligation of the inferior mesenteric artery during surgery for abdominal aortic aneurysm), but in the majority of patients no specific vascular disease or underlying cause is identified. It is presumed to be secondary to low flow without arterial occlusion. Angiogram has no diagnostic role. Clinical presentation depends on the severity of the ischemia. Most cases are mild and present with low abdominal pain, passage of bright red blood per rectum, and mild to moderate abdominal tenderness. The involved colonic segment usually is around the splenic flexure, which is the watershed area between the superior and inferior mesenteric arterial supply. Diagnosis is established by contrast studies that show "thumbprinting" of the involved colonic segment and colonoscopy that shows edema and ecchymosis of the mucosa. Mild and moderate cases respond to medical treatment, including intravenous fluids and antibiotic. Severe cases with full-thickness necrosis of the bowel wall require surgery and resection. Follow-up studies (barium enema or colonoscopy) are indicated a few weeks after the acute event to rule out postischemic strictures.

Radiation Proctitis

This usually is associated with radiation for cervical and uterine cancer, bladder cancer, or prostate cancer. The rectum, because of its proximity to the cervix and prostate, is the part of the large bowel most commonly affected by radiation. Injury usually occurs when radiation exceeds 5000 cGy. In early stages, it manifests with mucosal edema and acute ulceration. The patient presents with abdominal pain, diarrhea, nausea and vomiting, tenesmus, and rectal bleeding. In the chronic stages, there is progressive vasculitis with fibrosis and thickening of the bowel wall and possible stricture formation, perforation, or fistulization. The main symptoms in the chronic stage are tenesmus and bleeding. Treatment includes stool softeners, topical 5-aminosalicylic acid preparations, and steroid enemas. Local application of 10% formalin solution to the rectal

mucosa is effective in controlling persistent bleeding. In patients whose symptoms are not controlled by conservative measures, colostomy or proctectomy may be necessary.

Rectal Prolapse

This involves eversion and protrusion of the full thickness of the rectum through the anus. It is related to defective fixation of the rectum to the pelvic sidewalls. It is more common in women, in the elderly, and in institutionalized patients. Symptoms include sensation of a mass, anorectal pain, bleeding, mucous discharge, and incontinence. In the early stages the prolapse reduces spontaneously. As the condition progresses, manual replacement may be required. In extreme cases, the rectum may be irreducible with subsequent risk of necrosis, which may require an urgent operation. Surgical treatment options include transabdominal resection, fixation of the rectum to the sacrum, or resection of the prolapse by perineal approach. The latter, by avoiding laparotomy, can be done with relative safety on high-risk patients. Anal encircling procedures usually have poor results and are not recommended.

Anal Fissure

This is a painful lineal ulcer in the anal canal below the dentate line, located in the posterior midline in 90 percent of the patients. The typical symptoms are severe "cutting" type pain on defecation and a small amount of blood on the toilet paper or stool. The pain may last for a few hours after bowel movement. The cause is passage of hard stool through an anal sphincter that does not fully relax, causing a tear in the anoderm. When a fissure becomes chronic, a skin tag develops caudad to it ("sentinel pile"), and the anal papilla cephalad to it becomes hypertrophic. Diagnosis is by direct inspection, preferably in a jackknife position. Severe pain and tenderness may preclude any additional examination beyond inspection on the initial presentation. A large proportion of patients respond to dietary fiber (preferably psyllium derivatives) and stool softener (sodium docusate).

Two newly described treatments are aimed at relaxing the internal sphincter. Application of 0.3% topical nitroglycerine cream to the anal canal was reported to induce healing in 60 percent of patients. Intrasphincteric injection of botulinum toxin (Botox) transiently paralyzes the sphincter for 6 months, allowing healing of the fissure. Surgery is indicated in patients who fail conservative treatment and have significant symptoms. It should be used only as a last resort because of the associated risk of anal incontinence, es-

pecially in females. The operation is lateral internal sphincterotomy, dividing the distal part of the hypertrophic internal sphincter caudad to the dentate line. It usually is done under local anesthesia on an outpatient basis. The success rate is 90–95 percent.

Rectovaginal Fistula

The most common cause is obstetric injury, including midline episiotomies that do not heal well. Other causes include Crohn's disease, malignancies, and radiation injuries. The patient describes the distressing symptom of passing gas and stool through the vagina. Diagnosis usually is evident on sigmoidoscopy and vaginal examination. Treatment depends on the cause of the fistula, its size, and its level (high or low). Most patients with obstetric injury can be treated with endorectal mucosal advancement flap, which obliterates the fistula on its rectal aspect. In patients with malignancy or severe Crohn's disease, proctectomy and colostomy may be required.

Pruritus Ani

Perianal itching often is idiopathic but may be related to diet, specifically ingestion of coffee, dairy products, alcohol, and diet drinks. Pinworm infestation is the most common cause in children. Treatment includes dietary modification and short-term use of local steroid preparations.

Hemorrhoids

Hemorrhoidal tissue is a part of the normal anal anatomy, composed of a cushion of submucosal vascular and connective tissue, and is located in the upper part of the anal canal, above the dentate line. The tissue is more prominent in the right anterior, right posterior, and left lateral positions, thus forming three separate complexes. The presumed function of this tissue is to improve closure of the anal canal. The term *external hemorrhoids* refers to the vascular complexes underneath the anoderm, below the dentate line. Hard stool and prolonged straining on defecation may cause engorgement and dilation of the veins and stretching of the connective tissue, resulting in bleeding and prolapse of tissue, the two main symptoms of hemorrhoids. While hemorrhoids are the most common cause of rectal bleeding, other causes, especially neoplasms, have to be ruled out. This is particularly important in older patients. Uncomplicated internal hemorrhoids usually do not cause pain. In patients who complain of significant anal pain, other causes

have to be looked for (e.g., abscess, fissure, thrombosed external hemorrhoids).

Internal hemorrhoids are arbitrarily classified to four degrees of severity:

1. Bleeding only
2. Bleeding and prolapse of tissue outside the anus on defecation that reduces spontaneously
3. Prolapse that requires manual reduction
4. Irreducible prolapse

Treatment Most patients respond to dietary fiber (psyllium derivatives that are hydrophylic are preferable over "dry" fiber). For patients who continue to bleed, nonsurgical treatments, including rubber band ligation, photocoagulation with infrared light, and injection of sclerosants, are used. Cryosurgery, which was popular in the past, is not recommended because of its side effects. Excisional hemorrhoidectomy is not a minor operation, has a significant complication rate, and should be used only as a last resort.

External hemorrhoids occasionally present with thrombosis, manifested as a painful lump under the anoderm. This usually can be excised with local anesthesia as an office procedure. Incision and evacuation of the clot are not recommended because of the high rate of recurrence and bleeding.

For a more detailed discussion, see Kodner IJ, Fry RD, Fleshman JW, Birnbaum EH, and Read TE: Colon, Rectum, and Anus, chap. 26 in *Principles of Surgery,* 7th ed.

CHAPTER

27

APPENDIX

FUNCTION AND ANATOMY

Lymphoid tissue appears in the appendix 2 weeks after birth. The number of follicles peaks at 200 between ages 12 and 20 years. Secretory immunoglobulins are produced as part of gut-associated lymphoid tissues to protect the milieu interior. Appendectomy does not predispose to bowel cancer or alter the immune system. The appendix is useful but not indispensable. The base arises from the posteromedial aspect of the cecum, where three taeniae coli meet. The length and location of the free end are variable: pelvic, retrocecal, or either lower quadrant. Congenital defects are rare and clinically insignificant.

INFLAMMATION: ACUTE APPENDICITIS

Incidence Most common acute surgical condition of the abdomen. Most frequent in the second and third decades; parallels amount of lymphoid tissues in appendix. More common in males, especially during pubertal years. Overall incidence 1.3:1 male predominance. Incidence has been declining in the last several decades.

Etiology and Pathogenesis Obstruction of lumen caused by fecalith, lymphoid hypertrophy, inspissated barium, seeds, or intestinal worms. Symptomatic closed-loop obstruction develops because of the continued mucosal secretion into 0.1-mL capacity lumen and because of rapid multiplication of resident bacteria of the appendix. Distention stimulates visceral afferent pain fibers, producing vague, dull, diffuse middle and lower abdominal pain. Sudden distention may cause peristalsis with cramping. Venous pressure is exceeded, and arteriolar inflow causes vascular congestion of the appendix, with reflex nausea. Serosal engorgement inflames the parietal peritoneum with shift or more severe pain to the right lower quadrant. Mucosal compromise allows bacterial invasion, with consequent fever, tachycardia, and leukocytosis. With progressive

distention, antimesenteric infarction and perforation occur. Occasionally, episodes of acute appendicitis resolve if obstruction is relieved; subsequent pathologic examination reveals thickened, scarred appendiceal wall.

Clinical Manifestations *Symptoms* Classic progression of symptoms includes anorexia (almost all have it), followed by constant moderate periumbilical pain with shift in 4 – 6 h to sharp right lower quadrant pain. Variable position of the tip of the appendix or malrotation allows variability in pain location. Subsequent episodes of emesis may occur with obstipation or diarrhea, particularly in children.

Signs Determined by the position of the appendix and whether ruptured. Vital signs show mild tachycardia or temperature elevation of 1°C. Position of comfort is fetal or supine with legs drawn up, especially right. Positional movement causes pain. Anterior appendix gives maximal tenderness, guarding, and rebound at McBurney's point (one-third the distance from the anterosuperior iliac spine to the umbilicus). Cutaneous hyperesthesia may be present early in the area supplied by right spinal nerves T10, T11, and T12. Rovsing's sign (pain in the right lower quadrant with palpation in the left lower quadrant) indicates peritoneal irritation. Psoas sign (slowly extending the patient's right thigh when lying on the left side) demonstrates nearby inflammation when stretching the iliopsoas muscle. Obturator sign (passive internal rotation of the flexed right thigh with patient supine) indicates irritation near the obturator internus. A retrocecal appendicitis may present with flank pain. A pelvic appendicitis may give pain on rectal examination with pressure on the cul-de-sac of Douglas.

Laboratory Findings Mild leukocytosis of 10,000–18,000/mm^3 with moderate polymorphonuclear predominance. Pyuria is present when the inflamed appendix lies near the ureter or bladder. Bacteriuria indicates urinary tract infection.

Radiography Radiographs rarely are helpful. Plain abdominal films may show a nonspecific bowel gas pattern. A fecalith in the right lower quadrant is suggestive of appendicitis. Gentle barium enema shows nonfilling of the appendix and mass effect on the medial and inferior borders of the cecum; complete filling of the appendix rules out appendicitis. Graded compression sonography may reveal a noncompressible appendix, 6 mm or greater in the anteroposterior direction. Computed tomographic (CT) scan is useful, especially with suspected abscess. Chest radiography rules out

right lower lung field disease, which may simulate right lower quadrant pain by irritating T10, T11, and T12 nerves.

Laparoscopy can be diagnostic and therapeutic, especially in females to rule out gynecologic pathology. Laparoscopic appendectomy is possible.

Complications—Rupture Rupture occurs after unrelenting obstruction of the lumen leads to gangrene distal to the occlusion. Usually occurs distal to a fecalith. Spillage is contained locally in 95 percent of patients. A phlegmon of inflamed, matted loops of intestine and omentum may resolve or may expand in contained fashion to form a periappendiceal abscess or to cause intestinal obstruction.

Incidence Rupture is present in 15–25 percent of patients at presentation, with a higher incidence in pediatric and geriatric age groups.

Diagnosis Abdominal pain occasionally (only 4 percent) lessens temporarily after rupture because of sudden relief of distention; in most patients, pain continues unabated. A tender, boggy mass may be palpable on rectal examination in the right lower quadrant. Degree of distention, ileus, fever, tachycardia, leukocytosis, and toxic appearance parallel the severity of peritonitis. Temperature rise and degree of leukocytosis are markedly higher than with simple appendicitis.

Differential Diagnosis That of the acute abdomen. Preoperative diagnosis of acute appendicitis should be 85 percent accurate depending on the location of the appendix, the length of the symptoms, and the age and sex of the patient.

Acute Mesenteric Adenitis Most often in childhood, recent upper respiratory infection, generalized lymphadenopathy.

Acute Gastroenteritis Generally viral etiology; associated vomiting, diarrhea, cramping, and relaxation between hyperperistaltic waves. *Salmonella* gastroenteritis results from ingestion of contaminated food; historically disables groups of patients. *S. typhosa* infection is rare, characterized by rash, inappropriate bradycardia, leukopenia, and positive stool cultures.

Diseases of the Male The diseases that mimic abdominal pain are testicular torsion, epididymitis, and seminal vesiculitis.

Meckel's Diverticulitis Same preoperative picture as appendicitis. Requires diverticulectomy, occasionally bowel resection.

Intussusception Most under 2 years of age, currant jelly stool, intermittent crampy attacks of pain, right lower quadrant sausage-shaped mass. Initial attempt at reduction by barium enema.

Acute Ileitis or Regional Enteritis Associated with diarrhea and often a chronic history, but infrequency of anorexia, nausea, and emesis. If found at laparotomy, incidental appendectomy is indicated to decrease subsequent confusing symptoms (not done if the cecum is involved because of the greater risk of postoperative fistula).

Perforated Peptic Ulcer Right gutter spillage of upper gastrointestinal contents with rapid sealing of perforation causes prominence of right lower quadrant symptoms.

Diverticulitis or Perforating Carcinoma of the Colon Requires exploration.

Epiploic Appendagitis Infarction secondary to torsion. Pain present but no peritonitis or obstruction.

Urinary Tract Infection Right costovertebral angle tenderness and bacteriuria present.

Ureteral Stone Hematuria and referred pain to scrotum or labia present. Pyelography confirms diagnosis.

Primary Peritonitis Treated with antibiotics after paracentesis shows simple gram-positive flora.

Henoch-Schönlein Purpura Occurs several weeks after streptococcal infection; associated with purpura, joint pains, and nephritis.

Yersiniosis Transmitted via contaminated food; mimics appendicitis. *Campylobacter jejuni* causes diarrhea and pain with positive stool cultures.

Gynecologic Disorders Pelvic inflammatory disease, usually bilateral, associated with lower pelvic pain and cervical motion tenderness, occurs perimenstrually; Gram stain of vaginal discharge often shows gram-negative diplococci. Ruptured graafian follicle

mimics appendicitis with spillage of sufficient blood and fluid into pelvis; occurs at ovulation (Mittelschmerz). Ovarian torsion, endometriosis, ruptured ectopic pregnancy. Laparoscopy is useful in diagnosis.

Others Foreign-body bowel perforations, mesenteric vascular occlusion, right lower chest pleuritis, acute pancreatitis, hematoma of abdominal wall.

Select Groups

THE YOUNG

Faster progression of disease with high fever and emesis and more frequent rupture at diagnosis (15–50 percent).

THE ELDERLY

Deceptively mild clinical course with increased morbidity because of higher incidence of concomitant disease and higher perforation rate.

THE PREGNANT

Expected frequency for age group. Diagnosis more difficult because the appendix is displaced cephalad and lateral by gravid uterus; pain, nausea, and leukocytosis are common in normal pregnancy, but a left shift indicates an acute process. Maternal mortality is negligible. Fetal mortality overall is 2–8.5 percent, 20 percent with appendiceal perforation and peritonitis. Operation carries 10–15 percent risk of premature labor.

AIDS OR HIV INFECTION

Clinical presentation no different, although leukocytosis may be absent. Cytomegalovirus enteritis, tuberculosis, or lymphoma of distal ileum can mimic appendicitis.

Treatment

Treatment is always operative because the obstructed lumen will not resolve with antibiotics alone. Acute appendicitis without rupture is treated with immediate appendectomy after the medical evaluation is complete. Ruptured appendicitis with local peritonitis or phlegmon is operated on early after resuscitation for fluid and electrolyte losses. Ruptured appendicitis with spreading peritonitis requires more extensive fluid resuscitation, but the patient should undergo operation normally within 4 h to prevent continued peritoneal contamination.

Ruptured appendicitis with periappendiceal abscess formation may be treated acutely with operation, but this is associated with increased morbidity. If symptoms are of several days' duration, subsiding, and associated with right lower quadrant mass, initial nonoperative therapy with fluid resuscitation, bowel rest, and large doses of antibiotics is appropriate, possibly in conjunction with ultrasound-guided abscess drainage. If vital signs, leukocytosis, and abdominal signs progress, drainage of abscess may be indicated, followed by conservative therapy. Interval appendectomy in 6 weeks to 3 months is advised, although the overall rate of recurrence without interval appendectomy ranges from 0–37 percent.

Preoperative antibiotics lower infectious complications, but the regimen is controversial. If simple acute appendicitis, there is no benefit to more than 24 h of antibiotics. If perforated or gangrenous, antibiotics are given until the patient is afebrile and the white blood cell count is normal. Pathogens in acute appendicitis are mixed colonic flora, both aerobic and anaerobic; *Bacteroides fragilis* needs coverage. Clindamycin plus an aminoglycoside or a second-generation cephalosporin regimen is popular.

Procedure Incision should be in the right lower quadrant for patients with suspected appendicitis. A McBurney (oblique) or a Rocky-Davis (transverse) muscle-splitting incision is most common. If an abscess is suspected, a lateral incision is used to prevent peritoneal contamination. A lower midline incision is used if the diagnosis is in question. A lower midline incision also is used for general exploration but is contraindicated with abscess because infected material must be brought through the uncontaminated peritoneal cavity.

The appendiceal stump can be simply ligated or ligated with purse-string or Z-stitch inversion. If appendicitis is not found, the pelvic organs and remaining abdominal viscera are explored. The mesentery is examined for lymphadenitis. The ileum is "run" for terminal ileitis or Meckel's diverticulitis.

Drainage of localized pus is accomplished with lateral drains. The peritoneal cavity cannot be drained. If the appendix is ruptured, subcutaneous fat and skin are left open to heal by granulation or secondary closure. Primary wound closure is almost always used in children.

Appendectomy can be performed by the laparoscopic approach. This is especially suited to women in whom a differential diagnosis of gynecologic disease is entertained. Obese patients may benefit from the laparoscopic approach. Intracorporeal stapling devices are used to divide the mesoappendix and the appendiceal base.

Prognosis

Mortality is 0.1 percent if unruptured acute appendicitis, 3 percent if ruptured, and 15 percent if ruptured in the elderly. Death usually is from sepsis, pulmonary embolism, or aspiration; improving rates are seen with earlier diagnosis before rupture and better antibiotics.

Morbidity is increased with rupture and older age. Early complications are septic. Wound infection requires reopening of the skin incision, which predisposes to dehiscence (less common with muscle-splitting incision). Intraabdominal abscesses may occur from peritoneal contamination after gangrene and perforation. Fecal fistula results from necrosis of a portion of the cecum by an abscess or constricting purse-string suture or from a slipped ligature. Intestinal obstruction may occur with loculated abscesses and adhesion formation. Late complications include adhesion formation with mechanical obstruction and hernia.

TUMORS

Neoplasms are uncommon. Benign lesions may cause obstruction with acute appendicitis. Malignant tumors total less than 1 percent.

Carcinoid tumors of the gastrointestinal tract are found most commonly in the appendix (45–75 percent). Only 3 percent of these metastasize, and even fewer produce malignant carcinoid syndrome. Three-fourths present in the distal third of the appendix as small, firm, circumscribed, yellowish-brown tumors. If confined to appendix and less than 2 cm, treatment is with appendectomy and wide resection of mesoappendix; if greater than 2 cm, a right hemicolectomy is used.

Adenocarcinoma usually is discovered incidentally at appendectomy and behaves like colon carcinoma. Treatment is with right hemicolectomy.

Mucocele is a cystic dilatation of the appendix containing mucoid material. Appendectomy is the treatment for benign (retention cysts, mucosal hyperplasia, cystadenoma) or malignant (mucous papillary adenocarcinoma) lesions. Rupture or iatrogenic spillage results in pseudomyxoma peritonei.

For a more detailed discussion, see Kozar RA, Roslyn JJ: Appendix, chap. 27 in *Principles of Surgery,* 7th ed.

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CHAPTER

28

LIVER

ANATOMY

The liver constitutes approximately one-fiftieth of total body weight. True division into right and left lobes (hemilivers) is in line with the fossa for the inferior vena cava posteriorly and the gallbladder fossa anteroinferiorly (Cantlie's line). Couinaud proposed a functional division of the liver related to the hepatic venous drainage (Fig. 28-1).

Biliary Drainage Each sector is drained by a major segmental duct. The anterior and posterior sectoral ducts in the right lobe join

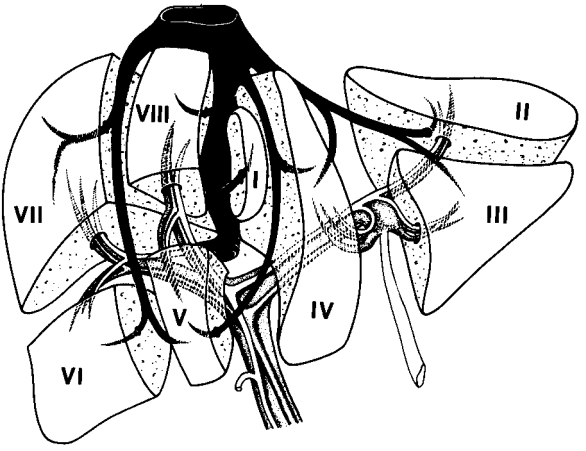

FIGURE 28-1 The functional division of the liver and the segments according to Couinaud's nomenclature. (From: Bismuth H: Surgical anatomy and anatomical surgery of the liver. *World J Surg* 6:2, 1982, with permission.)

to form the right hepatic duct, whereas the medial and lateral segmental ducts in the left lobe terminate in the left hepatic duct, which joins the right duct to form a common hepatic duct in the porta hepatis.

Blood Supply The afferent blood supply to the liver arises from two sources: (1) the hepatic artery, which carries oxygenated blood and accounts for approximately 25 percent of hepatic blood flow, and (2) the portal vein, which accounts for approximately 75 percent of hepatic blood flow and drains the splanchnic circulation. The common hepatic artery originates from the celiac axis, and it bifurcates into a right and left branch to the left of the line dividing the right and left lobes. The major right hepatic artery originates from the superior mesenteric artery in 17 percent of people. Intrahepatic anastomoses between the right and left hepatic arteries do not occur. The cystic artery usually is an extrahepatic branch of the right hepatic artery.

The portal venous system returns to the liver the blood that the celiac, superior mesenteric, and inferior mesenteric arteries supply to the gastrointestinal (GI) tract, pancreas, and spleen. The vessel is formed behind the pancreas by the confluence of the superior mesenteric and splenic veins and, at times, the inferior mesenteric vein. The portal vein resides posteriorly in relation to the hepatic artery and bile duct in the hepatoduodenal ligament. In the porta hepatis, the vein divides into two branches, which course to each lobe. The hepatic venous system begins in the liver lobules as a central vein into which the sinusoids empty, forming collecting veins that gradually increase in size and coalesce to form the three major hepatic veins. Total hepatic blood flow is 1500 mL/min/1.73 m^2 of body surface.

LIVER FUNCTION

The liver consists of four interrelated physiologic-anatomic units: the circulatory system, the biliary passages, the reticuloendothelial system, and functioning liver cells (hepatocytes).

Function Tests

The so-called liver function tests (Table 28-1) evaluate liver activity by assessing the degree of functional impairment.

Proteins Hepatic cells are responsible for the synthesis of albumin, fibrinogen, prothrombin, and other factors involved in blood

TABLE 28-1
NORMAL VALUES FOR HEPATIC "FUNCTION" TESTS

Test	Normal Value
Serum albumin	3.5–4.6 g/dL
Total protein	6.0–7.4 g/dL
Cholesterol	135–300 mg/dL
Alkaline phosphatase	24–100 IU/dL
Serum glutamic oxalacetic transaminase (AST)	10–36 units/dL
Serum glutamic pyruvic transaminase (ALT)	10–48 units/dL
Gamma glutamyl transferase (GGT)	0–48 units/dL males 4–26 units/dL females
Lactic acid dehydrogenase (LDH)	180–225 units/dL
Prothrombin time	90–100% of laboratory control
Fibrinogen	200–400 mg/dL
Blood "ammonia"	10–63 μg/dL
Serum bilirubin	
Total	Less than 1.4 mg/dL
Direct	Less than 0.3 mg/dL
Indirect	Less than 1.1 mg/dL
Urinary bilirubin	0

clotting. Because the half-life of albumin is 21 days, impairment of hepatic synthesis must be present for over 3 weeks before abnormalities are noted.

Carbohydrates and Lipids Glycogenesis, glycogen storage, glycogenolysis, and the conversion of galactose into glucose all represent hepatic functions. Hypoglycemia is a rare accompaniment of extensive hepatic disease. The more common effect of hepatic disease is a deficiency of glycogenesis with resulting hyperglycemia. The liver is the major organ involved in the synthesis, esterification, and excretion of cholesterol. In the presence of parenchymal damage, both the total cholesterol and percentage of esterified fraction decrease.

Enzymes The three enzymes that achieve abnormal serum levels in hepatic disease and have been studied widely are alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT). SGOT is present in the liver, myocardium, skeletal muscles, kidney, and pancreas. Cellular damage in any of the above-mentioned tissues results in elevation of the serum level, and in the liver, most marked increases accompany acute cellular damage regardless of cause. Extremely high levels are noted in patients with hepatitis. SGPT is a more specific marker of liver disease. Elevations accompany acute hepatocellular damage. Serum alkaline phosphatase provides an indication of the patency of the bile channels. Elevation occurs in any form of obstruction including calculi, neoplasm, or intrahepatic cholestasis. In the presence of space-occupying lesions such as metastases, primary hepatic carcinoma, and abscesses, the alkaline phosphatase level also is increased. Nucleotidase levels are elevated in hepatobiliary disease.

Dye Excretion The hepatic removal of dyes from the circulation depends on hepatic blood flow, hepatocellular function, and biliary excretion. The presence of jaundice, fever, shock, hemorrhage, or cellular damage causes a disproportionate indocyanine green or sulfobromophthalein (Bromsulphalein) retention.

Coagulation Factors In liver disease, multiple coagulation defects may occur. Two mechanisms contribute to the deficiency of coagulation factors: (1) in obstructive jaundice, the bile source required for the absorption of the fat-soluble vitamin K results in a decreased synthesis of prothrombin, and (2) hepatocellular dysfunction is accompanied by an inability of the liver to synthesize prothrombin. Decreases in factors V, VII, and IX and fibrinogen also have been noted in hepatic disease. Cirrhosis may have increased fibrinolysis.

SPECIAL STUDIES

Needle Biopsy Almost 100 percent accuracy has been demonstrated for both posthepatitic and postnecrotic cirrhosis. Intrahepatic cholestasis, hepatitis, and cellular degeneration resulting from toxicity are readily diagnosed. Focal lesions occassionally may be missed. Needle biopsy is contraindicated for suspected hemangioma.

Ultrasound, Computed Tomography, Magnetic Resonance Imaging, and Scintigrams Preoperative ultrasound (US) has its highest yield in defining hepatic abscesses, cystic lesions, and most

hemangiomas. US and duplex scanning can determine the patency of a portasystemic shunt noninvasively. Computed tomography (CT) is used with or without vascular enhancement. For most lesions, CT provides the best results. Magnetic resonance imaging (MRI) is particularly applicable for assessing vascular lesions.

Angiography Angiography may depict hepatic tumors, both primary and metastatic. When used in conjunction with CT, sensitivity and specificity are increased. Angiography also demonstrates extrahepatic vascular anatomy and provides a "road map" for the surgeon.

TRAUMA

See Chap. 6, Trauma.

HEPATIC ABSCESSES

Hepatic abscesses are related to two distinct groups of pathogens: pyogenic bacteria and *Entamoeba histolytica.*

Pyogenic Abscesses

Incidence The highest percentage occur in the sixth and seventh decades.

Etiology Causes include (1) ascending biliary infection, (2) hematogenous spread via the portal venous system, (3) generalized septicemia with involvement of the liver by way of the hepatic arterial circulation, (4) direct extension from intraperitoneal infection, or (5) other causes, including hepatic trauma. The most frequent antecedent cause has been cholangitis secondary to calculi or carcinoma in the extrahepatic biliary duct system. The second most common cause is related to generalized septicemia. There is an increased incidence in immunocompromised patients. Cultures are positive in over 90 percent; *Escherichia coli, Klebsiella,* and *Streptococcus* are most commonly isolated. *Staphylococcus* and *Pseudomonas* are occurring more frequently, and mixed bacterial and fungal abscesses are noted in about 25 percent. Abscesses may be solitary, multiple, and multilocular.

Clinical Manifestations The primary clinical manifestation is fever, frequently accompanied by chills, profuse sweating, nausea,

vomiting, and anorexia. Pain is a late symptom and is more common with large, solitary abscesses. Hepatic tenderness is present in 50 percent.

Diagnostic Studies Leukocytosis is usual; anemia is frequent. Positive blood cultures are seen in 40 percent of patients. Liver function tests are not diagnostic, but elevation of the alkaline phosphatase level is the most frequent abnormality. CT scan is the most accurate radiographic study (over 90 percent), followed by US (80 percent) and radionuclide scans (70 percent).

Treatment Treatment is based on appropriate antibiotic therapy combined with drainage in selected patients. Intravenous antibiotics are usually administered for 2 weeks, followed by 1 month of oral therapy. Abscesses may be drained percutaneously under US or CT control. Equivalent results have been reported for percutaneous and surgical drainage. Surgical access may be transthoracic or transabdominal. Occasionally, for multiple abscesses confined to a lobe, treatment is best managed by resection.

Prognosis and Complications For percutaneous and surgical drainage, there is 7.5–20 percent mortality (for multiple abscesses, the rate is significantly increased).

Amebic Abscesses

Ten percent of the population is infected with *Entamoeba histolytica*. Amebic abscesses usually are diagnosed in middle-aged adults with male-female ratio of 9:1. Organisms reach the liver via the portal system. The abscess is usually a solitary right lobe abscess with "anchovy paste" fluid.

Clinical Manifestations Clinical manifestations include fever, liver pain (88 percent), and occasionally right shoulder pain. Fever with diaphoresis and rigors is seen in 75 percent. Fifty percent of patients show antecedent diarrhea; bloody, mucous stools are seen in children. The liver is tender and enlarged on examination. Jaundice is rare.

Diagnostic Studies/Complications Leukocytosis and anemia accompany prolonged disease. The recovery rate of ameba in stool is 15.4 percent. Liver function tests are not helpful. The indirect hemagglutination test usually is positive. Scans also are useful. Aspiration of the cavity shows characteristic material, trophozoites in less than one-third. Secondary bacterial infection is evident in

22 percent. Abscesses may rupture (6–9 percent) or extend into adjacent organs.

Treatment Amebicidal drugs are used first; metronidazole is the drug of choice. Treatment may require aspiration and drainage if symptoms persist, the abscess remains apparent radiographically, or it is secondarily infected.

Prognosis The mortality rate is less than 5 percent in uncomplicated cases; with complications, the rate can rise to 43 percent.

CYSTS AND BENIGN TUMORS

Nonparasitic Cysts

These include degenerative, dermoid, lymphatic, retention, and proliferative cysts. Solitary cysts usually occur in the right lobe and have clear contents. The liver may be honeycombed, *polycystic*, which is associated with polycystic kidneys. Rarely, a polycystic liver may cause portal hypertension. *Traumatic cysts* usually are single and filled with bile. *Cystadenomas* are filled with mucoid material. Cysts usually grow slowly with few symptoms and present as painless right upper quadrant masses. Symptoms result from pressure on adjacent organs. Pain occurs with rupture, torsion, or hemorrhage. Jaundice is rare. Liver function tests have little value. CT and US are very useful for diagnosis.

Treatment Asymptomatic cysts require observation only. Surgical treatment can consist of complete extirpation. Large, deep, sterile cysts may be widely unroofed. Purulent contents demand external drainage. Polycystic livers may require nonanatomic resection and wide fenestration. Prognosis follows that of the associated renal polycystic disease, if any.

Hydatid Cysts

Hydatid cysts usually are unilocular and caused by *Echinococcus granulosus.* The alveolar type is caused by *E. multiocularis.* Seventy percent are located in the liver; one-third are multiple. The right lobe is affected in 85 percent. The cyst is two-layered and encapsulated with the contents under pressure and is colorless, opalescent. Daughter cysts can be inside the main cyst. *Alveolar* disease has no capsule with multiple metastases, blood, and lymphatic invasion.

Complications Complications include intrabiliary rupture (5–10 percent), suppuration with biliary bacteria, and intraperitoneal or intrapleural rupture.

Clinical Manifestations These cysts usually are asymptomatic. Early symptoms result from pressure on adjacent organs. Pain, tenderness, and palpable mass are common. If the cyst is secondarily infected, symptoms are those of pyogenic abscess. Hydatid cyst may present with anaphylaxis if there is an intraperitoneal rupture. Biliary rupture can present with colic, jaundice, and urticaria.

Diagnostic Studies Round, calcified shadows are seen on plain films. CT scan is very useful. Indirect agglutination is positive in 85 percent. Casoni's skin test is positive in 90 percent.

Treatment Treatment is surgical. Cysts must be removed without contaminating the peritoneal cavity. Cysts may be drained intraoperatively and flushed with hypertonic saline, alcohol, or hibitane before excision. Large cysts may require partial hepatectomy. The cavity may be managed by omentoplasty and simple closure. External drainage has a high complication rate. In the past, alveolar disease of the liver was inevitably fatal, but more recently, satisfactory results have been obtained with extensive hepatic resection.

Benign Tumors

Hamartoma This lesion is composed of normal tissues arranged in disorderly fashion. Hamartomas are firm, nodular, encapsulated, and cystic and usually are of no clinical significance.

Adenoma This tumor may be related to oral contraceptives, pregnancy, diabetes mellitus, or glycogen storage disease. It should be resected particularly if it is enlarging or bleeding. Because of the risk of bleeding and malignant potential, adenomas should be removed.

Focal Nodular Hyperplasia (FNH) Focal nodular hyperplasia is a solitary, tan, unencapsulated tumor near the liver edge that usually is asymptomatic; it rarely ruptures. It should be resected only if symptomatic. Deep biopsy is necessary for diagnosis.

Hemangioma This is the most common liver nodule. The female-male ratio is 5:1. There is no malignant potential. Most hemangiomas are asymptomatic; bruit is rare. Symptoms are related

to size. They rarely rupture and hemorrhage. Diagnosis is by angiography, CT, US, MRI, or scintigram. Avoid needle biopsy because of bleeding. Infants may have high-output congestive heart failure and may respond to steroids or hepatic artery ligation. Adults should only be resected for symptoms and when size is greater than 4–5 cm.

MALIGNANT TUMORS

Primary Carcinoma

Incidence Primary liver carcinoma is common in Asians and African aborigines. In children, hepatoblastoma is common before age 2. Aflatoxins and low-protein diets have been implicated etiologically. *Postnecrotic cirrhosis* frequently precedes, with serologic markers for hepatitis B virus or hepatitis C antibody in patients living in endemic areas.

Pathology *Hepatocellular carcinoma* (most common), followed by *cholangiocarcinoma* (bile duct cancer) and *hepatoblastoma*, an immature variant in children. *Fibrolamellar carcinoma* is a hepatocellular variant occurring in young adults.

There is frequent invasion of the portal and hepatic veins. Extension is via (1) centrifugal growth, (2) parasinusoidal extension, (3) venous spread, and (4) distal metastasis by lymphatic and vascular systems, most often to nodes and lungs. Metastases occurs in 48–73 percent.

Clinical Manifestations Weight loss and fatigue are evident in 80 percent, pain in 50 percent. Hepatomegaly is very common; splenomegaly and portal hypertension are likely in 33 percent. Jaundice and ascites are common. Children usually present with a mass.

Diagnostic Evaluation Alkaline phosphatase and 5'-nucleotidase levels usually are elevated. The bilirubin level often is normal. Alpha-fetoprotein (AFP) is present in 30–75 percent. Arteriography and CT/MRI are useful. Preoperative needle biopsy also is useful. Intraoperative US is used to define resection limits.

Treatment The only chance for survival is surgical excision. Cirrhosis compromises resection possibilities. Use of intraoperative US has permitted limited resections, particularly in cirrhotic patients. Transarterial chemoembolization has achieved 1-, 2-, and 5-year survival rates of 51, 24, and 6 percent, respectively, while

decreasing the tumor size in almost 33 percent of patients. Unresectable hepatocellular carcinomas may be converted to resectable lesions with combined radiation and chemotherapy.

Percutaneous ethanol injection has resulted in the disappearance of tumors less than 4.5 cm in diameter. Cryosurgery using an intraoperatively placed probe that delivers liquid nitrogen also has effected tumor necrosis and destruction. Transplantation and resection yield equivalent 5-year survival rates of approximately 50 percent, but the recurrence rate is lower in patients who were transplanted. Transplantation achieves the best results in patients with small, uninodular or binodular lesions. Resection of extrahepatic recurrences of hepatocellular carcinomas has resulted in several 5-year survivals.

In the case of hepatoblastoma, particularly in children, lesions often deemed not resectable can be converted into resectable tumors that have potential for cure. A combination of preoperative chemotherapy followed by resection has resulted in a cure rate of 90 percent in children.

Prognosis Prognosis is extremely poor for adults but better for fibrolamellar carcinoma. Resectable children under age 2 have better survivals.

OTHER PRIMARY NEOPLASMS

These include angiosarcomas (vinyl chloride, Thorotrast), mesenchymomas, and infantile hemangioendotheliomas.

Metastatic Neoplasms

Metastatic neoplasms are the most common malignant liver tumor with a ratio 20:1 to primary tumors. Metastases in the liver are noted in 25–50 percent of all cancer deaths. Routes to the liver are via (1) portal vein, (2) lymphatics, (3) hepatic artery, and (4) direct extension. Metastases often grow more rapidly than the original lesion.

Clinical Manifestations Symptoms are evident in 67 percent, with pain, ascites, jaundice, anorexia, and weight loss. A mass is seen in 50 percent. Flushing is evident in hepatic carcinoid.

Diagnosis The alkaline phosphatase level is elevated in over 80 percent, SGOT elevation is seen in 67 percent, and the AFT level is normal. Carcinoembryonic antigen (CEA) may be elevated in colon metastases. CT/MRI, particularly CT with intraarterial infusion, angiography, and intraoperative US are all useful.

Treatment Resection should be considered if (1) the primary is controlled, (2) there are no other metastases, (3) the patient will tolerate the procedure, and (4) total extirpation is possible. Resection of metastases has a survival benefit for colorectal carcinoma and Wilms' tumor. Twenty percent of colon carcinomas have metastases, of which 25 percent are resectable; 50 percent have other negating factors. A multi-institutional study of liver resection for colorectal metastases reported a 33 percent 5-year survival and a 21 percent 5-year disease-free survival. Colorectal hepatic metastases, initially considered unresectable, have been treated with doxorubicin. This resulted in regression to a size that permited resection.

Intraarterial infusion chemotherapy may provide symptomatic relief, but most series show no improvement over intravenous therapy. Cures of metastatic Wilms' tumor by liver resection combined with chemotherapy and radiation have been reported.

HEPATIC RESECTION

Indications include (1) trauma with devascularization of hepatic tissue, (2) cysts, (3) granulomas, (4) primary neoplasms, and (5) secondary neoplasms. Up to 80 percent resection may be tolerated in noncirrhotics. Regeneration occurs from marked hypertrophy of remaining tissue. Insulin is an anabolic factor.

Management of the Patient Preoperative therapy is directed at maintaining optimal liver function and correcting any defects that may be present. A diet high in calories, proteins, and carbohydrates is used, and the administration of albumin may be required to achieve normal levels. Vitamin K is given routinely until a normal prothrombin time results. In the presence of jaundice, other fat-soluble vitamins are added. Fresh frozen plasma will rapidly replenish coagulation factors. Because many patients have a reduced hematocrit, transfusion with fresh whole blood rich in platelets and coagulation factors is indicated. Major hepatic resection is attended by a prohibitive mortality rate in the patient with sulfobromophthalein retention greater than 35 percent, a serum albumin level lower than 2.0 g, and an increased prothrombin time that does not respond to parenteral vitamin K. Postoperatively, infusion of 10% glucose is continued until the patient maintains an adequate oral intake to obviate severe hypoglycemia, which has been reported. After more intensive resections, daily administration of 25–50 g albumin usually is required for 7–10 days to maintain the serum level above 3 g/dL. Antibiotics are administered prophylactically. Analgesics and hypnotics that are detoxified by the liver are used

only sparingly. Intraabdominal abscess formation and sepsis are the most common complications of major hepatic resection, occurring in 20–30 percent of patients. Subphrenic abscesses usually can be managed with percutaneous drainage.

Operative Procedures The major aim is to prevent/control hemorrhage. The porta hepatis may be clamped safely for 60 min. Resection follows anatomic planes of segmental anatomy based on portal distribution. The liver is mobilized by dividing the triangular ligament, coronary ligament, and ligamentum teres. Porta hepatis dissection defines the artery, vein, and duct to be removed, which are temporarily occluded. Glisson's capsule is incised, and the hepatic parenchyma is cleaved bluntly, ligating ducts and vessels and heading toward the hepatic veins, which are then doubly ligated at the cava. This is followed by division of porta hepatis structures.

On the basis of new concepts of segmental anatomy, the following classification of hepatic resection is applicable (Fig. 28-2): (1) *Subsegmental* or *wedge resection* is removal of an area of the liver that is less than a segment and without an anatomic dissection plane. (2) *Left lateral segmentectomy* (formerly "left lobectomy") is excision of the liver mass to the left of the left segmental fissure along an anatomic plane. (3) *Left medial segmentectomy* is resection between the main interlobar fissure and the left segmental fissure. (4) *Left lobectomy* ("left hepatectomy") is excision of all hepatic tissue to the left of the main lobar fissure. (5) *Right lobectomy* ("right hepatectomy") is removal of the liver to the right of the main lobar fissure. (6) *Extended right lobectomy* is excision of the entire lobe plus the medial segment of the left lobe *(trisegmentectomy)*, i.e., excision of all tissue to the right of the umbilical fossa, fossa for the ligamentum venosum, and the ligamentum teres. Based on portal distribution, there are eight hepatic segments that can be resected individually or as combinations (see Fig. 28-1).

PORTAL HYPERTENSION

Etiology (Table 28-2) The causes include (1) increased inflow (rare), (2) extrahepatic outflow obstruction, (3) extrahepatic portal obstruction, and (4) intrahepatic obstruction. The overwhelming majority (>90 percent) of cases result from *intrahepatic obstruction.* Contributing factors include (1) fibrosis with portal venule compression, (2) compression by regenerative nodules, (3) increased arterial flow, (4) fatty infiltration and inflammation, and (5) intrahepatic vascular obstruction. *Nutritional cirrhosis* is the most common cause worldwide, which is related to ethanol consumption in Western civ-

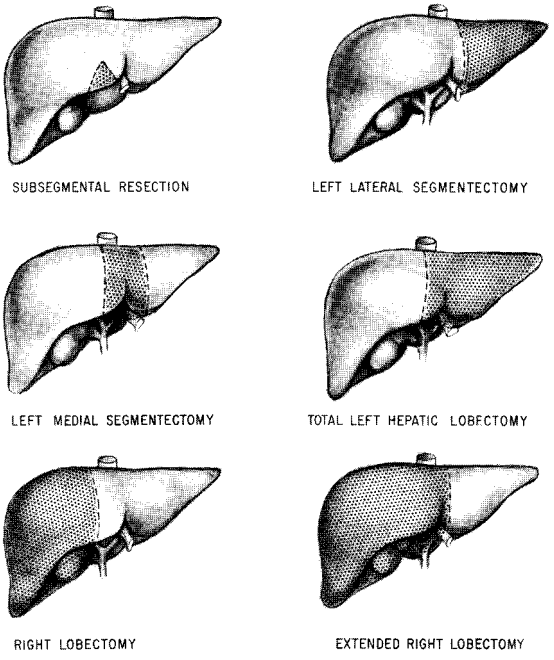

FIGURE 28-2 Nomenclature for hepatic resection.

ilization. Resistance to flow is postsinusoidal (on the hepatic venous side of the sinusoid). *Postnecrotic cirrhosis* accounts for up to 12 percent but represents the major cause in the Orient.

Pathophysiology Elevated pressure in the portal venous system leads to collateral venous flow. The normal portal pressure is less than 25 cmH_2O; mean is 21.5 cmH_2O. Pressure may be measured intraoperatively, by direct splenic puncture, or by occlusive hepatic venous pressure (OHVP), which is analogous to the pulmonary "wedge" pressure. Anatomy may be defined by *splenoportography* or the venous phase of mesenteric arteriography. Normally, no collaterals should be seen. Collaterals that become functional are (1) *hepatopetal collaterals,* which shunt blood from an obstructed

TABLE 28-2
ETIOLOGY OF PORTAL HYPERTENSION

- Increased hepatopetal flow without obstruction
  - Hepatic arterial-portal venous fistula
  - Splenic arteriovenous fistula
  - Intrasplenic origin
- Extrahepatic outflow obstruction
  - Budd-Chiari syndrome
  - Failure of right side of heart
- Obstruction of extrahepatic portal venous system
  - Congenital obstruction
  - Cavernomatous transformation of portal vein
  - Infection
  - Trauma
  - Extrinsic compression
- Intrahepatic obstruction
  - Nutritional cirrhosis
  - Postnecrotic cirrhosis
  - Biliary cirrhosis
  - Other diseases with hepatic fibrosis
    - Hemochromatosis
    - Wilson's disease
    - Congenital hepatic fibrosis
  - Infiltrative lesions
  - Venoocclusive diseases
    - *Senecio* poisoning
    - Schistosomiasis

extrahepatic portal system to the normal intrahepatic vasculature (they are the veins of Sappey and the cystic, epiploic, hepatocolic, hepatorenal, diaphragmatic, and suspensory ligament veins), and (2) *hepatofugal collaterals*, which are the most common type (they are the coronary and esophageal veins, the superior hemorrhoidal veins, the umbilical vein, and the veins of Retzius). These vessels shunt blood away from the liver to the systemic venous system.

Esophagastric Varices

Initially, submucosal veins enlarge; later, submucosa disappears, and veins that line the inside of the esophagus erode from esophagitis and hemorrhage. Gastric varices predominate in the cardia.

Thirty percent of cirrhotics with varices will bleed within 2 years of diagnosis. Seventy percent of these patients die within 1 year of the first hemorrhage; 60 percent rebleed within 1 year.

Acute Bleeding Usually this is the first sign of portal hypertension in children. In adults, varices account for 25–33 percent of massive upper GI bleeds. In cirrhotic patients, bleeding is a result of varices in 50 percent, gastritis in 30 percent, and ulcers in 9 percent. A specific diagnosis must be made before treatment. Physical examination shows stigmata for cirrhosis. Esophagoscopy is the most accurate tool. Arteriography may be useful in ulcer disease.

Treatment *Nonoperative Techniques* Balloon tamponade is risky and has a failure rate of 25–55 percent. Endoscopic variceal sclerosis or vein ligation may control bleeding in up to 93 percent of patients with similar mortality to emergency shunts. Ligation is equivalent to that of sclerotherapy, with fewer complications. Vasopressin or somatostatin reduces portal flow by 40 percent. Peripheral venous infusion is the route of choice. Vasopressin is risky in patients with coronary disease. Inderal may be used as prophylaxis. Transjugular intrahepatic portosystemic shunts (TIPS) can effectively lower portal pressure.

The incidence of TIPS shunt dysfunction is 15–60 percent over a 6- to 12-month period. Patency can be reestablished. TIPS are particularly applicable in patients with minimal hepatic reserve in whom a transplant is indicated.

Surgical Therapy This includes transesophageal ligation and emergency portosystemic shunt. The results of transesophageal ligation have improved significantly with stapling techniques, and results better than those with sclerotherapy have been reported. A more liberal use of emergency portacaval shunts to stop bleeding has been advised for the cirrhotic patients whose bleeding cannot be controlled by nonoperative measures. Emergency portosystemic shunt is an important option for selected patients with acute variceal bleeding. Emergency shunt performed on 400 unselected patients within 8 h of initial contact indicated survival rates of 85, 78, and 71 percent at 30 days, 5 years, and 10 years, respectively. In most series, the mortality rate for patients with Child's class C disease remains high. Pediatric variceal bleeding often stops spontaneously with bed rest and sedation. Important tenets in treatment include correction of coagulation deficits with component therapy. Acute bleeding in cirrhotics exacerbates or will induce encephalopathy.

Prevention of Recurrent Hemorrhage Shunting procedures in adults whose bleeding has stopped are much safer if performed electively. Prognosis is correlated with hepatic function as per Child's criteria. Patients with nutritional, alcoholic, or cryptogenic cirrhosis have a worse prognosis than do patients with biliary cirrhosis or extrahepatic portal vein obstruction. For patients with end-stage liver disease and marked hepatocellular dysfunction, after the bleeding has been controlled with sclerotherapy or TIPS, orthotopic liver transplantation often is appropriate.

Ascites

Mechanisms are poorly understood. Portal hypertension is a contributory but not sole etiologic factor. Hypoalbuminemia and reduced serum osmotic pressure contribute to ascites. Impairment of hepatic venous outflow appears to be most important. Accompanying ascites is the retention of sodium and water.

Treatment Treatment includes rest, nutritional supplementation, low sodium intake, and potassium repletion. Diuretics include furosemide, chlorothiazide (first line), and aldosterone antagonists (spironolactone). Multiple paracenteses are contraindicated. Intractable ascites may require peritoneal venous shunts (complications include disseminated intravascular coagulation). TIPS also have been effective.

Hypersplenism

Splenomegaly accompanies portal hypertension. Subsequent hypersplenism may follow (white blood cell count $< 4000/mm^3$, platelet count $< 100{,}000/mm^3$). Splenectomy *rarely* is indicated and negates future selective shunting.

Encephalopathy and Coma

Portal-systemic encephalopathy rarely occurs in portal hypertension without coexisting hepatocellular dysfunction. Portacaval shunts may show up to 38 percent incidence. Physiologically, there is hyperammonemia secondary to portal-systemic collaterals and impairment of the ornithine-citrulline-arginine cycle. Dietary protein and intraluminal intestinal blood (variceal bleed) are major contributors. Endogenous intestinal urea production also contributes. Clinical manifestations include altered consciousness, reflexes, and motor activity, which can progress from confusion to frank coma.

Treatment Treatment should focus on reducing nitrogen within the gut, reducing ammonia production, and enhancing ammonia metabolism. This includes (1) restriction of protein intake, (2) control of bleeding, (3) GI catharsis (lactulose), (4) intestinal bacterial reduction (neomycin), and (5) intraluminal ammonia trapping (lactulose).

Surgery of Portal Hypertension

PROCEDURES THAT DIRECTLY ATTACK BLEEDING VARICES

These include transesophageal ligation of varices and esophageal transection. Control is only temporary, with 50 percent of cirrhotic survivors rebleeding. The *Sugiura procedure* includes esophageal transection, paraesophageal devascularization, splenectomy, and vagotomy with or without drainage. It has a high mortality and has a significant rebleed rate.

PROCEDURES THAT REDUCE PORTAL PRESSURE

These are classified as totally or partially diverting shunts. The most basic procedure is the *end-to-side portacaval shunt,* which completely diverts all portal inflow from the liver to the vena cava. The *side-to-side portacaval shunt* diverts portal flow but additionally allows reversed portal outflow from the liver. Other functional side-to-side shunts include the mesocaval, central splenorenal, and H-graft procedures. In decompressing the portal vein, all these do not preserve hepatic portal inflow. The *distal splenorenal* or *Warren shunt* is truly selective in decompressing varices while maintaining portal perfusion via a continued hepatic portal hypertension. This procedure is associated with less encephalopathy, but statistical differences in true survival, long-term preservation of portal flow, and ascites are unproved.

Shunt Selection Shunt selection should include preoperative portograms to assess portal vein patency. Budd-Chiari syndrome mandates a side-to-side shunt. Ascites may or may not alter shunt preference, with side-to-side shunts having the lowest incidence. If subsequent orthotopic transplantation is anticipated, it is preferable to consider a distal splenorenal shunt.

Patient Selection This includes evaluation of ascites, coagulation deficits, and liver function (bilirubin, sulfobromophthalein retention). Child's classification is predictive of operative morbidity and mortality. Overall, group A patients have nearly no elective mortality, whereas group C patients have up to 53 percent operative mortality.

Operative Technique Should always include pre- and postshunt portal pressure measurements.

Complications of Portal-Systemic Shunts Complications include intraoperative bleeding or shunt failure, postoperative rebleeding, hepatic failure, hepatorenal syndrome, cardiorespiratory failure, and delayed complications such as encephalopathy, hemosiderosis, and ulcer disease.

PORTACAVAL SHUNT FOR GLYCOGEN STORAGE DISEASE AND HYPERCHOLESTEROLEMIA

Improvement occurs after portacaval shunt in children with type I glycogen storage disease; there is no evidence of encephalopathy. The shunts also are used for type 2 hypercholesterolemia.

FULMINANT HEPATIC FAILURE

This is sudden, severe hepatic failure secondary to massive cellular necrosis. The usual origin is acute viral hepatitis. It is also seen with Reye syndrome and with chemical toxins (carbon tetrachloride). Therapy is supportive and includes hemo- and peritoneal dialysis, exchange transfusions, and plasmapheresis. Mortality is 85–90 percent. Spontaneous recovery occurs in 10–20 percent. Orthotopic liver transplantation is the treatment of choice in moribund patients.

For a more detailed discussion, see Schwartz SI: Liver, chap. 28 in *Principles of Surgery*, 7th ed.

CHAPTER

29

GALLBLADDER AND EXTRAHEPATIC BILIARY SYSTEM

ANATOMY

Duct System The extrahepatic biliary system begins with the hepatic ducts and ends at the stoma of the common bile duct in the duodenum. The right hepatic and the left hepatic ducts join to form a common hepatic duct that is 3–4 cm in length. It is then joined at an acute angle by the cystic duct to form the common bile duct. The common bile duct is approximately 8–11.5 cm in length and 6–10 mm in diameter. The lower third of the common bile duct curves more to the right behind the head of the pancreas, which it grooves, and enters the duodenum at the hepatopancreatic ampulla (of Vater), where it is frequently joined by the pancreatic duct. The common bile duct and the main pancreatic duct may (1) unite outside the duodenum, (2) unite within the duodenal wall, or (3) exit independently into the duodenum. Separate orifices have been demonstrated in 29 percent of autopsy specimens, and injection into cadavers reveals reflux from the common bile duct into the pancreatic duct in 54 percent. Radiographically, reflux from the common bile duct into the pancreatic duct is present in about 16 percent of persons. The sphincter of Oddi surrounds the common bile duct at the ampulla of Vater. This provides control of the flow of bile and, in some cases, pancreatic juice. An ampullary sphincter that is present in one-third of adults may produce a common channel for the terminal common bile and pancreatic ducts.

Gallbladder The gallbladder is located in the bed of the liver in line with that organ's anatomic division into right and left lobes. It has an average capacity of 50 mL and is divided into four anatomic portions: the fundus, the corpus or body, the infundibulum, and the neck. The fundus is the rounded, blind end that normally extends beyond the liver's margin. It contains most of the smooth muscle of the organ, in contrast to the corpus or body, which is the major storage area and contains most of the elastic tissue. The body tapers into the neck, which is funnel shaped and connects with the cystic duct. The neck usually may be distended into a dilatation

known as the *infundibulum*, or *Hartmann's pouch*. The lumen is lined with a high columnar epithelium that contains cholesterol and fat globules. The mucus secreted into the gallbladder originates in the tubular alveolar glands in the globular cells of the mucosa lining the infundibulum and neck.

Blood supply to the gallbladder is by the cystic artery, which normally originates from the right hepatic artery behind the cystic duct. It is approximately 2 mm in diameter and courses above the cystic duct for a variable distance until it passes down the peritoneal surface of the gallbladder and branches. Venous return is carried through small veins, which enter directly into the liver, and a large cystic vein, which carries blood back to the right portal vein. Lymph flows directly from the gallbladder to the liver and drains into several nodes along the surface of the portal vein.

The nerves of the gallbladder arise from the celiac plexus and lie along the hepatic artery. Motor nerves are made up of vagus fibers mixed with postganglionic fibers from the celiac ganglion. Sensory supply is provided by fibers in the sympathetic nerves coursing to the celiac plexus through the posterior root ganglion at T8 and T9 on the right side.

The gallbladder is connected with the common duct system via the cystic duct, which joins the common hepatic duct. The segment of the cystic duct adjacent to the gallbladder bears a number of mucosal folds that have been referred to as the *valves of Heister*. Immediately behind the cystic duct resides the right branch of the hepatic artery. The length of the cystic duct is highly variable, although the average is around 4 cm. Variations of the cystic duct and its point of union with the common hepatic duct are surgically important. It may be extremely long and unite with the hepatic duct at the duodenum, or it may be absent or very short and have a high (cephalad) union with the hepatic duct, in some cases joining the right hepatic duct instead.

Anomalies

The classic description of the extrahepatic biliary passages and their arteries applies in only about one-third of patients. Congenital absence of the gallbladder or duplication is extremely rare. The gallbladder may be found in a variety of anomalous positions. The so-called floating gallbladder occurs when there is an increase in the peritoneal investment with no mesentery. An incomplete mesentery occurs in about 5 percent of patients and predisposes to torsion. The gallbladder also may be left sided or totally intrahepatic. In human beings, the partial or complete intrahepatic gallbladder is associated with an increased incidence of cholelithiasis. Accessory

hepatic ducts are present in approximately 15 percent of persons. Large ducts are usually single and drain a portion of the right lobe of the liver, joining the right hepatic duct, common hepatic duct, or infundibulum of the gallbladder. Small ducts (of Luschka) may drain directly from the liver into the body of the gallbladder. When these ducts go unrecognized and are not ligated or clipped at cholecystectomy, an accumulation of bile (biloma) may occur. Anomalies of the hepatic and cystic arteries are present in about 50 percent of persons. A large accessory left hepatic artery originating from the left gastric artery occurs in about 5 percent of persons. In about 20 percent of persons, the right hepatic artery originates from the superior mesenteric artery, and in about 5 percent there are two hepatic arteries, one originating from the common hepatic artery and the other from the superior mesenteric artery. The cystic artery is highly variable, sometimes originating from the left hepatic artery or from the junction of the left or right hepatic arteries with the common hepatic artery, and may be duplicated.

CYSTIC DISEASE OF THE EXTRAHEPATIC BILIARY TRACT (CHOLEDOCHAL CYST)

Congenital cystic abnormalities may occur throughout the entire biliary system. Intrahepatic cystic dilatation is discussed in Chap. 28. Choledochal cysts are discussed in Chap. 37. There are three major varieties: cystic dilatation involving the entire common bile duct and common hepatic duct, with the cystic duct entering the choledochal cyst; a small cyst usually localized to the distal common bile duct; and diffuse fusiform dilatation of the common bile duct.

PHYSIOLOGY

Bile Formation The normal adult with an intact hepatic circulation and consuming an average diet produces within the liver 250–1000 mL of bile per day. This takes place within the hepatocytes and is responsive to neurogenic, humoral, and chemical control. Vagal stimulation increases secretion, whereas splanchnic nerve stimulation results in decreased bile flow. The release of secretin from the duodenum increases bile flow and the production of an alkaline solution by the canaliculi.

Composition of Bile The main constituents of bile are water, electrolytes, bile salts, proteins, lipids, and bile pigments. Sodium, potassium, calcium, and chloride have the same concentration in bile as in extracellular fluid or plasma. The pH of hepatic bile is

usually neutral or slightly alkaline and varies with diet. Bile acids, produced endogenously or taken orally, reduce cholesterol synthesis and increase cholesterol absorption from the intestine. The principal bile acids are cholic and deoxycholic acids, and they are synthesized from cholesterol within the liver; they are conjugated there with taurine and glycine and act within the bile as anions that are balanced by sodium. Liver bile also contains mucoproteins, lipoproteins, unesterified cholesterol, lecithin, and neutral fats.The color of the bile secreted by the liver is related to the presence of the pigment bilirubin diglucuronide, which is the metabolic product of the breakdown of hemoglobin and is present in bile in concentrations 100 times greater than in plasma. After this pigment has been acted on by bacteria within the intestine and converted into urobilinogen, a small fraction of the urobilinogen is absorbed and secreted into the bile.

Gallbladder Function During storage, the selective absorption of sodium, chloride, and water results in a concentration of bile salts, bile pigments, and cholesterol that is 10 times higher than in liver bile. Secretion of mucus, approximately at the rate of 20 mL/h, protects the mucosa from the lytic action of bile and facilitates the passage of bile through the cystic duct. This mucus makes up the colorless "white bile" present in hydrops of the gallbladder resulting from obstruction of the cystic duct.

Motor Activity The passage of bile into the duodenum involves the coordinated contraction of the gallbladder and relaxation of the sphincter of Oddi mainly in response to the ingestion of food and the release of cholecystokinin (CCK) by the duodenum. After the intravenous injection of CCK, the gallbladder is two-thirds evacuated within 30 min. CCK exerts its contractile effects mainly through action directly on the gallbladder smooth muscle cells. The vagus nerve stimulates contraction of the gallbladder, and splanchnic sympathetic stimulation is inhibitory to its motor activity. There is an increased risk of gallbladder disease in patients on prolonged total parenteral nutrition (TPN) perhaps because of the lack of intestinal stimulus and consequent stasis of bile within the organ. During the interdigestive periods, the hormone motilin regulates sphincteric pressure to allow continuous flow of small amounts of bile into the duodenum. Resting sphincteric pressure is around 30 cmH_2O. After the ingestion of food, the sphincteric pressure is reduced to 10 cmH_2O. The term *biliary dyskinesia* has been used to describe disturbances of biliary tract motility that occur in the absence of anatomic changes. It has been applied as a primary condition and as a complication of biliary tract surgery often when

pain has been noted to occur after the ingestion of fatty foods or on injection of CCK.

Enterohepatic Circulation After the bile enters the duodenum, over 80 percent of the conjugated bile acids are absorbed in the terminal ileum, and the remainder is deconjugated by bacterial activity and absorbed in the colon. Only 5 percent is excreted in the stool.

DIAGNOSIS OF BILIARY TRACT DISEASE

Radiologic Studies

Abdominal ultrasound imaging is the most widely applied diagnostic technique for biliary tract disease in elective and emergent situations. The gallbladder is readily imaged because echo-free bile contrasts with the organ's wall and the liver parenchyma. The intrahepatic and extrahepatic major bile ducts are also defined. Calculi can be demonstrated in more than 95 percent of patients in whom they are present. The discrimination of ductal dilatation has an accuracy of 90 percent. Ultrasonography is the most cost-effective and reliable method for demonstrating gallstones. They appear as reflective foci within the gallbladder or ducts and cast acoustic shadows. Ultrasound imaging also provides diagnostic information for acute and chronic cholecystitis. The characteristic signs include edema and thickening of the gallbladder wall, occasionally gas in the wall, pericholecystic fluid, and absence of visualization of the organ. Ultrasound is the first radiologic step in the evaluation of jaundice because it provides a sensitive method for detecting intrahepatic and extrahepatic ductal dilatation.

Abdominal Radiography Plain x-ray films of the abdomen are of limited value in assessing patients with gallstones or jaundice. They may be useful in excluding other causes of abdominal pain, such as a perforated viscus or a bowel obstruction. Stones are demonstrable on plain film in those 15–20 percent of patients with calcium-containing stones. The presence of gas within the biliary tree occurs in patients with a cholecystenteric fistula. Opacification of the gallbladder, or of parts of it, occurs in patients with a "porcelain" gallbladder. Gas bubbles may be present in the wall of the gallbladder in patients with emphysematous cholecystitis.

Oral Cholecystography This was introduced by Graham and Cole in 1924. This test permits visualization of gallstones and assessement of the absorptive ability of the gallbladder. A radiopaque

dye is ingested and absorbed by the gastrointestinal tract and extracted by the liver into the biliary ductular system. Ultimately, if the gallbladder has normal mucosal function, the dye becomes concentrated through the physiologic absorption of water and solutes. A "positive" study occurs when stones are noted as filling defects in a visualized, opacified gallbladder or when the dye is not adequately concentrated and the gallbladder cannot be visualized. A number of important limitations have reduced its use. False-positive results may occur when patients have been noncompliant or have been unable to ingest the tablets because of nausea and emesis or general medical conditions or when the tablets have not been absorbed through the gastrointestinal tract or have not been excreted into the biliary tract as a result of hepatic dysfunction. Oral cholecystography largely has been replaced by the development and refinement of abdominal ultrasonography.

Computed Tomography (CT) This is inferior to ultrasonography for the detection of stones. The major application of CT is to define the course and status of the extrahepatic biliary tree and adjacent structures. Use of CT is an integral part of the differential diagnosis of obstructive jaundice. Magnetic resonance imaging (MRI) can noninvasively image the biliary tree and is seeing increased application.

Biliary Scintigraphy This provides functional and anatomic information. Technetium 99m–labeled derivatives of iminodiacetic acid (HIDA) are injected intravenously, and they are cleared by the Kupffer's cells in the liver and excreted in the bile. The gallbladder is visualized within 60 min in fasting subjects. The test is particularly applicable when the diagnosis of acute cholecystitis is being considered. Evidence of cystic duct obstruction, as indicated by nonvisualization of the gallbladder, is highly diagnostic. Isotopic visualization of the gallbladder essentially precludes the diagnosis.

Percutaneous Transhepatic Cholangiography (PTC) This uses fluoroscopic guidance to place a small needle into a bile duct. PTC facilitates diagnosis by providing a cholangiogram and permits therapeutic intervention such as intubation of the bile ducts. The technique has little role in the management of patients with uncomplicated gallstone disease, but it has been particularly useful in patients with more complex biliary problems, including strictures and tumors.

Endoscopic Retrograde Cholangiopancreatography (ERCP) This uses a side-viewing endoscope to visualize and intubate the

biliary and pancreatic ducts. This test is useful for patients with common bile duct disease (benign and malignant), particularly obstructive jaundice.

Rigid and Flexible Choledochoscopy This visualizes the lumen of the ducts and has been used to determine the presence or absence of calculi. The technique is used as an adjunct to operative cholangiography when the common duct is explored. Choledochoscopy also can aid in the removal of stones and bile duct tumors and in inspecting and obtaining biopsy samples from stenoses.

TRAUMA

Injuries of the gallbladder are rare. Penetrating injuries are usually caused by gunshot wounds or stab wounds or during a needle biopsy procedure of the liver. Nonpenetrating injuries are extremely rare. The types of traumatic injuries to the gallbladder include contusion, avulsion, laceration, rupture, and traumatic cholecystitis. Laceration is the most common type of injury following penetrating wounds but also may result from blunt trauma. When infected bile escapes into the peritoneal cavity, a fulminating and often fatal peritonitis results. When bile is sterile, however, it is well tolerated and results in a chemical peritonitis that may be relatively mild. In general, it is preferable to remove the traumatized gallbladder.

Complete transection of the common hepatic duct or the common bile duct (e.g., by a penetrating knife wound) may be treated by debridement and an end-to-end anastomosis over a T tube. With injuries caused by blunt trauma, however, the proximal end of the duct should be anastomosed to a Roux-en-Y limb of jejunum.

The great majority of injuries of the extrahepatic biliary duct system are iatrogenic, occurring in the course of laparoscopic or open cholecystectomy. Some of these injuries are recognized intraoperatively, but the majority become manifest by either increasing obstructive jaundice or profuse and persistent drainage of bile through a fistula postoperatively. ERCP or PTC most clearly defines the site of obstruction or leak.

Injury of the bile duct recognized during surgical operation should be corrected with an immediate reconstructive procedure. Restoration of the continuity of the duct with an end-to-end anastomosis over a T tube may be feasible after a sharp transection, but stricture develops in about half the patients. In most patients, the proximal end of the duct should be anastomosed to a Roux-en-Y of jejunum.

GALLSTONES

Composition The major elements involved in the formation of gallstones are cholesterol, bile pigment, and calcium. Other constituents include iron, phosphorus, carbonates, proteins, carbohydrates, mucus, and cellular debris. In Western cultures, most stones are made up of the three major elements and have a particularly high content of cholesterol. "Pure" pigment stones are usually associated with hemolytic jaundice.

Formation Gallstones form as a result of precipitation of bile constituents. Lecithin is the predominant phospholipid in bile, and although it is insoluble in aqueous solutions, it is dissolved by bile salts into micelles. Cholesterol is also insoluble in aqueous solution but becomes soluble when incorporated into the lecithin–bile salt micelle. Current theory suggests that there is an equilibrium between the physicochemical phases of these vesicles such that the formation of liquid crystals may or may not result in actual gallstones. When crystals achieve macroscopic size during a period of entrapment in the gallbladder, gallstones form. The basic secretory defect in nonobese patients is decreased bile salt and phospholipid secretion. Chenodeoxycholic acid and ursodeoxycholic acid, which replenish the bile acid pool and reduce cholesterol synthesis and secretion, administered to potential stone formers may return supersaturated bile to its normal composition, preventing stone formation.

Asymptomatic Gallstones

The liberal use of ultrasonography has resulted in the diagnosis of calculi in patients without symptoms referable to the biliary tract. In general, patients with asymptomatic gallstones should not be treated. Cholecystectomy for asymptomatic stones may be appropriate for elderly patients with diabetes and for individuals who will be isolated from medical care for an extended period.

Cystic Duct Obstruction

Temporary obstruction to the outflow of bile from the gallbladder is responsible for the most common manifestation of calculous disease, which is biliary colic. This consists of intermittent spasmodic pain in the right upper quadrant, often radiating to the shoulder or scapula, that is precipitated by a fatty or fried meal. The attacks are self-limiting but have a tendency to recur in an unpredictable manner. The treatment is cholecystectomy, preferably by the laparo-

scopic approach, and it is best performed during that hospitalization but not as an emergent procedure.

Choledocholithiasis

Common duct stones may be single or multiple and are found in 4–12 percent of patients subjected to cholecystectomy. Most common duct calculi are formed within the gallbladder and migrate down the cystic duct into the common bile duct. Less commonly, stones are thought to form within the ducts. Although small stones may pass via the common duct into the duodenum, the distal duct with its narrow lumen (2–3 mm) and thick wall frequently obstructs their passage. Pain and jaundice may result. Chronic biliary obstruction may cause secondary biliary cirrhosis or infection within the bile duct, giving rise to ascending cholangitis and occasionally extending up to the liver, resulting in hepatic abscesses. Gallstone pancreatitis is generally associated with the presence or passage of common bile duct stones.

The manifestations of calculi within the common duct are variable. Characteristically, the symptom complex consists of colicky pain in the right upper quadrant radiating to the right shoulder with intermittent jaundice accompanied by pale stools and dark urine. Liver function tests demonstrate the pattern of obstructive jaundice, and the alkaline phosphatase level usually becomes elevated earlier and remains abnormal for longer periods than the serum bilirubin level. In patients with ascending cholangitis, Charcot's intermittent fever accompanied by abdominal pain and jaundice is characteristic. The diagnosis may be established by ERCP or PTC. The indications for the removal of common duct stones are (1) their presence as defined preoperatively in a symptomatic patient or by palpation or cholangiographically at the time of operation, (2) a dilated extrahepatic duct, (3) jaundice, (4) recurrent chills and fevers suggestive of cholangitis, and (5) gallstone pancreatitis. Common duct stones can be removed by ERCP, and the performance of an adequate destruction of the sphincter of Oddi will permit stones that were not extracted or which form at a later date to pass into the duodenum without obstruction in the extrahepatic ducts. In a patient undergoing an elective cholecystectomy in whom common duct stones are thought to be present, a preoperative ERCP and sphincterotomy can be followed by laparoscopic cholecystectomy. If common duct stones are detected during laparoscopic cholangiogram, they can be removed by subsequent ERCP or during the procedure by trans-cystic duct retrieval or pushing them into the duodenum. Alternatively, the common duct can be opened, the stones extracted, and a T tube inserted.

If stones are noted to be present when a T-tube cholangiogram is performed postoperatively, several approaches can be entertained. Mechanical extraction of the retained stone can be performed under radiographic control. The T tube is generally left in place for at least 4 weeks after the operation; it is then extracted, and a polyethylene catheter is used to instill radiopaque material into the common duct. A Dormia basket is then advanced through the catheter to entrap the stone. The most commonly used approach is transduodenal papillotomy with extraction of the stone under endoscopic control.

Biliary Enteric Fistula and Gallstone Ileus

A stone in the ampulla of the gallbladder (Hartmann's pouch) can encroach on and erode the common bile duct. This is known as *Mirizzi's syndrome.* Operative management depends on the extent to which the common duct has been compromised. If there is only a pressure effect, cholecystectomy is sufficient. If the common duct segment is partially or completely destroyed, a reconstructive procedure is mandated and may require a Roux-en-Y limb anastomosis to the proximal normal duct. When biliary enteric fistulas develop, they usually run between the gallbladder and the duodenum, but 15 percent are cholecystocolic fistulas. Mechanical obstruction of the gastrointestinal tract caused by gallstones is a relatively infrequent occurrence. Gallstone ileus causes 1–2 percent of mechanical small intestine obstructions. It is characteristically a disease of the aged. Typically, intraluminal obstruction is produced by erosion of the stone into the gastrointestinal tract. Almost always the offending calculus enters through a cholecystenteric fistula. Having entered the alimentary tract, the gallstone, which is usually single, may be vomited or passed spontaneously via the rectum. The size of the stone is important, since stones smaller than 2–3 cm usually pass. When obstruction occurs, the site is usually at the terminal ileum, which is the narrowest portion of the small intestine. When a gallstone blocks the small intestine, the morbid anatomic and physiologic effects of a mechanical obstruction obtain.

A past history suggestive of cholelithiasis or symptoms of acute cholecystitis immediately preceding the onset of gallstone ileus may be present. There is associated cramping, nausea, and vomiting, which may be intermittent. Radiologic examination may be diagnostic if gas is demonstrated within the biliary tract. Biliary enteric fistulas are managed by cholecystectomy and closure by primary repair of the intestinal opening. Definitive therapy consists

of locating the stone or stones, enterotomy proximal to the stone, and removal of the offending calculi with closure of the intestine.

INFLAMMATORY AND OTHER BENIGN LESIONS

Acute cholecystitis is usually associated with an obstruction of the neck of the gallbladder or cystic duct caused by stones impacted in Hartmann's pouch. Direct pressure of the calculus on the mucosa results in ischemia, necrosis, and ulceration with swelling, edema, and impairment of venous return. A bacterial cause has been proposed, and positive bile cultures have been noted in 60 percent of patients. *Escherchia coli, Klebsiella* species, streptococci, *Enterobacter aerogenes*, *Salmonella* species, and *Clostridium* species have all been implicated. Acute cholecystitis in which the gallbladder is devoid of stones is known as *acalculous cholecystitis.*

Acute cholecystitis can occur at any age, but the greatest incidence is between the fourth and eighth decades. Women are afflicted more than men. Moderate to severe pain is experienced in the right upper quadrant and epigastrium and may radiate to the back in the region of the angle of the scapula or in the interscapular area. The patient is often febrile, and vomiting may be severe. Tenderness, usually along the right costal margin and often associated with rebound tenderness and spasm, is characteristic. The gallbladder may be palpable, or a palpable mass in the region may be the result of omentum wrapped around the gallbladder. The differential diagnosis includes perforation or penetration of peptic ulcer, appendicitis, pancreatitis, hepatitis, myocardial ischemia or infarction, pneumonia, pleurisy, and herpes zoster involving an intercostal nerve.The hemogram usually demonstrates leukocytosis with a shift to the left. Radiographs of the chest and abdomen are indicated to rule out pneumonia. The serum bilirubin level may determine the presence of common duct obstruction. To rule out myocardial ischemia, an electrocardiogram should be performed on any patient over age 45 being considered for surgical treatment. An ultrasonogram may demonstrate calculi and/or a thickened wall of the gallbladder and is the diagnostic procedure of choice. Radionuclide scanning with DISIDA (diisopropyl iminodiacetic acid) or PIPIDA (*N-para*-isopropyl-acetanilide-iminodiacetic acid) is the most effective diagnostic study in this situation. There have been conflicting opinions on the management of acute cholecystitis, particularly on the optimal time for surgical intervention. Most surgeons now favor early operation, i.e., within 24–48 h. In the majority of patients, laparoscopic cholecystectomy is successful.

Emphysematous cholecystitis is a rare form of acute, usually gangrenous cholecystitis associated with the presence of gas in the gallbladder. Pathogenesis is related to acute inflammation of the gallbladder, which often begins aseptically, complicated by a secondary infection with gas-forming bacilli. Cholelithiasis is also present in half the patients, who are frequently diabetic. The diagnosis is usually made on the basis of radiographs that show a globular, gas-filled shadow in the region of the gallbladder, or later, intramural or submucosal gas may appear. The treatment of choice is early operation.

Chronic inflammation of the gallbladder is generally associated with cholelithiasis and consists of round cell infiltration and fibrosis of the wall. Patients generally present with moderate intermittent abdominal pain. Diagnosis is usually established by ultrasonography that demonstrates the presence of stones.

The treatment of chronic cholecystitis and cholelithiasis is cholecystectomy, and the results are usually excellent. Laparoscopic cholecystectomy is the procedure of choice. Acute acalculous cholecystitis frequently is a complication of burns, sepsis, multiple organ-system failure, cardiovascular disease, diabetes, prolonged illness, or a major operation. The DISIDA or PIPIDA scan and ultrasonography are occasionally normal in these patients, but characteristically ultrasonography demonstrates thickening of the wall. Cholecystectomy is the preferred treatment. Infection within the biliary duct system or cholangitis is most frequently associated with choledocholithiasis but also has accompanied choledochal cysts and carcinoma of the bile duct and has followed sphincteroplasty. Clinically, the condition is characterized by intermittent fever, upper abdominal pain, exacerbation of jaundice, pruritus, and at times rigor. Antibiotics usually control the infection, but if the patient's temperature does not fall, surgical drainage should not be delayed. This can be accomplished percutaneously by the transduodenal or transhepatic route or operatively.

Suppurative cholangitis, in which there is gross pus within the biliary tract, constitutes one of the most urgent causes for laparotomy in patients with obstructive jaundice. The condition was first described in 1877 by Charcot, who suggested a diagnostic triad of jaundice, chills and fever, and pain in the right upper quadrant. To these, Reynolds and Dargan added shock and central nervous system depression as specific identifying features of the condition. The disease occurs almost exclusively in patients over 70 years of age. All patients are febrile, and most are jaundiced. Bilirubin, SGOT, and alkaline phosphatase levels are characteristically elevated. Patients have been managed emergently by establishing initial drainage via ERCP or PTC, followed by definitive operation. Surgical treatment is directed at rapid decompression of the duct

system and is combined with large doses of antibiotics, particularly those which achieve high levels in the bile.

Sclerosing cholangitis is an uncommon disease that involves all or part of the extrahepatic biliary duct system and often affects the intrahepatic biliary radicals as well. A significant number of cases have been associated with ulcerative colitis, Crohn's disease, Riedel's struma, retroperitoneal fibrosis, and porphyria cutanea tarda. The cause of sclerosing cholangitis is unknown.

Grossly, there is diffuse thickening of the wall of the extrahepatic biliary tract and sometimes of the intrahepatic ducts, with a marked luminal narrowing. The gallbladder is usually not involved. Biopsy examination of the liver may reveal bile stasis or, in long-standing cases, biliary cirrhosis. The histologic evaluation is critical, since it is difficult to differentiate this disease from sclerosing carcinoma of the bile ducts.

The diagnosis is to be considered in patients with a clinical and laboratory picture of extrahepatic jaundice. Jaundice is usually associated with intermittent pain in the right upper quadrant, nausea, vomiting, and occasionally, chills and fever. In long-standing cases with biliary cirrhosis, the manifestations of portal hypertension may appear. The diagnosis is often established by cholangiography. The appropriate management of sclerosing cholangitis remains unclear. No drug therapy has achieved consistent or even usual success. The asymptomatic anicteric patient is not treated. The pruritic and icteric patient is treated for 4–6 weeks with prednisone; if there is no improvement, or if cholangitis is present or develops, an operation is performed with a preoperative cholangiogram as a guide. If possible, the stenotic segment should be excised and reconstructed with a Roux-en-Y limb of jejunum. Carcinoma must be ruled out by biopsy. In patients with more diffuse or advanced parenchymal disease, hepatic transplantation has become the procedure of choice.

The term *papillary stenosis* refers to a wide variety of conditions that share a benign abnormality of the sphincter of Oddi. The main symptom of fibrosis or stenosis is abdominal pain, usually colicky and frequently associated with nausea and vomiting. Many patients indicate that they have had previous cholecystectomy without relief of symptoms. The diagnosis generally is made when there is difficulty in passing a No. 3 Bakes dilator through the ampulla of Vater. Transduodenal sphincteroplasty is the preferable treatment.

TUMORS

Carcinoma of the gallbladder accounts for 2–4 percent of gastrointestinal malignancies. Approximately 90 percent of patients with carcinoma of the gallbladder have cholelithiasis, but the

pathogenesis has not been defined. There is also an association with polypoid lesions of the gallbladder. Malignant changes have been noted more frequently in polypoid lesions greater than 10 mm. The calcified "porcelain" gallbladder is associated with a 20 percent incidence of gallbladder carcinoma. Most tumors are adenocarcinomas. When metastases are present, the liver is involved in two-thirds of patients and the regional lymph nodes in about one-half. Signs and symptoms of carcinoma of the gallbladder are generally indistinguishable from those associated with cholecystitis and cholelithiasis. Half the patients are jaundiced, and two-thirds of those with clinical manifestations have a palpable mass. Ultrasound or CT scanning may suggest the diagnosis. Most long-term survivors are patients who underwent cholecystectomy for cholelithiasis and in whom the malignancy was an incidental finding. Advanced tumors may have a better prognosis if a radical second procedure, which includes lymphadenectomy and partial hepatic resection for lesions located adjacent to the liver, is performed. Large cumulative series report 5-year survival rates of 5 percent.

Bile duct carcinoma is slightly less common than gallbladder cancer. There is no evidence that bile duct stones have a role, and the relationship between the tumors and sclerosing cholangitis remains ill-defined. Approximately two-thirds of the lesions are located in the proximal ducts, often at the confluence of the right and left main hepatic ducts (so-called Klatskin tumors). The tumors are generally small but result in ductal obstruction. Ductal lesions are cholangiocarcinomas of the adenocarcinoma type. The liver and regional lymph nodes are the most frequent sites of metastasis. Characteristically, patients present with the recent onset of obstructive jaundice and pruritus. Patients may have had weight loss, abdominal pain, and cholangitis. The laboratory findings are compatible with the diagnosis of obstructive jaundice. Serum Ca19-9 levels may be elevated. Ultrasonography and CT scanning demonstrate intrahepatic ductal dilatation and distention of the extrahepatic ducts proximal to the point of obstruction. Precise demonstration of the site of obstruction is achieved by cholangiography. Treatment is directed at resecting the tumor, if possible, or palliation by relieving the obstruction. Cure can be achieved only by surgical removal of the lesion, whereas palliation can be effected by operation, radiologic intervention, or endoscopic decompression. Curative resection generally entails removal of the common duct and the common hepatic duct up to and sometimes including the confluence of the right and left hepatic ducts, followed by anastomosis of the proximal dilated system to a Roux-en-Y limb of small intestine. The cure rate remains under 15 percent. If a proximal lesion extends into the liver parenchyma, varying amounts of the

liver are removed en bloc. The cure of distal bile duct tumors has been improved by radical lymphadenectomy and pancreaticoduodenectomy (Whipple procedure).

OPERATIONS OF THE BILIARY TRACT

Prophylactic antibiotics are indicated for patients undergoing elective cholecystectomy with specific risk factors such as jaundice, common duct stones, diabetes, and age greater than 65 years.

Cholecystostomy accomplishes decompression and drainage of the distended, hydropic, or purulent gallbladder. It is applicable if the patient's general condition is such that it precludes prolonged anesthesia, since the operation may be performed under local anesthesia. The procedure is principally performed percutaneously with ultrasound guidance.

Cholecystectomy is one of the most commonly performed abdominal procedures. It may be performed laparoscopically or as an open procedure. The gallbladder may be approached through an oblique right upper quadrant or upper midline incision. The cystic duct is identified and a silk ligature passed around it. Dissection is continued craniad, and the cystic artery is identified. The cystic artery should be doubly ligated and transected. The peritoneum overlying the gallbladder is then incised close to the liver, and dissection is begun from the fundus of the gallbladder down to an ultimate pedicle of cystic duct. The cystic duct is transected and ligated 3–5 mm from the common bile duct.

Laparoscopic cholecystectomy has emerged as the preferred way of treating symptomatic gallstone disease. Trocars are introduced after the instillation of a pneumoperitoneum, and the procedure begins by retracting the gallbladder up over the edge of the liver so as to facilitate exposure of the triangle of Calot. The cystic duct and artery are then identified and divided. The gallbladder is dissected from this area up toward the fundus. The gallbladder is then carefully withdrawn through one of the ports and the pneumoperitoneum released.

Common duct exploration for choledocholithiasis may be indicated when ductal stones have not been removed by preoperative ERCP. After the anterior aspect of the duct has been visualized, a vertical incision is made through the anterior wall. A choledochoscope can be introduced at this time to visualize the lumen and determine whether any stones are present. Ductal stones can be removed by irrigation, balloon-tipped catheters, scoops, or forceps. When the duct is clear of stones, a T tube is inserted into the duct. A completion cholangiogram confirms the absence of stones and

the passage of dye into the duodenum. The latter can be facilitated by the injection of glucagon. A postoperative cholangiogram is performed about 1 week postoperatively, and if absence of stones and clear passage of opaque contrast medium into the duodenum are demonstrated, the tube is removed. The common duct can be explored and cleared of stones laparoscopically.

Sphincterotomy or division of the sphincter of Oddi is occasionally indicated for a stone impacted at the ampulla, a stricture, or a functional disorder. A generous Kocher maneuver should be performed initially, followed by a longitudinal anterior duodenotomy. The passage of a Bakes dilator or cathether down the duct facilitates identification of the sphincter, which should be incised at the 11-o'clock position to avoid damaging the pancreatic duct. A pie-shaped segment is removed from the sphincter, and the duodenal and ductal mucosae are coapted with fine absorbable sutures. A T tube may be inserted into the common duct, and the duodenotomy is closed longitudinally.

Choledochoduodenostomy is applicable to elderly patients with multiple common duct stones and a substantially dilated common duct. A Kocher maneuver is performed to relieve any tension on the anastomosis. The distal common duct is incised longitudinally, as is the anterior portion of the duodenum, and a one-layer, large-diameter anastomosis is made.

Most ductal injuries and strictures are preferably repaired with choledochojejunostomy or a hepaticojejunostomy using a 45-cm defunctionalized Roux-en-Y limb of jejunum. Anastomosis should be performed using the antimesenteric side of the jejunum with interrupted absorbable sutures. A stent should be used unless the bile duct is dilated and infection and tumor are demonstrably absent.

For a more detailed discussion, see Schwartz SI: Gallbladder and Extrahepatic Biliary System, chap. 29 in *Principles of Surgery*, 7th ed.

CHAPTER

30

PANCREAS

ANATOMY

The pancreas lies behind the stomach in a lesser sac. It is composed of the head (over L2), the body, and the tail. The uncinate process curls behind the head. The superior mesenteric vein and artery lie behind the neck of the pancreas. The duct of Wirsung is major duct, 3–4 mm diameter, that joins the common bile duct at the papilla of Vater. The minor duct is the duct of Santorini, which joins the main duct in the neck and drains via the minor papilla into the duodenum. In 5–10 percent of persons, major drainage of the pancreas is via the duct of Santorini, with a vestigial Wirsung duct; this is *pancreas divisum*, which can cause pancreatitis. Arterial supply to the head is via anterosuperior and posterosuperior pancreaticoduodenal arcades from the gastroduodenal artery, which anastomose with anteroinferior and posteroinferior pancreaticoduodenal arteries from the superior mesenteric artery. The splenic and transverse pancreatic arteries supply the body. Venous drainage closely parallels arterial supply. In up to 25 percent of persons, the right hepatic artery arises from the superior mesenteric artery and courses behind the pancreas and bile duct. Lymphatic drainage is diffuse. Innervation is sympathetic via splanchnic nerves and parasympathetic via the celiac branch of the posterior (right) vagus.

Anatomic Variants Annular pancreas is rare. The duodenum is encircled by the head of the pancreas. Symptoms are from duodenal obstruction. Cure is duodenojejunostomy. Ectopic pancreas most common in the stomach (antrum, greater curvature) or Meckel's diverticulum.

PHYSIOLOGY

Exocrine Pancreas

Fluid and electrolyte secretion is 1000–2000 mL/day (pH 8.0–8.3), and secretion is isosmotic, from centroacinar cells. The Na^+/K^+

content is similar to plasma. The principal anions are HCO_3^- and Cl^-, with increased Cl^- (110 mmol/L) and decreased HCO_3^- (50 mmol/L) at low secretory rates and decreased Cl^- (20 mmol/L) and increased HCO_3^- (140 mmol/L) at high secretory rates. Alkaline secretions neutralize gastric acid. The major stimulus is secretion released from duodenal mucosa in response to acid.

Enzymes are released by cholecystokinin (CCK) and vagal cholinergics. CCK is released from the proximal small bowel by fatty acids and oligopeptides. Proteases are trypsin, chymotrypsin, elastase, ribonuclease, and carboxypeptidase. Lipases are lipase, colipase, phospholipase A_2. Amylase digests starches. Lipase and amylase are secreted in active forms; the others are secreted as *zymogens*, which are activated by trypsin. Trypsinogen is activated by enterokinase. Lysosomal enzymes and zymogens are segregated intracellularly.

Enzyme secretion is 90 percent in excess of enzymes needed for digestion. Malabsorption occurs only when secretion falls to about 10 percent of normal. This may be from ductal blockage (cancer), destruction (chronic pancreatitis), or surgical procedures. Insufficiency results mainly in fat malabsorption and steatorrhea. Fat-soluble vitamins, however, *are not* affected. Therapy is oral lipase, a low-fat diet, and histamine H_2 blockers.

Endocrine Pancreas

The islets of Langerhans constitute 1–2 percent of the pancreatic mass, 60–80 percent beta (insulin), 15–20 percent alpha (glucagon), 5–10 percent delta (somatostatin), and 15–20 percent pancreatic polypeptide (PP). PP cells are located mainly in head, and alpha cells are seen mostly in body and tail.

Insulin comes from beta cells as proinsulin. It decreases the blood glucose level, increases cellular glucose uptake, increases glycogenesis, decreases gluconeogenesis, increases lipogenesis, decreases lipolysis, increases protein synthesis, and increases amylase synthesis. Its release is stimulated by hyperglycemia, arginine, and free fatty acids.

Glucagon comes from alpha cells. It increases the blood glucose level, increases glycogenolysis, increases gluconeogenesis, and relaxes gastrointestinal smooth muscle. Its release is stimulated by hypoglycemia, stress, CCK, and sympathetics. Insulin and hyperglycemia suppress glucagon release.

Somatostatin comes from delta cells. It inhibits insulin release and most gastrointestinal hormones. It is an important pancreatic regulator.

Pancreatic polypeptide comes from PP cells. Its release is stimulated by proteins, vagal cholinergic stimulation, and hypoglycemia. It decreases pancreatic exocrine secretion.

PANCREATITIS

Acute Pancreatitis

Definition Nonbacterial inflammation of pancreas caused by pancreatic enzymes.

Etiology About 40 percent is caused by gallstones, but the mechanism is unclear. Bile reflux (*common channel theory*) may have a role, from transient obstruction of the ampulla by a stone. However, sterile bile in the pancreatic duct that is not under pressure does not cause pancreatitis. Deconjugated bile salts and lysolecithin are toxic to the pancreas. Another 40 percent results from alcoholism, probably due to increased pancreatic ductal pressure with hypersecretion, protein precipitation, spasm of the sphincter of Oddi, calcium precipitation, and increased ductal permeability. Dietary-induced hypertriglyceridemia may play a role in alcoholics. *Postoperative pancreatitis*, which may occur after biliary, gastric, cardiac, or splenic procedures, has a high mortality. Metabolic factors have been associated, such as hyperparathyroidism, aminoaciduria, hypertriglyceridemia (Type IV), and possibly hemochromatosis. Other factors include vascular stasis, drugs and toxins (e.g., methyl alcohol, chlorothiazide), and viral illnesses (e.g., mumps, Coxsackie viruses), pancreas divisum, and idiopathic (15–20 percent).

Clinical Manifestations Severe midepigastric pain is seen that radiates through to the back; it is relieved by sitting and frequently is accompanied by severe retching. Upper abdominal tenderness and guarding are present. About 90 percent of patients have fever, leukocytosis, and tachycardia. Ileus is common. Shock from fluid sequestration and myocardial depression may be present. Jaundice is seen in 20–30 percent. Occasionally, there is carpopedal spasm from hypocalcemia. About 1 percent of patients have retroperitoneal blood around the umbilicus (Cullen's sign) or in the flanks (Grey-Turner's sign).

Laboratory Studies Patients may show hyperamylasemia, which can be very nonspecific. Cholecystitis, cholangitis, perforated peptic ulcer, strangulated small bowel obstruction, salpingitis,

renal failure, macroamylasemia, and mumps are among many disorders that may cause an elevated amylase level. A serum lipase determination might be more specific. A urine amylase clearance determination can be useful. The calcium level may fall; a value of less than 7.5 mg/dL indicates a poor prognosis. Radiographs may show a sentinel loop of bowel air. A computed tomographic (CT) scan can be very useful in predicting the severity of disease and in the diagnosis of complications.

Treatment Critical to care are replacement of fluid and electrolyte losses, monitoring of vascular volume (e.g., by Foley catheter, central line), repeated assessments of hematocrit and electrolytes (including calcium), and bowel rest. Nasogastric suction is of no proven benefit in uncomplicated pancreatitis without uncontrolled vomiting. Likewise, drugs such as glucagon, Trasylol, and atropine show no benefit. The routine use of antibiotics is not proven in uncomplicated pancreatitis. Cholycystectomy is indicated in biliary pancreatitis, but surgery is generally contraindicated in uncomplicated pancreatitis. Peritoneal lavage can decrease cardiopulmonary complications but does not decrease mortality. Surgery may be needed for impacted stones, debridement of necrosis, and abscess drainage.

Complications, Morbidity, and Mortality Overall mortality can be predicted via Ranson's criteria (Table 30-1). Across the board, mortality is 10 percent. Pseudocyst is the most common complication, usually occurring after 2 – 3 weeks. Pseudocyst may resolve, but persistence or symptoms require surgical drainage. Infected pseudocysts are generally drained externally. Abscess is uncommon but has high mortality and demands effective drainage, without which mortality is 100 percent. Most common organisms are coliforms, Streptococcus faecalis, and clostridia. Pancreatic necrosis is diagnosed by contrast-enhanced CT scan. Infected pancreatic necrosis requires operative debridement and placement of drainage catheters. Multiple operations are frequently employed. Likewise, necrosis may lead to biliary or enteric perforation. Systemic complications include adult respiratory distress syndrome (ARDS), renal failure, and myocardial depression. Biliary obstruction may occur, more often in chronic disease. Hemorrhage may occur from the splenic artery or erosion of the mesenteric or portal vessels.

Chronic Pancreatitis

The definition is vague but generally includes changes that result after repeated episodes of acute pancreatitis. Pancreas becomes

TABLE 30-1
Ranson's Prognostic Criteria for Acute Pancreatitis
Morbidity and Mortality Rates Correlate with the Number of Criteria Present: 0–2 = 2% Mortality; 3–4 = 15% Mortality; 5–6 = 40% Mortality; 7–8 = 100% Mortality

Present on admission:
Age > 55 years
White blood cell count > 16,000/μL
Blood glucose > 200 mg/dL
Serum lactate dehydrogenase > 350 I.U./L
SGOT (AST) > 250 I.U./dL
Developing during first 48 h:
Hematocrit fall > 10%
Blood urea nitrogen increase > 8 mg/dl
Serum Ca^{2+} < 8 mg/dL
Arterial PO_2 < 60 mmHg
Base deficit < 4 mEq/L
Estimated fluid sequestration > 600 mL

small, indurated, and nodular with acini and islets surrounded by fibrous tissue. There is ductal stricture and dilatation; calcification is common.

Clinical Manifestations Symptoms include continuous or intermittent epigastric/back pain, anorexia, and weight loss. Vomiting occurs with acute attacks. Steatorrhea and diabetes may be present. Pseudocysts are common. Personality deficits are also common. *This picture almost never occurs with repeated episodes of biliary pancreatitis*, compared with alcoholism.

Diagnosis Diagnosis is difficult at best. There are few physical findings. Endoscopic retrograde choleangiopancreatography (ERCP) and CT scan are useful and may show ductal dilatation, calculi, and strictures. Amylase and lipase levels are of little use. Calcification is pathognomonic.

Treatment Recurrent biliary pancreatitis is best avoided by performing cholecystectomy and possible bile duct exploration at the index attack; this is of little use in alcoholics. With chronic

alcoholic pancreatitis, chronic pain, and alternating ductal dilatation and strictures (chain of lakes), longitudinal pancreaticojejunostomy (Peustow procedure) is appropriate. When chronic pancreatitis is associated with a stricture of the pancreatic duct in the head of the pancreas, pancreaticoduodenectomy is effective. With a small duct, a 95 percent pancreatectomy may be of some benefit, but morbidity is high. Abstinence is critical. Chronic pain is difficult to manage (Fig. 30-1).

TRAUMA

Mechanisms of Injury Penetrating trauma accounts for 70–80 percent of pancreatic injuries. Adjacent organs are also injured in 70–90 percent. Blunt trauma may contuse or fracture the pancreas.

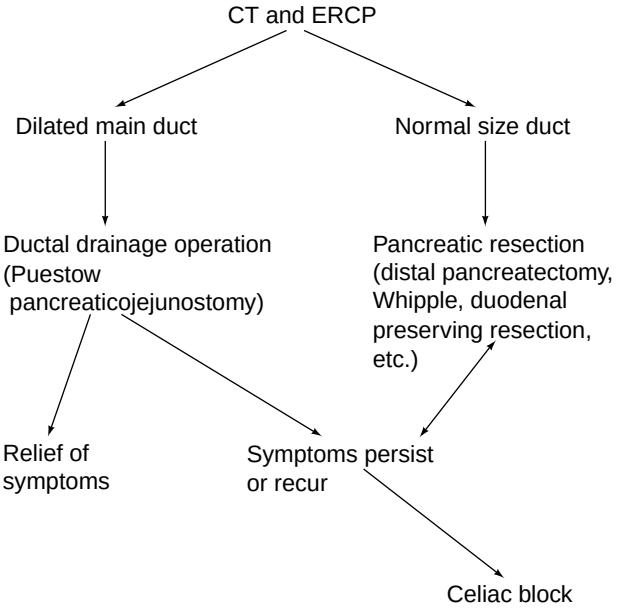

FIGURE 30-1 Algorithm for the surgical management of patients with chronic pancreatitis.

Disruption usually occurs at the neck, and associated injuries are less frequent. The consequences of injury usually are the result of parenchymal and ductal disruption, leading to fistula, pseudocyst, or abscess.

Clinical Manifestations Blunt injuries may result in delayed presentation. Abdominal findings may be minimal in the absence of hemorrhage or other injuries. CT scans may be helpful. Clinical suspicion and mechanism of injury are important. Negative paracentesis does not exclude injury. Hyperamylasemia is very nonspecific in the multiple-trauma patient.

Treatment Careful and total inspection via lesser space exploration and the Kocher maneuver is paramount. Hematomas may indicate deeper injury. Damaged tissue should be gently debrided. Without ductal injury or with minor ductal injury, drainage alone usually suffices. Major distal injuries are best treated by resection, generally as a distal pancreatectomy with splenectomy. Major injury to the head can be treated with debridement and drainage with or without Roux-en-Y reconstruction or pyloric exclusion. Pancreaticoduodenectomy is indicated when severe injuries involve two of the three structures near or within the head of the pancreas: the bile duct, pancreatic duct, and duodenum. Occasionally, major hemorrhage within or behind the head requires pancreaticoduodenectomy. *Definition of ductal injury is critical.*

Morbidity and Mortality Complications include fistulas, pseudocysts, infection, and delayed hemorrhage and usually occur in around 30 percent of patients. Complications are more common after blunt injury. Mortality averages 20 percent.

CYSTS AND PSEUDOCYSTS

True Cysts

True cysts are fluid-filled, with an epithelial lining. They may be congenital, parasitic, retention, or neoplastic. Most are rare. Cystadenoma and cystadenocarcinoma are relatively uncommon.

Pseudocysts

Pseudocysts are so called because there is no epithelial lining. They consist of fibrous wall surrounding pancreatic juice. Most are seen in the lesser sac. Etiology is usually ductal disruption from pancreatitis (75 percent, alcoholism, biliary) or trauma (25 percent).

Clinical Manifestations Symptoms include persistent pain, fever, and ileus, usually 2–3 weeks after acute pancreatitis or trauma. Pain is usually epigastric or back pain. There may be a palpable mass (75 percent), nausea, vomiting, and jaundice from duodenal and bile duct compression. The serum amylase level usually remains moderately elevated.

Diagnosis Diagnosis is most readily made with CT scan or ultrasound. ERCP is usually unnecessary.

Morbidity Associates morbidity includes secondary infection (14 percent), gastric outlet obstruction (3 percent), erosion into adjacent organs, rupture (7 percent), hemorrhage into the cyst (6 percent), and bile duct obstruction (6 percent).

Treatment Enlarging pseudocysts or those present for more than 6 weeks should be treated. The cysts should be allowed to mature prior to intervention; usually this takes 6 weeks. Most efficacious is internal drainage, usually via cystogastrostomy, but cystojejunostomy, cystoduodenostomy, and distal pancreatectomy are options. External drainage is indicated only for thin, flimsy cysts or true abscesses. Infected mature cysts may be drained internally via cystogastrostomy. Percutaneous CT-guided drainage is being used more frequently and is successful in a significant portion of patients but is best reserved for infected pseudocysts. Ruptured cysts and pancreatic ascites are treated by internal drainage. Mature, asymptomatic pseudocysts of more than 5 cm may be observed. The possibility of a cystic pancreatic neoplasm must be ruled out by biopsy.

Pancreatic Ascites This is seen following pancreatic ductal disruption or a leaking pseudocyst. Initial therapy is with total parenteral nutrition and somatostatin. Persistent disease is diagnosed with ERCP, and then appropriate surgical drainage, resection, or enteric anastomosis can be done.

TUMORS

Carcinoma of the Pancreas and Periampullary Carcinoma

Incidence Pancreatic carcinoma is the most common periampullary tumor; manifestations are similar for all. It is the fourth leading cause of cancer death in the United States. Average age at onset is 60 years; males are affected more than females. Etiologies

are unclear; links with smoking and coffee consumption are unproved. Twenty-eight thousand deaths per year are seen in the United States. Fewer than 20 percent of carcinomas are resectable at diagnosis, and median survival, even after resection, is 20 months.

Pathology Adenocarcinoma arises from the ducts in 90 percent and acini in 10 percent. Often a major portion of the tumor is fibrous stroma with a zone of pancreatitis. About 75 percent arise from the head of the pancreas, causing biliary obstruction that may lead to an earlier diagnosis. The tumor may invade the portal vein or adjacent organs or metastasize to the liver or peritoneum. The lymph nodes are positive in 90 percent of patients. Ampullary and duodenal carcinomas may be diagnosed as pancreatic, cause jaundice early, and thus may be small at presentation. Cystadenoma and cystadenocarcinoma are slow growing, have a better prognosis, and should be treated aggressively.

Clinical Manifestations Painless jaundice alone is seen in 13 percent. About 75 percent of patients with carcinoma of the head of the pancreas present with obstructive jaundice, weight loss, and pain. Pain is dull, aching, midepigastric, and often radiates to the back. Back pain suggests retroperitoneal invasion. Cystadenocarcinoma may be asymptomatic. Anorexia, fatigue, and pruritus are common. Cholangitis is uncommon. Examination shows jaundice, palpable liver (50–70 percent), and palpable gallbladder (30 percent, if nontender and jaundiced, diagnostic for pancreatic cancer; Courvoisier's sign). Recent onset diabetes is seen in 20 percent. With ampullary carcinoma, pain is less frequent, often colicky, and jaundice is intermittent. Body and tail tumors produce symptoms late and therefore are more advanced at diagnosis. Left supraclavicular node (Virchow's node), umbilical (Sister Mary Joseph's node), and pelvic floor (Blumer's shelf) metastases indicate incurable disease on examination.

Laboratory and Diagnostic Studies A laboratory test may reveal an elevated bilirubin level (which tends to be higher than with benign causes), an increased alkaline phosphatase level, and only mild transaminase elevation (contrast with hepatitis). Amylase elevations are uncommon. Screening tests would be useful, but none are available. CA 19-9 is a serum tumor marker that is 80 percent sensitive and 90 percent specific and sometimes useful. Many patients are evaluated with abdominal ultrasound first, but a spiral CT scan is most accurate overall. ERCP may be useful, particularly when no mass is found on CT scan. Fine-needle aspiration is indicated primarily when there is CT evidence of unresectability so that

a tissue diagnosis can be confirmed without operation. (Negative aspiration *does not* rule out disease.) Percutaneous transhepatic cholangiography and stenting are an alternative to ERCP. Angiography may be indicated if CT has not adequately evaluated vascular anatomy. Magnetic resonance imaging (MRI) does not appear to be superior to CT. On occasion, MR cholangiography and MR angiography may be informative. Endoscopic ultrasound is highly sensitive in the detection of small masses in the pancreas and assessing tumor invasion of the mesenteric blood vessels. It is highly user dependent. Fine-needle aspiration is justified when the result will change the patient's treatment. It is not required when the patient's tumor is deemed resectable by appropriate radiographic evaluation. Laparoscopy can be used to stage for unresectability in a high-risk patient and obtain tissue for diagnosis when fine-needle aspiration is unsuccessful. It is not necessary routinely. Spiral CT provides the best overall initial assessment and may be the only test required. Chronic pancreatitis or focal acute pancreatitis occasionally present clinically as a possible pancreatic carcinoma. History, particularly with regard to risk factors for pancreatitis or prior episodes, is often telling. On occasion, an interval CT scan may demonstrate resolution of the apparent mass. It may be impossible to distinguish between chronic pancreatitis and cancer even at operation.

Treatment and Prognosis Rapidly correct nutrition, anemia, and volume status and assess renal function. Transhepatic biliary drainage usually is unwarranted. Pancreaticoduodenectomy is the only hope for cure of tumors in the head of the pancreas and is most useful in localized ampullary, duodenal, or distal bile duct carcinoma. It may be helpful in small, confined pancreatic head adenocarcinomas. Overall, only 20 percent of patients with pancreatic carcinoma are potentially resectable for cure. The rate is even lower with distal pancreatic lesions because of their late presentation.

Unresectable patients may benefit from palliative cholecystoor choledochoduodenostomy and gastrojejunostomy (duodenal obstruction in 30 percent). Intraoperative celiac plexus injection may alleviate pain. Patients with widely metastatic disease or poor-risk patients with locally unresectable disease are unlikely to benefit from surgery unless duodenal obstruction requires bypass. ERCP or transhepatic drainage may benefit the poor-risk patient. Combined radiation therapy and 5-fluorouracil (5-FU) may be of some value as an adjuvant and as palliation (Table 30-2).

Pancreaticoduodenal Resection Classically, this included resection of the antrum of the stomach with the duodenum, distal bile duct, and head of the pancreas to the neck, just at the level of the mesen-

TABLE 30-2
PROGNOSIS OF PERIAMPULLARY TUMORS

Site	5-year Survival Rate, %
Pancreas	10
Ampulla of Vater	35
Duodenum	30
Bile duct	15
After pancreaticoduodenectomy, the 5-year survival rate for pancreatic cancer without lymph node metastases is 35%. Rates as high as 50% have been reported.	

teric vessels. Currently, a pylorus-preserving resection is performed most often. Reconstruction is via choledocho-, pancreatico-, and gastrojejunostomy (or duodenojejunostomy if the pylorus was preserved), with the gastric anastomosis below the others to prevent marginal ulceration. Vagotomy is not necessary. Most patients lose weight, with some malabsorption postoperatively. Exocrine supplements may be necessary. Total pancreatectomy is of questionable, if any, advantage, has severe morbidity, and shows no documented increased survival.

Cystic Neoplasms

These are of duct cell origin. Serous (microcystic) neoplasms are benign, whereas mucinous cystadenoma is premalignant and may evolve into cystadenocarcinoma. They often present with vague discomfort; jaundice is seen in less than 10 percent, along with anorexia and weight loss. Surgery is indicated for symptoms and any question of malignancy. All macrocystic lesions should be excised. It may be possible to distinguish mucinous from serous tumors by needle aspiration with cytology, mucin stains, and carcinoembryonic antigen (CEA) and CA 19-9 levels.

Islet Cell Tumors

INSULINOMA

The most common islet cell neoplasm, the insulinoma, is from the beta cell. Hyperinsulinemia causes severe hypoglycemia and leads to convulsions, depression, and coma. Glucose promptly reverses

symptoms. The classic diagnostic criteria, Whipple's triad, include fasting hypoglycemia (< 50 mg/dL) during attacks, central nervous system changes and hypoglycemic symptoms brought on by fasting, and reversal of changes with glucose. Measurement will show insulin inappropriately high for ambient glycemia. About 80 percent are benign adenomas, and 15 percent are malignant. Moreover, 15 percent are multiple. Most are 1–3 cm in size. They may be seen in multiple endocrine neoplasia, Type I (MEN-I) syndrome (5 percent). Preoperative localization is difficult and may be aided by angiography, selective venous sampling, CT scan, or octreotide scintigraphy.

Treatment is surgical, except in advanced metastatic disease, where streptozotocin is helpful (destroys islets). Intraoperative management includes meticulous inspection of the entire gland with enucleation of the adenoma. Intraoperative ultrasound can be useful. Resection is performed for malignancy. Distal pancreatectomy may be of benefit when no lesion is located. In children, nesidioblastosis is diffuse islet hyperplasia, usually controlled with adrenocorticotropic hormone (ACTH), cortisone, and diet. If necessary, the surgical approach is a distal subtotal pancreatectomy.

GASTRINOMA

Clinical Manifestations Original Zollinger-Ellison triad: fulminant, atypically located peptic ulcers; extreme gastric hypersecretion; and non-beta pancreatic islet cell tumor. Gastrinoma may start as a simple disease and end up with severe complications (e.g., perforation, obstruction, hemorrhage, intractability). It is unresponsive to standard medical and surgical therapy. Patients may have high-output diarrhea and steatorrhea.

Diagnosis High basal secretory rates are seen and a BAO/MAO ratio of more than 0.6, hypertrophic gastric folds, a fasting hypergastrinemia (> 200 pg/mL) or paradoxical rise in gastrin after *secretin* infusion, and a pancreatic mass on CT scan.

Pathology and Pathophysiology These are 2-mm to 10-cm non-beta pancreatic islet cell neoplasms. There are various reports of malignant potential, although it may be more than 90 percent. There may be a lesion in the duodenal wall. Lesions are slow growing and metastasize late; death is often the result of ulcer disease. Gastrinomas are seen in MEA-I syndrome (Wermer's: pituitary, parathyroid, pancreas), where lesions are multiple and benign.

Treatment Originally, patients with gastrinoma were treated with total gastrectomy; however, the use of histamine H_2 antagonists and

omeprazole with or without parietal cell vagotomy may control patients with unresectable disease. Efforts should be to completely excise lesions in patients without metastatic disease because of the high malignant potential. Lesions are often found in the gastrinoma triangle: (1) junction of the cystic and common ducts, (2) junction of the second and third parts of the duodenum, and (3) junction of the neck and body of the pancreas.

OTHER ISLET CELL TUMORS

VIPomas may produce diarrhea, "pancreatic cholera," the WDHA syndrome (*w*atery *d*iarrhea, *h*ypokalemia, and gastric *a*chlorhydria). About 50 percent are malignant. Glucagonomas show cutaneous lesions (migratory necrolytic erythema), diabetes, glossitis, anemia, weight loss, depression, and venous thrombosis. About 75 percent are malignant. They are best treated by resection. Somatostatinomas manifest diabetes, diarrhea, steatorrhea, achlorhydria, gallstones, malabsorption, and abdominal pain. Symptoms are all attributable to somatostatin excess. They are most often treated with streptozocin, dacarbazine, and doxorubicin.

For a more detailed discussion, see Reber HA: Pancreas, chap. 30 in *Principles of Surgery,* 7th ed.

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CHAPTER

31

SPLEEN

ANATOMY

The spleen arises along the left side of the dorsal mesogastrium. Its weight in the average adult is 75–100 g. Located in the left upper quadrant, its superior relationship is the left leaf of diaphragm, and it is protected on all sides by the rib cage. It is supported by the splenophrenic, splenorenal, splenocolic, and gastrosplenic ligaments. These ligaments are all avascular except the gastrosplenic, which contains the short gastric vessels. The splenic artery arises from the celiac axis; the splenic vein joins the superior mesenteric vein to form the portal vein.

Accessory spleens are found in 14–30 percent of patients; they are found in decreasing order of frequency in the splenic hilus, gastrosplenic and splenocolic ligaments, gastrocolic ligament, splenorenal ligament, greater omentum, female pelvis, and rarely, the scrotum (Fig. 31-1).

The spleen is surrounded by a 1–2-mm capsule. Its pulp is divided into white, red, and marginal zones. The marginal zone surrounds white pulp and contains end-arterial branches of the central arteries. Lymphocytes, macrophages, and red cells are found in the marginal zone. The red pulp surrounds the marginal zone and consists of cords and sinuses.

Blood traverses the trabecular arteries that enter the white pulp as central arteries. These central arteries give off vessels at right angles or cross the white pulp and end in the marginal zone or red pulp, where they collect in splenic sinuses and then into the pulp veins, the trabecular veins, and the main splenic vein. Splenic cords are located between the sinuses. Red blood cells must deform to pass from sinus to cord. Total splenic blood flow is 300 mL/min.

PHYSIOLOGY AND PATHOPHYSIOLOGY

The spleen forms red and white blood cells that enter the circulation only between the fifth and eighth months of fetal life.

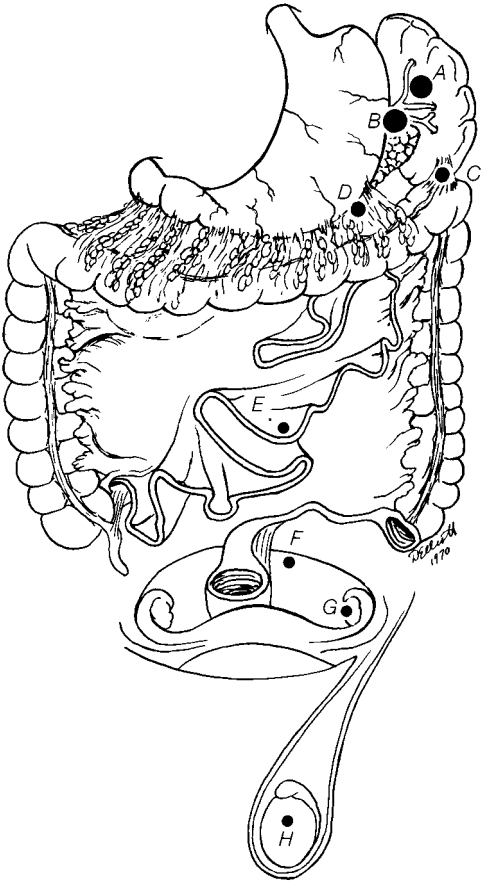

FIGURE 31-1 Location of accessory 3 spleens. *A.* Splenic hilus. *B.* Along splenic vessels; tail of pancreas. *C.* Splenocolic ligament. *D.* Greater omentum; perirenal regions. *E.* Mesentery. *F.* Presacral region. *G.* Adnexal region. *H.* Peritesticular region. (From: Schwartz SI, Adams JT, Bauman AW: Splenectomy for hematologic disorders. *Curr Probl Surg*, May 1971. Copyright 1971, Chicago, Year Book Medical Publishers. Used by permission.)

Reticuloendothelial tissue removes cellular elements from circulating blood. With splenomegaly, blood elements pool in the spleen.

Abnormal and aged erythrocytes, abnormal granulocytes, normal and abnormal platelets, and cellular debris are cleared from the circulation by the spleen.

Pathologic reduction of cellular elements by the spleen may be due to (1) excessive destruction and (2) splenic production of antibody directed at a particular cellular element. *Hypersplenism* refers to overactivity of splenic function leading to accelerated removal of any or all of the circulating elements.

Howell-Jolly bodies, nuclear remnants of erythrocytes, are removed by the spleen. Postsplenectomy blood smears therefore contain red cells with Howell-Jolly bodies.

Each day 20 mL of aged red blood cells is removed. A hypoxic, acidotic, and glucose-deprived environment promotes further cell injury, compounded by low ATP levels. Red cell surface area is lost with each passage.

Neutrophils are removed from the circulation with a half-life of 6 h. Neutropenia occurs in some hypersplenic states because of accelerated sequestration or enhanced removal of altered granulocytes.

The platelet survives 10 days in circulation. One-third of the total platelet pool is sequestered in the spleen, but up to 80 percent may be sequestered in hypersplenism. Postsplenectomy platelet counts may reach as high as 1 million cells/mm^3. It may be transient but in the extreme situation may result in intravenous thrombosis. Immunologic states without hypersplenism (e.g., idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura) also cause increased sequestration.

DIAGNOSTIC CONSIDERATIONS

Evaluation of Size Normally, the spleen is not a palpable organ except in 2 percent of adults. With enlargement, it may be felt below the left costal margin with a notching on its anteromedial surface.

Routine radiographs are useful. Splenomegaly is suggested by medial or caudal displacement of the stomach bubble and caudal displacement of the splenic flexure. Computed tomographic (CT) scans and magnetic resonance imaging (MRI) both depict abnormalities such as cysts, abscesses, and tumors. Radioisotopic scanning with technetium-99m (^{99m}Tc) sulfur colloid also is useful.

Evaluation of Function Hypersplenism is manifest by a reduction in the number of red cells, neutrophils, or platelets in the

peripheral blood smear; marrow production should increase unless there is concomitant marrow disease. The diagnosis of hemolysis, increased red cell turnover, is supported by a reticulocytosis and increase in the serum bilirubin level.

The spleen's role in hemolytic anemia can be assessed by determining relative uptake of chromium-51 (^{51}Cr)-tagged red cells by the spleen and liver. A 2:1 spleen-liver ratio implicates the spleen and anticipates beneficial effects of splenectomy. Radioisotope labeling also is used to evaluate neutrophil and platelet survival.

RUPTURE OF THE SPLEEN

See Chap. 6.

HEMATOLOGIC DISORDERS FOR WHICH SPLENECTOMY IS POTENTIALLY THERAPEUTIC

Hemolytic Anemias

These are disorders in which there is accelerated destruction of mature red cells. They are classified as *congenital,* in which there is an intrinsic red cell defect, and *acquired,* in which the red cells are normal. Abnormal red blood cell survival may be demonstrated by measuring the disappearance of ^{51}Cr-labeled red cells.

Hereditary Spherocytosis This disorder is transmitted as an autosomal dominant trait. The erythrocyte membrane is defective, and the cell has a thickened and spherical shape and is small. There is increased osmotic fragility; i.e., lysis occurs at a higher than normal concentration of sodium chloride. The abnormal spherocytic red cells are unable to pass through the spleen and are more susceptible to trapping and disintegration with each passage. Decreased red cell ATP may be a precise defect.

Clinical features are anemia, reticulocytosis, jaundice, and splenomegaly. Fatal crises have been reported rarely. Cholelithiasis is present in 30–60 percent. Leg ulcers are uncommon.

Diagnosis is by peripheral blood smear, which shows spherocytic cells with a smaller diameter and increased thickness. Increased osmotic fragility is diagnostic, but such tests are rarely performed.

Splenectomy is the only therapy and should be delayed until age 4. Intractable leg ulcers mandate early splenectomy. Results are

uniformly good. The underlying erythrocyte defect is unchanged, but hemolysis and jaundice resolve, and erythrocyte life span becomes normal. Preoperative ultrasound or an oral cholecystogram should be done, and if gallstones are present, cholecystectomy should be performed concomitant with splenectomy.

Thalassemia Also known as *Mediterranean anemia*, this disorder is transmitted as an autosomal dominant trait. There is a defect in hemoglobin synthesis. Heinz bodies are present as intracellular precipitates. The disease is classified into alpha, beta, and gamma types, depending on the specific chain involved. Beta thalassemia results in a decreased rate of beta-chain synthesis and a decrease in hemoglobin A (Hb-A).

Two degrees of severity have been determined: thalassemia major (homozygous) and minor (heterozygous). Thalassemia major occurs in the first year of life with pallor, retarded body growth, and a large head. It may result in a severe chronic anemia with icterus, splenomegaly, and early death. Most thalassemia minor patients lead normal lives. Thalassemia major is diagnosed by blood smear. Nucleated red cells are present. The reticulocyte count is elevated. There is persistence of hemoglobin F (Hb-F) and a decrease in Hb-A. In thalassemia minor, Hb-A_2 is increased.

Treatment is indicated only for symptomatic patients; transfusions are given as needed, and splenectomy may reduce transfusion requirements and the hemolytic process. Other indications for splenectomy include marked splenomegaly and repeated splenic infarcts.

Hereditary Hemolytic Anemia with Enzyme Deficiency Included are anaerobic glycolytic deficiencies, e.g., pyruvate-kinase (PK) deficiency, and hexose monophosphate shunt deficiencies, e.g., glucose-6-phosphate (G-6-PD) deficiency. Red cells are more susceptible to hemolysis. Most patients are asymptomatic, with hemoglobin levels above 8 g/dL. Transfusion is appropriate for significant anemia. Splenectomy may help severe PK deficiency but plays no role in G-6-PD deficiency. Postsplenectomy mesenteric or caval thrombosis may occur in PK deficiency. Splenectomy worsens those with hereditary high red cell phosphatidylcholine anemia.

Sickle Cell Disease This is a hereditary hemolytic anemia that occurs predominantly in blacks. Hb-A is replaced by hemoglobin S (Hb-S), the sickle hemoglobin. Hb-F is also mildly increased. With reduced oxygen tension, the Hb-S molecule crystallizes, and the cells elongate and distort. This increases blood viscosity and

stasis, leading to thrombosis, ischemia, necrosis, and organ fibrosis. Early in the disease the spleen enlarges, but with repeated infarction, autosplenectomy occurs.

Most patients with the *trait* are asymptomatic. In those with the *disease*, chronic anemia and jaundice may be interrupted by acute crises related to thrombosis. Symptoms include bone or joint pain, hematuria, priapism, neurologic symptoms, ulcers of the malleolus, abdominal pain, and splenic abscess.

Diagnosis is made by blood smear and hemoglobin electrophoresis. Leukocytosis, thrombocytosis, and hyperbilirubinemia may be present.

Treatment is palliative. Sodium cyanate prevents sickling of Hb-S. Hydration and exchange transfusions are performed for crises. Splenectomy rarely is indicated unless hypersplenism is present. There usually is autosplenectomy from infarction.

Idiopathic Autoimmune Hemolytic Anemia This is a disorder in which there is a shortened erythrocyte life span secondary to an endogenous hemolytic mechanism with normal red cells. The cause is unknown but presumed to be autoimmune. The spleen may serve as a source of destructive antibody. "Warm" and "cold" antibodies have been described; most are hemagglutinins rather than hemolysins. Immunologically altered cells are trapped and destroyed by the reticuloendothelial system of the spleen.

This disorder is more common in women and in those older than age 50. Mild jaundice is present. Splenomegaly is present in 50 percent and gallstones in 25 percent. Tubular necrosis occurs in severe cases, and the prognosis in this group is grave.

Diagnosis is made by demonstrating anemia, reticulocytosis, and products of red cell destruction in the urine, blood, and stool; hypercellular bone marrow; and a positive direct Coombs' test.

Treatment is not necessary for those who run a self-limiting course. Corticosteroids and transfusions may be required. With "warm" antibody, splenectomy is indicated when steroids are ineffective, required in excess, cause toxic manifestations, or are contraindicated. Splenic sequestration as demonstrated by ^{51}Cr-tagged red cells is useful in predicting success after splenectomy. Relapses may occur after splenectomy.

Idiopathic Thrombocytopenic Purpura (ITP)

This is an acquired disorder in which platelets are destroyed when exposed to immunoglobulin G (IgG) antiplatelet factors. The spleen is both the source of antibody and the site of sequestration. Features

include a bone marrow with normal to increased megakaryocytes and no evidence of systemic disease or drug ingestion known to cause thrombocytopenia. This disorder occurs in some patients with HIV/AIDS.

There is a 3:1 female-male ratio. Clinical manifestations include petechiae, bleeding gums, vaginal bleeding, gastrointestinal bleeding, and hematuria. Central nervous system bleeding occurs in 1–2 percent. The spleen is normal in size and rarely palpable.

Laboratory data include platelet counts of less than 50,000/mm^3, a prolonged bleeding time, and a normal clotting time. There is no anemia or leukopenia. Bone marrow examination shows normal to increased megakaryocytes in addition to qualitative histologic changes.

Acute ITP resolves in 80 percent of children under age 16 without specific therapy; 75–85 percent of adults with chronic ITP respond permanently to splenectomy without further steroid requirements. Platelet counts should increase to over 100,000/mm^3 within 7 days.

Treatment begins with 6–8 weeks of steroid therapy; occasionally, gamma-globulin infusions and plasmapheresis have been useful. Splenectomy is performed if there is no response; if there is a response, the steroids are tapered. Splenectomy is indicated if thrombocytopenia recurs. Emergent splenectomy is indicated for any intracranial bleeding.

Even if platelet levels approach zero, platelets should not be given until the spleen is removed. Accessory spleens may be responsible for recurrence and may be treated effectively by removal.

Systemic Lupus Erythematosus (SLE) Splenectomy may benefit SLE patients with refractory cytopenias.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a disease of arterioles and capillaries, but in some patients splenectomy is beneficial. The etiology is probably immune; 5 percent occur during pregnancy. Histologically, there is widespread occlusion of capillaries and arterioles.

The pentad of clinical features includes fever, purpura, hemolytic anemia, neurologic manifestations, and renal disease. Laboratory data include anemia, reticulocytosis, thrombocytopenia, and leukocytosis. Occasionally, hyperbilirubinemia, proteinuria, hematuria, casts, and azotemia are seen. A blood smear shows fragmented, distorted red cells.

Most cases show a rapid fulminant and fatal course, usually secondary to renal failure or an intracranial bleed. Treatment includes heparin, exchange transfusions, plasmapheresis, and administration of dextran, antimetabolites, and steroids. Splenectomy with high-dose steroids may be useful if there is no response to the preceding.

Secondary Hypersplenism

Pancytopenia may occur with splenomegaly or splenic congestion. This is seen in portal hypertension. Bleeding and petechiae, however, are uncommon. Hypersplenism per se is not an indication for surgery in portal hypertension. If splenectomy becomes necessary, it should be combined with a splenorenal shunt to decrease the portal pressure.

Myeloid Metaplasia

This is a panproliferative process with connective tissue proliferation of the bone marrow, liver, spleen, and lymph nodes, as well as simultaneous proliferation of the hemopoietic elements in the liver, spleen, and long bones. The cause is unknown. Splenic enlargement may occur. Portal hypertension also may occur as a result of hepatic fibrosis or increased forward flow.

The presenting manifestations (not until middle age) usually are that of anemia and increasing splenomegaly. Symptoms include abdominal pain of splenic infarction, fullness after meals, spontaneous bleeding, secondary infection, bone pain, pruritus, and hyperuricemia. Hepatomegaly is common.

A hallmark is the peripheral blood smear. Red cells are fragmented with poikilocytosis and teardrop and elongated forms. The white blood cell count is usually below 50,000/mm^3 but may be much higher. The platelet count may be low, normal, or high. Marrow biopsy shows fibrous replacement of elements.

Treatment consists of transfusions, hormones, chemotherapy, and radiation therapy. Busulfan and cyclophosphamide have been used. Although not curative, splenectomy is indicated for control of anemia, thrombocytopenia, and symptoms secondary to an enlarged spleen. In patients with esophagogastric varices, splenectomy alone usually is sufficient. Postoperative thrombocytosis and thrombosis of the splenic vein extending into the portal and mesenteric veins commonly occur in these patients. Operative mortality is 13 percent, with morbidity of 45 percent.

Hodgkin's Disease, Lymphomas, and Leukemias

Splenectomy is indicated for symptomatic splenomegaly, with anemia and increasing transfusion requirements, or with cytopenia limiting systemic therapy.

Hairy cell leukemia, or reticuloendotheliosis, is characterized by malignant cells with filamentous cytoplasmic projections. Splenectomy is indicated when neutropenia, thrombocytopenia, and anemia occur. This may result in improvement in 67–75 percent. Failures are managed with steroids and chemotherapy.

Staging of Hodgkin's Disease and Non-Hodgkin's Lymphoma Diagnosis usually is made by biopsy of suspicious lymphadenopathy or splenomegaly. The Sternberg-Reed cell is pathognomonic. There are four major histologic types: lymphocyte predominant, nodular sclerosis, mixed cellularity, and lymphocyte depletion. Survival is related to the histology and presence or absence of symptoms. Stage I is limited to one anatomic region; Stage II shows two or more regions of disease on the same side of the diaphragm; Stage III shows disease on both sides of diaphragm, with disease limited to lymph nodes, spleen, and Waldeyer's ring; and Stage IV shows involvement of bone marrow, lung, liver, skin, gastrointestinal tract, and any nonnodal tissues.

A staging laparotomy is indicated for Stage I patients or patients with supradiaphragmatic Stage II nodular sclerosis without clinical symptoms. The indications for staging are decreasing because of greater reliance on CT scans and increasing use of chemotherapy.

A staging laparotomy is performed in the following fashion: (1) wedge liver biopsy before any retraction/manipulation, (2) splenectomy, (3) lymph node sampling from entire periaortic chain, mesentery, and hepatoduodenal ligament, and (4) iliac crest marrow biopsy. After laparotomy, surgical staging upgraded clinical stage in 27–36 percent and downgraded in 7–15 percent. Regarding non-Hodgkin's lymphoma, routine staging is not accepted by many.

Miscellaneous Diseases

Felty's Syndrome This disorder involves the triad of rheumatoid arthritis, splenomegaly, and neutropenia. Mild anemia, thrombocytopenia, and gastric achlorhydria are seen occasionally. Corticosteroids and splenectomy are used to treat neutropenia and reduce susceptibility to infection.

Splenectomy is indicated for (1) neutropenic patients with serious or recurrent infections, (2) patients requiring transfusions for anemia, (3) patients with profound thrombocytopenia, and (4) patients with intractable leg ulcers. The course of the arthritis usually is not altered, whereas the neutrophilic response to infection is improved.

Sarcoidosis This is a disease of young adults, with cough, dyspnea, generalized lymphadenopathy, pulmonary and mediastinal involvement, and skin lesions. Splenomegaly is present in 25 percent.

No specific treatment is known. Spontaneous recovery is the rule. Splenectomy is indicated for splenomegaly with hypersplenism.

Gaucher's Disease This is a familial disorder. There is abnormal storage or retention of glycolipid cerebrosides in reticuloendothelial cells. Spleen, liver, and lymph node enlargement occur. Clinical manifestations include an abdominal mass (spleen or liver), yellow-brown pigmentation of the head and extremities, bone pain and pathologic fractures, and hypersplenism. Treatment is either splenectomy or partial splenectomy.

Erythropoietica Porphyria This is a congenital disorder of erythrocyte pyrrole metabolism resulting in excessive deposition of porphyrins in the tissues. Splenectomy is indicated for splenomegaly and hemolysis.

MISCELLANEOUS LESIONS

Ectopic Spleen This is a rare condition resulting from lengthening of ligaments and extreme mobility of the spleen. Acute torsion may occur, requiring surgery.

Cysts and Tumors These are rare. Parasitic cysts usually are echinococcal. Nonparasitic cysts are dermoid, epidermoid, epithelial, and pseudocysts (after trauma).

Primary and malignant tumors of the spleen are sarcomatous. Metastases in the absence of widespread disease are extremely rare.

Abscesses Clinical manifestations include fever, chills, splenomegaly, and left upper quadrant tenderness. Diagnosis is by CT scan or ultrasound. Splenectomy is the treatment of choice. Splenotomy and drainage have been successful in some patients.

Fungal abscesses are found in patients on steroids and chemotherapy. Treatment includes antifungal drugs and splenectomy.

SPLENECTOMY

Technique The incision may be left subcostal or midline. Short gastric vessels are divided. Ligamentous attachments are divided for mobilization of the spleen. The splenic artery and vein in the hilus are divided, taking care to avoid injury to the tail of the pancreas. It is necessary to search for accessory spleens when performing splenectomy for hematologic disease. Drainage of the bed not performed routinely unless circumstances dictate. In the case of normal sized or slightly enlarged spleens, laparoscopic removal can be performed.

Postoperative Course and Complications Characteristic blood smear changes include (1) Howell-Jolly bodies and siderocytes and (2) leukocytosis and thrombocytosis. Complications include left lower lobe atelectasis, subphrenic hematoma and abscess, pancreatic fistula and pancreatitis, and thrombocytosis.

Overwhelming postsplenectomy infection (OPSI) is a rare occurrence and is seen more frequently after splenectomy for disease than that for trauma.

Immunologic defects include poor response to immunizations, deficiency in phagocytosis-promoting peptide, decreased serum immunoglobulin M (IgM), and decreased properdin. Most common organisms causing OPSI are *Streptococcus pneumoniae* and *Haemophilus influenzae.*

Pneumococcus vaccine and vaccine against *H. influenzae* should be given as prophylaxis; these are best given 10 days before elective splenectomy and preoperatively in anticipation of splenic trauma. Oral penicillin should be given until age 18. Splenectomy should be avoided or delayed, if possible, in pediatric patients.

For a more detailed discussion, see Schwartz SI: Spleen, chap. 31 in *Principles of Surgery,* 7th ed.

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CHAPTER

32

INTRAABDOMINAL INFECTIONS

Intraabdominal infections are a common occurrence in surgical practice. They may be the initial presenting complaint in a patient with ongoing disease or a complication of surgical therapy. Infections can result in considerable morbidity and mortality as a result of the activation of local and systemic inflammatory responses. A good outcome is highly dependent on prompt and effective decision making. Delay in the treatment of intraabdominal infection allows inflammatory and infectious processes to dominate, resulting in multisystem organ failure or death.

STRUCTURE AND FUNCTION OF THE PERITONEAL CAVITY

The peritoneum lining the abdominal cavity and organs is a single layer of mesothelial cells with a surface area of approximately 1.8 m^2. There are microvilli that increase the surface area and allow fluid exchange, as well as two distinct populations of cells, cuboidal and flattened. With infection or trauma, the gap between neighboring cells enlarges, allowing free diffusion of molecules and leading to the accumulation of intraabdominal fluid (ascites).

The peritoneal cavity creates several dependent areas where fluid and blood can accumulate. These are the areas where the subsequent development of abscesses is likely. The peritoneum reflects from the posterior aspect of the anterior abdominal musculature to cover the aorta, vena cava, ureters, and kidneys, creating the retroperitoneal space. The reflection continues over the mesentery and becomes the parietal peritoneum, which covers the small bowel, stomach, spleen, liver, gallbladder, ovaries, and uterus.

Normally, the peritoneal cavity is largely a potential space with only a thin film of fluid separating the parietal and visceral layers. This fluid serves as a lubricant that allows the abdominal viscera to slide freely within the peritoneal cavity. The space can be greatly expanded; e.g., during peritoneal dialysis, up to 3 L of fluid can be instilled in the cavity without discomfort. During laparoscopy, up

to 5 L of CO_2 can be insufflated, although this requires anesthesia because of the pain of acute abdominal muscle distention.

Potential Spaces for Fluid Accumulation There are several areas created by the compartmentalization of the peritoneal cavity where fluid can accumulate. These include the subphrenic spaces above the liver and spleen, the right and left pericolic gutters between the abdominal wall and the mesentery of the colon, and the pouch of Douglas in the pelvis between the rectum and vagina in females or the rectum and bladder in males. When these become infected, an abscess can occur.

Innervation It is important to understand the innervation of the peritoneal lining to correlate clinical examination with pathophysiology; e.g., a subphrenic collection presents as shoulder pain as a result of irritation of the cervical dermatone extending to the diaphragm. Direct peritoneal irritation as with an inflamed appendix presents as localized pain. Hollow visceral distention as seen in biliary colic, renal colic, or bowel obstruction is referred to the primary dermatome, upper back for gallbladder, groin for kidney, and periumbilical area for bowel.

In localized inflammation of the parietal peritoneum, sensitivity can extend beyond the area of infection. This rebound tenderness is seen on release of the abdominal wall after placing it under tension. Referred pain similarly occurs when compression away from the source of infection refers pain to the site of inflammation.

PHYSIOLOGY OF PERITONEAL FLUID EXCHANGE

The mesothelial lining cells of the peritoneum secrete a serous fluid that circulates within the cavity, with a normal volume of 50–100 mL. Fluid and solutes of less than 30 kD are continuously resorbed by the peritoneal mesothelial lining cells and subdiaphragmatic lymphatics. Infection leads to alterations in molecular permeability, allowing larger particles to be absorbed. Peritoneal fluid movement is based on the balance of two forces; gravity, which pulls fluid to the most dependent areas of the abdomen, and negative pressure, created beneath the diaphragm with each respiratory cycle. Normally, fluid moves from inferiorly to superiorly, with the negative-pressure areas under the diaphragm favored for accumulation of fluid and subsequent abscess.

The normal response to peritoneal injury is rapid filling of the mesothelial defect by adjacent cell movement and healing within

3–5 days. When extensive destruction has occurred leading to basement membrane exposure, adhesions form. These adhesions increase over the first week to 10 days after surgery and become maximal 2–3 weeks after injury.

HOST DEFENSE AGAINST INTRAABDOMINAL INFECTION

There are three major peritoneal defense mechanisms to deal with infection:

1. Mechanical clearance of bacteria via lymphatics
2. Phagocytic killing of the bacteria by immune cells
3. Mechanical sequestration by abscess formation to limit diffusion of bacteria

Diaphragmatic movement produces an influx of fluid into the lymphatics. Because of their small size, bacteria rapidly pass through the diaphragmatic stomata into the thoracic duct and central circulation. This explains why patients with gastrointestinal perforation often present with rigors and fevers. The second defense component is the direct activity of immune cells. Macrophages including peritoneal macrophages are involved in direct microbial killing through phagocytosis via a respiratory burst. This release of proteolytic enzymes is a major component of the inflammatory response and is further mediated by cytokines.

Neutrophils are partially responsible for the parenchymal destruction noted during inflammation. Neutrophils contain granular enzymes that directly digest cell membranes inducing direct toxic effects on bacteria. This defense mechanism has an obligatory requirement for molecular oxygen to create superoxide radicals. Patients with devitalized tissues and shock have inadequate oxygen delivery limiting this defense component.

Endothelial cells lining the blood vessels and lymphatics are injured as bystanders to the inflammatory response. This increases permeability, which allows not only fluid but also additional macrophages and neutrophils to move from the systemic circulation into the abdominal cavity. Mesothelial cells secrete a variety of inflammatory molecules, which attracts neutrophils to the area of infection. Platelet activation and adherence result in the release of platelet-activating factors. Monocyte mediation releases immunoglobulins.

Mechanisms of Cell Recruitment to the Site of Injury: Cytokines and Other Chemoattractants Systemic inflammatory cells must

be drawn to the area of infection. The release of chemoattractants recruits neutrophils to the area and induces them to adhere to the endothelium and then pass into the area of inflammation. Leukocytes also must exit the systemic circulation to migrate into the area of infection. The cell initially moves from the circulating state in the center of the bloodstream, rolling along the wall of the capillary. At some point, the leukocyte adheres firmly and is activated by the aforementioned chemotactic agents. Migration is mediated by adherence to integrins and subsequent movement to the extravascular space.

BACTERIOLOGY OF PERITONITIS AND INTRAABDOMINAL INFECTION

Most bacteria in the colon are anaerobic and contribute little to intraabdominal infection. The most common bacteria isolated in clinical infections, *Escherichia coli, Enterobacter, Klebsiella,* and *Pseudomonas,* make up less than 0.1 percent of normal colonic flora. Even the most common anaerobic pathogen, *Bacteroides fragilis,* accounts for only 1 percent. The presence of a large number of nonpathogenic bacteria provides a measure of protection to the host by suppressing the growth of potentially pathogenic bacteria. This balance often is altered with chronic broad-spectrum antibiotic treatment, leaving the remaining bacteria increasingly virulent (Table 32-1). The concentration of bacteria also varies along the length of the gastrointestinal tract. The stomach, because of its high acid content, contains fewer than 10^3 bacteria/mm^3, which rises with acid-reduction therapy. The proximal small bowel contains 10^4–10^5 bacteria/mm^3, rising to 10^9/mm^3 in the terminal ileum and 10^{12}/mm^3 in the colon, with more anaerobic bacteria predominant distally.

After perforation, multiple species of bacteria adhere to the peritoneum and colonize the mesothelium. *B. fragilis* emerges as the predominant organism and becomes a major factor in the development of intraabdominal abscess. The synergy between anaerobic and aerobic bacteria increases the virulence of the infection. In animal studies, pure cultures of *E. coli* caused peritonitis with moderate mortality but no intraabdominal abscess. The coinjection of *B. fragilis* led to both abscess formation and a significant mortality. The inoculum of bacteria needed to establish a significant infection is less if there are adjunctive substances such as blood present. In experimental *E. coli* models, hemoglobin alone decreased the lethal dose of bacteria by five orders of magnitude. Other substances, including bile salts and pancreatic secretions, as well as

Cerra FB (eds): *Intensive Care Medicine*, 3d ed, Boston, Little, Brown, 1996. Used

foreign materials such as talc, fragments of cotton sponges, sutures, or barium, also increased morbidity and mortality associated with peritoneal contamination.

EVOLUTION OF INTRAABDOMINAL INFECTION

A single inoculum of intraperitoneal bacteria does not invariably lead to infection. The combination of bacteria and devitalized tissues in the presence of other facultative media increases the risk of developing peritonitis. The sooner that the contamination is contained and the debris evacuated, the better is the chance of resolution. Although early diagnosis is key, the classic combination of fever, leukocytosis, and abdominal pain is not present in all patients. The initial physiologic response is to dilute the noxious influence by the third spacing of fluid. Patients will then show signs of volume depletion but may not have localized peritonitis. A pneumonic process such as lower lobe pneumonia can mimic an intraabdominal process via referred somatic pathways. It is important to examine and image the chest before proceeding with any type of intervention of the abdomen.

Plain radiographs of the abdomen will reveal free air in the presence of visceral perforation. Abdominal abscesses can be seen without free air. Air-fluid levels above the liver or spleen suggest subphrenic abscess.

The preoperative preparation of patients with peritonitis involves the restoration of intravascular volume. Therapeutic doses of broad-spectrum antibiotics should be started. Patients developing ongoing acidosis or respiratory compromise should be intubated promptly and their respiratory status supported. Metabolic acidosis should not be attributed to infection only but also may reflect inadequate resuscitation. Determination of blood pressure plus monitoring of urinary output is an important measure of the adequacy of resuscitation.

The administration of pharmacologic doses of corticosteroids to septic patients should not be done. Some studies have shown that large doses of steroids may delay immediate mortality in sepsis, but overall outcome is not altered. One situation where steroids are useful is that of acute adrenal insufficiency, where the hypotensive and febrile state may mimic that of peritonitis. Patients at risk for bilateral adrenal hemorrhages include those on large doses of anticoagulation and postinjury patients.

MANAGEMENT OF PERITONITIS

When the patient has been resuscitated, celiotomy should commence promptly. A long midline incision allows wide exploration of the abdomen. Specific areas of perforation should be controlled quickly either with clamps or with sutures pending definitive therapy. It is important to explore the dependent areas of the abdomen carefully because multiple abscesses can occur in the subphrenic, subhepatic, and pelvic areas. The small bowel often will form interloop abscesses that should be gently exposed and evacuated. The definitive management of peritonitis depends on its cause. The perforation associated with stomach and duodenum is more chemical as opposed to bacterial peritonitis. Simple patching can treat duodenal perforations. Gastric perforations require resection, especially if there is concern regarding malignancy. Unless the gastric perforation is clearly associated with a high-acid ulcer, vagotomy is unnecessary. Small bowel perforations usually result from bowel obstruction with ischemia or embolic events. After resection, the question of reanastomosis depends on the location of the bowel and the underlying state and extent of the peritonitis. It is safer to exteriorize proximal and distal ends of the bowel in cases of severe peritonitis, especially when the perforation is more distal. Proximal perforations that are exteriorized can lead to difficulties with a high ostomy output state requiring long-term total parenteral nutrition, although subsequent reanastomosis is possible. Colonic perforation is a result of diverticulitis, acute colitis, carcinoma, or distal obstruction. Resection of the perforated colon with the obstruction is appropriate, and exteriorization of the bowel should be undertaken.

Postoperative peritonitis usually results from an anastomotic leak. Rather than developing the fulminate form of sepsis often seen in acute perforation, this is a more indolent type of syndrome beginning 5–8 days postoperatively. It often is associated with a rising white blood cell count and spiking temperatures. Computed tomography (CT) will demonstrate a fluid collection that can be drained percutaneously under ultrasound or radiologic guidance.

OTHER FORMS OF PERITONITIS

Not all peritonitis is a result of contamination from the gastrointestinal tract. Patients with cirrhosis and those with autoimmune diseases can develop primary bacterial peritonitis as a monomicrobial infection. Treatment is antibiotics and expectant management. Patients with peritoneal dialysis catheters often manifest infections,

usually related to the presence of a chronic foreign body that is accessed on a regular basis. Treatment normally is nonoperative using parenteral and intradialytic antibiotics. Nonresponse mandates catheter removal. Other forms of peritonitis not associated with bacteria include postoperative bile leak, retained foreign bodies, or chemical peritonitis from a perforated and sealed duodenal ulcer.

MANAGEMENT OF LOCALIZED ABSCESS

Intraabdominal abscess often is diagnosed by CT scan. Rectal and vaginal examinations confirming a mass in the lumen allows diagnosis and subsequent drainage.

There are some patients who cannot be drained percutaneously or transrectally. Subphrenic abscesses are amenable to drainage under ultrasound or radiologic guidance, although there is concern about passing the catheter through the previously sterile pleural space. In this situation, a small subcostal or posterolateral incision often allows open drainage. Abscesses in the retroperitoneum usually can be drained percutaneously. If surgical intervention is undertaken, the incision should remain in the retroperitoneal space.

ANTIMICROBIAL THERAPY FOR INTRAABDOMINAL INFECTIONS

In addition to drainage, a cornerstone of therapy for peritonitis is adequate tissue levels of antibiotics. Broad-spectrum empirical therapy is started before identification of the offending organism and is based on expected organisms. Most intraabdominal infections are caused by *E. coli, B. fragilis, Pseudomonas,* or *Streptococcus.* Perforations of the upper gastrointestinal tract such as the stomach often yield only isolates of yeast because of the high-acid state of the stomach.

Aminoglycosides have been the mainstay of therapy for serious gram-negative infections for many years. Although they do have nephro- and ototoxicity, careful monitoring can minimize these effects. Aminoglycosides are synergistic with penicillins, yielding improved response. Aminoglycosides work through suppression of bacterial DNA and RNA synthesis at the nucleus. Penicillin-type antibiotics open the bacterial cellular wall, allowing for greater entrance of the aminoglycocides. Beta-lactam antibiotics such as the cephalosporins have more gram-positive than gram-negative activity. They should be combined with metronidazole or clindamycin for anaerobic coverage.

TABLE 32-2
APPROPRIATE ANTIBIOTIC CHOICES IN PERITONITIS*

Secondary peritonitis
Monotherapy:
Ampicillin/sulbactam
Cefotetan
Cefoxitin
Piperacillin
Piperacillin/tazobactam
Combination therapy:
Aminoglycoside/metronidazole *or* clindamycin
Aztreonam/metronidazole *or* clindamycin

Tertiary peritonitis
Monotherapy (seldom possible):
Imipenem/cilastatin
Piperacillin/tazobactam
Combination therapy:
Aminoglycoside/metronidazole *or* clindamycin *or* imipenem/cilastatin
Aztreonam/metronidazole *or* clindamycin
Cefepime/metronidazole *or* clindamycin
Ceftazidime/metronidazole *or* clindamycin
Ciprofloxacin/metronidazole *or* clindamycin
For *Enterococcus:*
Ampicillin *or* piperacillin *or* vancomycin (only if ampicillin-resistant or the patient is allergic to penicillin
For methicillin-resistant staphylococci:
Vancomycin
For *Pseudomonas:*
Aminoglycoside *plus* aztreonam *or* cefepime *or* ceftazidime *or* piperacillin/tazobactam *or* imipenem/cilastatin
For *Candida:*
Fluconazole *or* amphotericin B

*Reflecting the preferences of the authors. Other antibiotics, alone or in combination, may be appropriate in individual circumstances, as long as the spectrum of activity includes activity against both aerobic and anaerobic gram-negative bacilli.

The fluoroquinolones are a relative newcomer whose effect results from targeting DNA gyrase, a repair enzyme. The quinolones have a fairly wide spectrum of activity against gram-negative bacilli including *Pseudomonas.* They can be used in either an oral or an intravenous form and have minimal nephrotoxicity (Table 32-2).

Pharmacology of Antibiotics It is important that suitable tissue levels of antibiotics are maintained depending on their activity. The aminoglycocides are most effective when a certain peak is reached between dosages, whereas the other beta-lactam antibiotics are most effective when the minimum inhibitory concentrations (MICs) are maintained at a relatively high level over the entire 24-h period. Frequent, small doses may accomplish this. Some antibiotics such as cefoperazone, piperacillin, and mezlocillin are excreted in the bile, achieving high levels within the biliary tree and lumen of the bowel. Route, timing, and dosages will maximize response.

For a more detailed discussion, see Solomkin JS, Wittman DW, West MA, and Barie PS: Intraabdominal Infections, chap. 32 in *Principles of Surgery,* 7th ed.

CHAPTER

33

ABDOMINAL WALL, OMENTUM, MESENTERY, AND RETROPERITONEUM

ANTERIOR ABDOMINAL WALL

Rectus Sheath Hematoma

Bleeding into the rectus sheath produces a surgical picture that may simulate the acute surgical abdomen. Bleeding is usually the result of rupture of the epigastric artery or veins and may follow direct trauma or occur spontaneously in patients with debilitating diseases or blood dyscrasia and in patients on anticoagulation therapy. Bleeding also occurs without obvious trauma or disease after minor straining.

Clinical Manifestations Rectus sheath hematoma is three times more frequent in women; it is rare in children. The peak age of incidence is the fifth decade. The sudden onset of pain is localized to the side of the abdomen where the bleeding occurred. Anorexia, nausea, low-grade fever, and a moderate leukocytosis are frequent. A tender mass may be palpable. Ultrasonography or computed tomography (CT) shows complex lesions within the rectus sheath.

Treatment Rectus sheath hematoma may be managed nonoperatively with bed rest and analgesics. Surgical intervention is necessary occasionally; ideally, the hematoma is evacuated without entering the peritoneal cavity. Bleeding points are then ligated and the wound closed without drainage.

Desmoid Tumor

This is an aggressive variant within a group of conditions referred to as *fibromatoses*. Desmoid tumor is of aponeurotic origin and usually is found within or deep to the flat muscles of the anterior abdominal wall. It is often seen in women of childbearing age, frequently after a recent gestation, and it may be the result of hemorrhage. It also frequently occurs in patients with familial polyposis

coli (Gardner syndrome) trait. Desmoid tumors are locally invasive benign tumors that rarely undergo malignant transformation to a low-grade fibrosarcoma; metastases have not been reported, but there is a tendency to recur after local excision. The microscopic appearance varies from an acellular fibroma to that of a cellular, low-grade fibrosarcoma.

Clinical Manifestations Desmoid tumor is usually a painless, deeply situated mass that is solitary, rarely crosses the midline, and may be fixed. It may vary in size from a few centimeters to a tumor weighing several kilograms. Desmoid tumors have a pseudocapsule with extensions into surrounding tissue, a feature critical to surgical management. The tumor locally invades and, although usually painless, can cause symptoms by compression of adjacent tissues such as nerves, bone, and viscera. Abdominal CT scan will show a homogeneous soft tissue mass with displacement of adjacent structures.

Treatment Once the diagnosis is established by biopsy, ideal treatment is wide excision with at least a 1–2-cm margin of normal tissue. This will include skin, muscle, and peritoneum. Every effort should be made to excise the tumor completely at the first operation, since there is a high propensity for local recurrence following incomplete excision.

In patients who are unresectable or with gross disease left at the margins, radiation therapy is recommended, although the reported response has been variable. Pharmacologic treatments also have been unpredictable, with most favorable reports anecdotal.

Recurrences can be treated by reexcision. For abdominal wall desmoids, prognosis is excellent. Prognosis for extraabdominal desmoids is less favorable.

OMENTUM

Torsion

Torsion is a twist on the long axis of the omentum to an extent causing vascular compromise. Primary omental torsion is relatively rare. Secondary omental torsion is associated with adhesions of the free end of the omentum to tumors, foci of intraabdominal inflammation, postoperative wounds, or internal or external hernias. Secondary torsion is more common than primary.

Clinical Manifestations Pain begins suddenly and is usually localized to the right lower quadrant. Tenderness, rebound tenderness, and voluntary spasm are frequent. The finding of free serosan-

guineous fluid at the time of celiotomy in the absence of a pathologic condition in the appendix, gallbladder, or pelvic organs should alert the surgeon to the possibility of omental torsion.

Treatment Treatment involves resection of the involved omentum with correction of any underlying etiologic condition.

Idiopathic Segmental Infarction

This is an acute vascular disturbance of the omentum not accompanied by omental torsion or an intraabdominal pathologic condition. It is precipitated by thrombosis of omental veins secondary to endothelial injury. The right lower segment of the omentum, which is the most mobile and richest in fat, is the portion usually involved. The involved segment is well demarcated, and serosanguineous fluid in the free peritoneal cavity is a constant finding.

Clinical Manifestations and Treatment Most patients are young or middle-aged adults who present with right-sided abdominal pain. There is always tenderness and often rebound tenderness over the region of the infarction. Resection of the infarcted area is indicated to prevent the possible complications of gangrene and adhesions.

Cysts

True omental cysts have an endothelial lining similar to cystic lymphangiomas. Dermoid cysts are lined with squamous epithelium and may contain hair, teeth, and sebaceous material. Pseudocysts of the omentum probably result from trauma with hematoma formation.

Clinical Manifestations Large cysts present as a palpable abdominal mass or with manifestations of torsion, infection, rupture, or intestinal obstruction.

Plain radiographs sometimes show a circumscribed soft tissue haziness. Ultrasound or CT shows a fluid-filled mass that often contains internal septations. Treatment consists of local excision.

Solid Tumors

The most common solid tumor of the omentum is metastatic carcinoma, which generally involves the omentum by tumor implant. Frequently there is associated ascites. Primary solid tumors of the omentum are rare. Most are tumors of smooth muscle, and about one-third are malignant. Excision is indicated.

MESENTERY

Mesenteric Circulatory Disease

ACUTE OCCLUSION OF THE SUPERIOR MESENTERIC ARTERY

This is due more often to an embolus than to thrombosis. Most emboli come from the heart and more often lodge near a major branch where the artery narrows, usually at the egress of the middle colic artery. The initial effect of the embolus on the artery is to cause spasm of its distal branches; secondary thrombosis of the distal artery then occurs. Sudden occlusion of the main stem superior mesenteric artery produces ischemia of the entire small intestine distal to the ligament of Treitz and also ischemia of the proximal half of the colon. Acute thrombosis of the superior mesenteric artery usually occurs in an artery partially occluded by atherosclerosis. The extent of intestinal ischemia or infarction depends on the site of the thrombosis and the status of collateral channels.

Pathology Early the bowel is pale due to intense vasospasm. At this stage, the bowel is hypertonic and contracted. Within 1–2 h, the initial vessel spasm subsides, and anoxic bowel wall becomes engorged with blood. Thrombosis of the visceral veins follows, and the bowel wall becomes inert, boggy, and cyanotic. As the infarction progresses to full-thickness necrosis of the intestine, the bowel wall becomes blood-soaked and cyanotic and "weeps" serosanguineous fluid into the peritoneal cavity.

Clinical Manifestations The clinical features are usually the same whether occlusion is the result of embolism or thrombosis. Males are affected more often than females. The peak age of incidence is the fifth and sixth decades. The most striking and constant complaint is sudden extreme abdominal pain initially out of proportion to the physical findings. Muscle spasm may be present, but the rigidity is almost never boardlike. Tenderness and rebound tenderness become severe as intestinal infarction occurs. Bowel sounds are first hyperactive, but within a short time the abdomen becomes silent. As infarction of the intestine progresses, the patient becomes febrile, the pulse rate increases, and the patient becomes hypotensive. Once bowel necrosis and perforation occur, the findings are those of generalized peritonitis and sepsis. The leukocyte count increases to over 20,000/mm^3 as hemorrhagic infarction occurs. Suspicion of the diagnosis of acute mesenteric ischemia is itself an indication to obtain an immediate mesenteric arteriogram. In addition to demonstrating emboli, thrombosis, and mesenteric vasocon-

striction, the arteriogram will define the adequacy of the splanchnic circulation. The angiographic catheter also provides a route for the intraarterial administration of vasodilating agents.

Treatment An occasional patient can be treated successfully by arterial infusion of a vasodilating agent. Early surgical intervention before gangrene and perforation of the intestine have occurred is optimal. The number of patients who present with a situation amenable to arterial reconstruction is small. If the occlusion is limited to a branch of the superior mesenteric artery or to the superior mesenteric artery distal to the origin of the ileocolic artery, the relatively short segments of affected intestine are best handled by resection with a primary anastomosis. As much as 70 percent of the small intestine can be removed without creating serious digestive disturbances.

In the situation where the main stem superior mesenteric artery is occluded, the decision to establish arterial flow is based on whether the process in the ischemic intestine is reversible. If the intestines are clearly gangrenous, the only surgical procedure that can be considered is resection. This usually will require removal of the entire small intestine distal to the ligament of Treitz and resection of the right half of the colon. Although this extensive resection is associated with a high operative mortality and late morbidity, it is worth consideration in an otherwise hopeless situation, and with the use of parenteral central hyperalimentation postoperatively, some patients can be salvaged.

If there is any question of the reversibility of ischemia of all or part of the intestine, an attempt at arterial reconstruction is indicated. An embolus usually can be extracted using a Fogarty catheter; a thrombus within a sclerotic vessel will require a thromboendarterectomy. An alternative approach is revascularization with a bypass venous graft between the aorta and the superior mesenteric artery distal to the site of occlusion.

Clinical assessment, such as return of intestinal color and arterial pulsations and the presence of visible peristalsis, is usually reliable in determining that a segment of revascularized intestine will remain viable. Intraoperative use of the Doppler ultrasonic flowmeter to detect pulsatile mural blood flow can give added objective confirmation. Intravenous infusion of a vital dye, usually fluorescein, also has been advocated to define intestinal recovery. If there is any question about the viability of long segments of intestine, they should be left and reexamined at a planned second operation 24–36 h later.

Most patients will have a depleted circulating blood volume resulting from loss of plasma and whole blood into the bowel lumen,

bowel wall, and peritoneal cavity. Replacement should be started while readying the patient for the operation. Added intravenous fluids are necessary postoperatively to combat the reactive hyperemia that occurs after revascularization of the intestine. Broad-spectrum antibiotics should be administered in large doses beginning preoperatively and continuing throughout the postoperative period. Anticoagulation, preferably with heparin, also has been recommended for patients who have arterial reconstruction.

The overall mortality after sudden occlusion of the superior mesenteric artery varies between 60 and 85 percent. Mortality is higher after acute occlusion by thrombosis than from embolization.

NONOCCLUSIVE MESENTERIC INFARCTION

In about 30 percent of patients with mesenteric infarction, careful examination will reveal no major arterial or venous occlusion. The infarction has been related to a sustained decrease in cardiac output, such as in prolonged circulatory collapse and hypoxic states that may accompany septicemia, acute myocardial infarction, and profound hypovolemia. Many patients presenting with nonocclusive mesenteric infarction have received digitalis, an agent that has been shown to induce mesenteric vasoconstriction.

Pathology The outer surface of the bowel is initially mottled, with segmental areas of cyanosis distributed throughout the length of the intestine. Later, gangrenous changes become advanced and lead to perforation.

Clinical Manifestations The clinical picture may be identical to that of patients with acute arterial or venous mesenteric occlusions. There may be prodromal symptoms of malaise and vague abdominal discomfort. Infarction of the intestine is heralded by the sudden onset of severe abdominal pain and vomiting. The patient usually becomes acutely hypotensive with a rapid pulse. Watery diarrhea is frequent, and the stools may be grossly bloody. The abdomen becomes diffusely tender and rigid. Bowel sounds are diminished or absent. Fever and leukocytosis are usual, and frequently there is a thrombocytopenia related to intravascular thrombosis. A characteristic early laboratory finding is a markedly elevated hematocrit due to "trapping" of serum in the bowel and seepage into the peritoneal cavity. Selective superior mesenteric arteriograms will demonstrate patent major vessels with multiple segmental areas of narrowing of both small and medium-sized vessels and diminution or absence of mural intestinal circulation.

Treatment The underlying disorder producing the low-flow state should be corrected. An attempt should be made to improve mesen-

teric artery flow. Direct infusion of a vasodilating drug, such as papaverine hydrochloride, into a catheter positioned in the superior mesenteric artery is used to improve mesenteric arterial flow. Antibiotics should be administered.

If abdominal signs and symptoms persist, operation is mandatory. The process usually involves all of both the large and small intestines and also may involve the stomach. For this reason, resection is not usually feasible. With involvement of lesser portions of the intestine, primary resection with anastomosis should be attempted. The reported mortality rates are upward of 80 percent.

CHRONIC OCCLUSION OF THE SUPERIOR MESENTERIC ARTERY (INTESTINAL ANGINA)

Intestinal ischemia, "intestinal angina," without infarction is due to collateral blood supply sufficient for life but not for function of the affected bowel. This is analogous to angina pectoris and intermittent claudication.

Etiology Collateral anastomoses among the three main gastrointestinal arteries from the aorta (celiac axis, superior mesenteric, and inferior mesenteric) provide for maintenance of intestinal viability and function when one of these branches is gradually occluded. When one main vessel is occluded and blood flow through one of the remaining patent vessels becomes (or has been) compromised, the now relatively ischemic intestine is unable to respond to the demands of digestion for an increased blood supply.

Chronic occlusion of the major visceral arteries is most often due to atherosclerosis. Less frequently, the stenosis is due to compression of the celiac axis by a celiac ganglion or arcuate ligament of the diaphragm, by involvement of the arteries in an expanding aortic aneurysm, or by an arteritis.

Clinical Manifestations The dominant feature of intestinal angina is generalized cramping abdominal pain that comes on soon after eating. The food-pain relationship soon leads to a reluctance on the part of the patient to eat. Subsequent rapid and severe weight loss characterizes the syndrome. As the intestinal ischemia progresses, a form of malabsorption syndrome contributes to the weight loss. An arteriogram will show stenosis or complete occlusion of the celiac axis or superior mesenteric arteries or both, usually within 1 cm of their origin.

Treatment Most surgeons prefer improving the circulation with a bypass graft. For a lesion in the celiac artery, a graft is inserted between a major branch of the celiac artery, usually the splenic artery, and the aorta.

Occasionally, the splenic artery itself may be mobilized and anastomosed to the side of the aorta. Bypassing of a superior mesenteric artery stenosis is best handled by inserting a graft to the side of the artery just beyond the egress of the middle colic artery and to the aorta below the origin of the renal arteries.

COLONIC ISCHEMIA

Etiology This occurs in elderly patients with underlying atherosclerotic stenoses or inflammatory arteriopathies. It sometimes follows ligation of the inferior mesenteric artery during aortic aneurysmectomy in the setting of stenosis of the superior mesenteric artery. The ischemia most often involves the descending and sigmoid colon.

Clinical Manifestations The clinical manifestations are characterized by sudden cramping lower abdominal pain and the urge to defecate followed in 12–24 h by passage of melena or bloody stool.

Plain x-rays may show thumbprinting of the colon, indicative of submucosal edema. The primary diagnostic study is flexible sigmoidoscopy, which will visualize patchy areas of ischemia or, if advanced, frank mucosal necrosis.

Treatment The condition is reversible in 40–50 percent of patients requiring only supportive measures, with results ranging from complete healing to stricture formation. This occurs when the ischemia is limited to mucosa or submucosa. When frank transmural necrosis is seen on initial sigmoidoscopy (serially), or when symptoms and endoscopic findings are progressive, early operation is indicated. Because the bowel is rarely prepared, ideal treatment is resection of all ischemic colon with end-colostomy and mucous fistula or Hartman's procedure.

MESENTERIC VENOUS OCCLUSION

Etiology and Pathology When visceral venous occlusion produces symptoms, it is almost always due to acute thrombosis. Mesenteric venous thrombosis may be idiopathic or evolve secondarily as a complication of several clinical disorders. Predisposing conditions include (1) intraabdominal infection, (2) portal hypertension, (3) hematologic conditions such as polycythemia vera, myeloproliferative disorders, or postsplenectomy state, (4) oral contraceptive use, (5) malignancy, and (6) the postoperative state. Congenital absence of naturally occurring antithrombotic proteins such as protein S, protein C, and antithrombin III explains the pathogenesis of most cases previously thought to be idiopathic.

About 50 percent of patients give a history of prior episodes of peripheral deep venous thrombosis.

Clinical Manifestation Frequently, the patient complains of vague abdominal discomfort, anorexia, and a change in bowel habits a few days or even weeks before the onset of severe symptoms. Early symptoms are followed by sudden severe abdominal pain, vomiting, and circulatory collapse. Bloody diarrhea is more frequent than with arterial occlusion. Rigidity is not present unless gangrene and perforation of the bowel have occurred. A marked leukocytosis and elevated hematocrit are characteristic findings in venous thrombosis. Paracentesis invariably yields serosanguineous fluid. Contrast-enhanced abdominal CT scan is the most useful diagnostic modality. This will show thickening of the bowel wall, possibly air in the bowel wall or portal vein, and often thrombus in the superior mesenteric vein.

Treatment Without operation, the mortality approaches 100 percent. Once diagnosed, heparin anticoagulation should be started immediately. Patients with peritoneal sign should undergo early operation soon after receiving supportive fluids and antibiotics. Shorter segments of intestine are usually involved than that noted if occlusion is primarily arterial. All devitalized intestine is resected, and a primary end-to-end anastomosis is performed. Resection should include adjacent normal bowel and mesentery until all grossly thrombosed veins are encompassed.

A "second look" operation 24–36 h later should be performed because of the frequent recurrence of thrombosis or extension of residual clots. Anticoagulation with heparin should be continued for 6–8 weeks. The prognosis is somewhat better than in mesenteric infarction due to arterial occlusion.

Aneurysms of the Splanchnic Arteries

Aneurysms of the splanchnic arteries are rare. Arteriosclerosis is the usual etiology in older patients; congenital or acquired defects in the medial wall of the artery are more often incriminated in the young.

Splenic artery aneurysms compromise about 60 percent. Most occur in women, and in about 40 percent of patients the aneurysms are multiple. Hepatic artery aneurysms make up 16–20 percent. Aneurysms of the celiac artery and the superior mesenteric artery and its branches each account for about 3 percent. Most are due to arteriosclerosis, but a relatively large number of aneurysms of the

superior mesenteric artery result from mycotic involvement or necrotizing arteritis.

Most splanchnic artery aneurysms are less than 2 cm in diameter. About 2–10 percent of splenic artery aneurysms rupture; the risk of rupture of hepatic, celiac, and superior mesenteric artery aneurysms is high, approximating 50 percent.

Clinical Manifestations Before rupture, most splanchnic artery aneurysms are asymptomatic. Concentric calcification of a splenic artery aneurysm may be detected on plain x-rays of the abdomen. Occasionally, a visceral artery aneurysm will be diagnosed prior to rupture on an incidental arteriogram obtained for another purpose.

When rupture occurs, the major symptom is acute abdominal pain and signs of acute blood loss. A splenic artery aneurysm rarely will rupture into the adjacent stomach or pancreatic duct, causing massive gastrointestinal bleeding. Erosion of a hepatic artery aneurysm into the bile duct is an unusual cause of hemobilia, with the classic triad of gastrointestinal bleeding, biliary colic, and jaundice.

Treatment A conservative approach is justified for the asymptomatic patient with a small splenic artery aneurysm. There is a hazard of rupture during pregnancy, notably during the third trimester. Operation is indicated for women of childbearing age. The preferred treatment is proximal and distal ligation of the aneurysm with obliteration of all feeding vessels in order to avoid splenectomy. If this is not feasible, resection of the aneurysm and splenectomy will be necessary. Because risk of rupture of other splanchnic artery aneurysms is high, asymptomatic patients should undergo surgical correction as soon as the aneurysm is recognized. Percutaneous transcatheter embolization is useful for treatment of intrahepatic aneurysms and other aneurysms of noncritical vessels.

Patients presenting with a ruptured aneurysm and with either intraabdominal or intraintestinal blood loss require immediate resuscitation and surgical intervention. If time allows, preoperative localization by arteriography should be carried out. The chances of finding the bleeding site are better if the blood pressure can be elevated preoperatively, but sometimes bleeding is so brisk that it is necessary to go to the operating room while the patient is in shock.

Rupture of a celiac artery aneurysm can be treated by ligation, and although most hepatic artery aneurysms also can be treated safely by ligation, an attempt should be made to reconstruct the hepatic artery with a graft. Rupture of a main superior mesenteric artery aneurysm will require replacement with a graft, preferably of autogenous vein. Overall mortality following rupture of a splenic

artery aneurysm is about 25 percent, with a 65 percent maternal and 95 percent fetal mortality if rupture occurs during pregnancy. The mortality subsequent to rupture of a celiac or superior mesenteric artery aneurysm is between 40 and 60 percent, whereas rupture of a hepatic aneurysm is associated with a 70 percent mortality rate.

Nonspecific Mesenteric Lymphadenitis

Nonspecific mesenteric lymphadenitis is one of the common causes of acute abdominal pain in young children. The lymph nodes primarily involved are those which drain the ileocecal region.

Clinical Manifestations The disease most commonly occurs in patients under age 18, without sex predilection. The initial pain is usually in the upper abdomen. Eventually the pain localizes to the right side; however, an important point in differentiating the disease from acute appendicitis is that the patient is unable to indicate the exact site of the most intense pain. The usual finding on examination of the abdomen is tenderness in the lower aspect of the right side, which is somewhat higher and more medial and considerably less severe than in acute appendicitis. The clinical similarity to acute appendicitis is marked.

Mesenteric Panniculitis

Mesenteric panniculitis is a process of extensive thickening of the mesentery by a nonspecific inflammatory process. Many consider it a variant of retroperitoneal fibrosis. The cause is unknown. Usually it involves the mesenteric root of the small bowel. Grossly, the normal fat lobulations of the markedly thickened and firm mesentery are lost. Scattered throughout are irregular areas of discoloration that vary from reddish-brown plaques to pale-yellow foci resembling fat necrosis.

Clinical Manifestations Men are affected more often than women. The disease is rarely described in children. The clinical features are nonspecific; they include recurrent episodes of moderate to severe abdominal pain, nausea, vomiting, and malaise. CT scan demonstrates mesenteric panniculitis as a localized fat-dense mass containing areas of increased density representing fibrosis.

Treatment Laparotomy is necessary to establish the diagnosis and to rule out other tumefactions of the abdomen. Widespread involvement of the mesentery precludes more than biopsy. Since

neoplasms of the mesenteric lymph nodes may present a similar gross appearance, several biopsies from different sites should be obtained. The inflammatory process is self-limiting and seldom causes any serious complications.

Tumors of the Mesentery

Tumors originating between the leaves of the mesentery are quite rare. In contrast, malignant implants from intraabdominal or pelvic tumors or metastases to mesenteric lymph nodes are relatively common.

Pathology Primary tumors of the mesentery may be cystic or solid. A classification of these tumors is shown in Table 33-1. Most cystic mesenteric tumors are benign. Benign solid tumors of the mesentery are more common than malignant ones. Solid malignant tumors arise near the root of the mesentery; solid benign tumors have a greater tendency to develop peripherally near the intestine.

TABLE 33-1
CLASSIFICATION OF PRIMARY MESENTERIC TUMORS

Origin	Benign	Malignant
Cystic tumors		
Developmental defects	Chylous cyst Serous cyst	
Lymphatic tissue	Lymphangioma	Lymphangiosarcoma
Trauma	Traumatic cyst	
Embryonic rests	Enteric cyst	
	Dermoid	Malignant teratoma
Solid tumors		
Adipose tissue	Lipoma	Liposarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Nerve elements	Neurilemoma Neurofibroma	Malignant schwannoma
Smooth muscle	Leiomyoma Fibromyoma	Leiomyosarcoma Fibromyosarcoma
Vascular tissue	Hemangioma	Hemangiopericytoma

Clinical Manifestations In most patients, symptoms are few or nonexistent, and the tumor is detected during routine examination. Only rarely will the patient present with symptoms of complete intestinal obstruction or symptoms resulting from complications of the tumor per se such as torsion, hemorrhage, or infarction of the tumor mass. In the absence of intestinal obstruction or these complications, the sole finding will be the presence of a nontender intraabdominal mass, usually in the lower right part of the abdomen. The mass varies in size from a few inches in diameter to one that may fill the entire abdomen. Extremely large masses are usually cystic, in which case they are tense and fluctuant. Both cystic and solid tumors of the mesentery are laterally mobile; they can be moved easily from side to side but only slightly in an upward and downward direction.

Imaging techniques are the most useful means for diagnosing both cystic and solid mesenteric tumors. On ultrasonography, a mesenteric cyst appears as a well-outlined sonolucent transonic abdominal mass. CT demonstrates a simple mesenteric cyst as a nonenhancing near-water-density mass with a thin wall and a solid tumor as a mass lesion with a soft tissue density.

Treatment Surgical excision is the only treatment for benign and malignant lesions. All mesenteric cysts of a size sufficient to be palpated should be removed if at all possible, since even benign lesions eventually cause pain and compression of neighboring structures. Benign cystic tumors can be removed by enucleation or local excision. Wide excision, together with resection of adjacent intestine, is recommended for benign solid tumors, since these have a tendency toward local recurrence and malignant degeneration. Few patients with malignant primary mesenteric tumors are alive after 5 years.

RETROPERITONEUM

Idiopathic Retroperitoneal Fibrosis

This is a nonspecific, nonsuppurative inflammation of fibroadipose tissue that produces symptoms by the gradual compression of the tubular structures in the retroperitoneal space. The disease represents one of the manifestations of a widespread entity termed *systemic idiopathic fibrosis.* Idiopathic mediastinal fibrosis, Riedel's struma, sclerosing cholangitis, panniculitis, Peyronie's disease, and desmoid tumor are other fibromatoses that are considered localized forms of a systemic idiopathic fibrosis.

The lesion consists of a plaque of woody, white fibrous tissue that is distributed along the course of the periaortic lymphatics. In

about one-third of patients it is bilateral. The involved tissue surrounds and constricts but does not invade the regional structures in the retroperitoneum. The pattern varies from a subacute cellular process with polymorphonuclear cells, lymphocytes, fibroblasts, and fat cells to a completely hyalinized, relatively acellular sclerosis.

Clinical Manifestations Retroperitoneal fibrosis is two to three times more common among men than among women. Two-thirds of patients are 40–60 years old. The natural history of the disease has been divided into three periods: (1) the period of incidence and development, (2) the period of activity, i.e., spread of the cellular and fibrotic process to envelopment of the retroperitoneal structures, and (3) the period of contraction of the fibrotic mass with compression of the involved structures. The disease is apparently self-limiting once the fibrotic stage is reached, a factor of major importance in considering types of therapy. The first complaint is invariably dull, noncolicky pain. It usually originates in the flank or low back and often radiates to the lower abdomen, groin, genitalia, or anteromedial aspect of the thigh. The pain is unilateral at first but may become bilateral later, as the fibrotic process spreads. Moderate fever and leukocytosis are often present early; the erythrocyte sedimentation rate is elevated. A transabdominal or pelvic mass is palpable in about one-third of patients.

Symptoms due to compression of the tubular retroperitoneal structures may follow the initial complaints by 1 month to 2 years. The major structures involved are the ureters, aorta, and inferior vena cava. Partial or complete ureteral obstruction occurs in 75–85 percent of patients. As many as 40 percent of patients will have oliguria or anuria with laboratory evidence of uremia. Lower extremity edema occurs occasionally. Arterial insufficiency due to fibrous constriction of the aorta or iliac arteries is uncommon.

CT scan shows a homogeneous, soft tissue mass enveloping the ureters, aorta, and inferior vena cava. A triad that is highly suggestive of retroperitoneal fibrosis on the pyelogram is (1) hydronephrosis with a dilated, tortuous upper ureter, (2) medial deviation of the ureter, and (3) extrinsic ureteral compression.

Treatment Some patients improve with supportive measures. With the onset of urinary infection or depression of renal function, surgical intervention usually becomes necessary. Steroid-induced regression of the inflammatory edema may reestablish urinary patency and thus facilitate elective, rather than emergency, surgery.

Ureterolysis with intraperitoneal transplantation is currently the most effective means of relieving obstruction of the involved ureter.

This consists of freeing the ureter from the enveloping mass of fibrous tissue and transferring it into the peritoneal cavity, closing the posterior peritoneum behind it. Aortic or iliac artery obstruction is best treated by arteriolysis or bypass with a synthetic vascular graft.

Symptoms due to venous obstruction are best treated with elevation and elastic support to the lower limbs until a sufficient collateral venous system develops. Release of the obstructed vein from its fibrous encasement may be difficult and hazardous, and bypass procedures for obstruction of the inferior vena cava have been uniformly unsuccessful. Prognosis of the disease is generally good if appropriate treatment begins before the development of irreversible renal damage.

Retroperitoneal Tumors

Lymphomas and retroperitoneal liposarcomas and leiomyosarcomas are the most common nonvisceral malignant tumors of the retroperitoneum. The majority occur in the fifth or sixth decade, with a peak incidence at about age 60. Approximately 15 percent are found in children under age 10. A classification of the benign and malignant tumors according to tissue type is given in Table 33-2.

The tumors may be solid, cystic, or a combination of both. Their color varies from white (fibroma), yellow (lipoma), or pinkish to red (sarcoma) depending on the predominant tissue. As a rule, the predominantly cystic tumors are benign; solid tumors are usually malignant.

Clinical Manifestations The tumor may attain large size before producing symptoms. As the tumor grows, it compresses, obstructs, or invades adjacent organs or structures so that the presenting symptoms are often referable to these organs. The initial manifestations include an enlarging abdomen, backache, a sense of fullness or heaviness, and vague, indefinite pain that later may become more severe and radicular. Pain radiating into one or both thighs is usually late and due to involvement of lumbar and sacral nerve routes; it invariably denotes a malignant tumor. The predominant physical finding is an abdominal mass.

The CT scan can demonstrate the contours of the tumor mass, its size and relationships, as well as its effects on adjacent viscera and other tissues. This information is useful in determining resectability of the tumor and in planning a surgical approach. Ultrasonography differentiates between solid and cystic tumors. Percutaneous needle biopsy directed by CT or ultrasonography can be used to obtain preoperative histologic diagnosis and for the detection of treatment failures and early recurrences.

TABLE 33-2
CLASSIFICATION OF RETROPERITONEAL TUMORS

Tissue Type	Benign Tumors	Malignant Tumors
Lymphatic tissue	Lymphangioma	Lymphangiosarcoma
Lymph nodes		Lymphosarcoma
		Hodgkin's disease
		Reticulum cell sarcoma
Adipose tissue	Lipoma	Liposarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Nerve elements	Neurilemoma	Malignant schwannoma
	Neurofibroma	
	Ganglioneuroma	Sympathicoblastoma (neuroblastoma)
		Chordoma

Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Mucoid tissue	Myxoma	Myxosarcoma
Vascular tissue	Hemangioma	Malignant hemangioperictyoma
Mesothelial tissue		Mesothelioma
Mesenchyme		Mesenchymoma
Extraadrenal chromaffin tissue	Benign pheochromocytoma	Malignant pheochromocytoma
Gland tissue	Adenoma	Carcinoma
Embryonic remnants	Nephrogenic cysts	Urogenital ridge tumor
Cell rests	Dermoid	Teratoma
Miscellaneous	Xanthogranuloma	Synovioma
	Aggressive fibromatosis	Dysgerminoma
		Undifferentiated malignant tumor

Aortography should be a part of the workup of patients with a retroperitoneal tumor to define tumor size and can give useful information about the vascular anatomy.

Treatment Some retroperitoneal tumors are benign and can be cured by simple excision; some are histologically benign but clinically malignant; others grow slowly and tend to recur and invade locally; and still others are rapidly malignant from the start. Treatment of these growths consists of surgical or irradiation therapy or a combination of the two. With the exception of lymphomas, chemotherapy has only limited therapeutic application. Surgical treatment is most effective and offers the greatest prospect for cure. A cure may be anticipated following complete resection of a benign tumor. Because malignant tumors typically develop a pseudocapsule, local recurrence is frequent when they are simply enucleated. The tumors extend into the loose retroperitoneal tissue planes, and their frequent relationship to vital structures makes it difficult to obtain negative margins during tumor excision.

Metastases typically spread hematogenously. The most frequent site of metastases is to the liver and lung. Lymph node metastases are rare except for lymphomas.

Histologic grade is the most important factor in determining prognosis. As many as one-third of patients with malignant tumors may be inoperable because of distant metastases to liver, lungs, and bone, in order of frequency.

For a malignant tumor, the initial operation offers the best chance of cure. Fewer than 25 percent of malignant tumors can be resected completely with anticipation of cure.

Malignant retroperitoneal tumors have a high recurrence rate, 30–50 percent in most large series. The tumors become more malignant with each recurrence, and reoperation becomes more hazardous. Nevertheless, long-term survival has been reported after multiple resections. Five-year survival free of tumor is less than 10 percent.

For a more detailed discussion, see Daly JM, Adams JT, Fantini GA, and Fischer JE: Abdominal Wall, Omentum, Mesentery, and Retroperitoneum, chap. 33 in *Principles of Surgery,* 7th ed.

CHAPTER

34

ABDOMINAL WALL HERNIAS

Hernias of the abdominal wall are among the most common conditions requiring operation. Despite the frequency of surgical repair, the rate of recurrence is high. The outcome of hernia surgery is highly surgeon-dependent.

Definitions A *hernia* is a protrusion of a viscus through an opening in the wall of the cavity in which it is contained. The important features of a hernia are the hernial orifice and the hernial sac. The *hernial orifice* is the defect in the innermost aponeurotic layer of the abdomen, and the *hernial sac* is the outpouch of peritoneum. The neck of a hernial sac corresponds to the orifice. The hernia is *external* if the sac protrudes completely through the abdominal wall and *internal* if the sac is within the visceral cavity. A hernia is *reducible* when the protruded viscus can be returned to the abdomen and *irreducible* when it cannot. A *strangulated hernia* is one in which the vascularity of the protruded viscus is compromised. Strangulation occurs in hernias that have small orifices and large sacs. An *incarcerated hernia* is an irreducible hernia but not necessarily strangulated. A *Richter's hernia* is a hernia in which the contents of the sac consist of only one side of the wall of the intestine (always antimesenteric).

Sites of Herniation The common sites of herniation are the groin, umbilicus, linea alba, semilunar line of Spieghel, diaphragm, and surgical incisions. Other similar but very rare sites of herniation are the perineum, superior lumbar triangle of Grynfelt, inferior lumbar triangle of Petit, and the obturator and sciatic foramina of the pelvis.

Clinical Manifestations The natural history of hernias is a slow enlargement to the point of irreducibility and disfigurement, with the risk of strangulation. The discomforts produced by hernias are always worse at the end of the day and are relieved at night when the patient reclines and the hernia reduces. Groin pain without a demonstrable hernia usually does not indicate the onset of a hernia.

Most hernias develop insidiously, but some are precipitated by a single forceful muscular event. Typically, a hernial sac with its contents enlarges and transmits a palpable impulse when the patient strains or coughs. Usually, the patient must stand during the examination because it is impossible to palpate a reduced groin hernia when the patient is supine. Hydroceles transilluminate, but hernias do not. Hernias undetectable by physical examination can be demonstrated by using ultrasound or computed tomography (CT). Strangulation produces intense pain in the hernia, followed quickly by tenderness, intestinal obstruction, and signs or symptoms of sepsis. Reduction of a strangulated hernia is contraindicated if there is sepsis or the contents of the sac are thought to be gangrenous.

Indications for Surgery All hernias should be repaired unless local or systemic conditions of the patient preclude a safe outcome. The possible exception is a hernia with a wide neck and shallow sac that is anticipated to enlarge slowly. Trusses are helpful in the management of small hernias when operation is contraindicated. Trusses are contraindicated for patients with femoral hernias.

HERNIAS OF THE GROIN

The groin is one of the naturally weak areas in the abdominal wall and is the most common site for herniation. Males are 25 times more likely to have a groin hernia. Hernias arising above the abdominocrural crease are inguinal, and those arising below the crease are femoral. Inguinal hernias can be direct or indirect. The sac of an indirect inguinal hernia passes obliquely or indirectly toward and ultimately into the scrotum. The sac of a direct inguinal hernia protrudes directly outward and forward. Clinically distinguishing an indirect from a direct inguinal hernia often is impossible and is of little importance because the operation to repair them is the same. In males, indirect hernias outnumber direct hernias 2:1, whereas in females, direct hernias are a rarity. Femoral hernias occur occasionally in females but not as frequently as inguinal hernias; in males they are rare. Femoral hernias almost always appear as an irreducible mass at the medial base of Scarpa's femoral triangle. A femoral hernia can appear irreducible even though the sac may be empty because fat and lymph nodes surround the sac. A solitary enlarged lymph node can mimic a femoral hernia exactly.

Epidemiology Hernias are a common health problem; the accepted incidence is 3–4 percent. Strangulation occurs in 1.3–3.0 percent of groin hernias. Most strangulated hernias are indirect inguinal hernias,

but femoral hernias have the highest rate of strangulation. The probability of strangulation is greatest in the first 3 months.

Anatomy An indirect hernial sac is a dilated persistent processus vaginalis. It passes though the deep inguinal ring and follows the cord to the scrotum. At the deep ring, the sac occupies the anterolateral side of the cord. Properitoneal fat often is associated with the indirect sac and is known as a *lipoma of the cord,* although the fat is not a tumor.

Retroperitoneal organs such as the sigmoid colon, cecum, and ureters may slide into an indirect sac. They thereby become a part of the wall of the sac. Sliding hernias are often large and partially irreducible.

Direct inguinal hernial sacs originate through the floor of the inguinal canal (Hesselbach's triangle), protrude directly, and are contained by the aponeurosis of the external oblique muscle. Rarely, they enlarge enough to force their way through the superficial ring and descend into the scrotum. The bladder is common as a sliding component of a direct hernial sac.

Femoral hernial sacs originate from the femoral canal through a defect in the medial side of the femoral sheath. The femoral canal contains one or two lymph nodes, the largest of which is named *Cloquet.* These nodes are expelled from the femoral canal by a peritoneal protrusion and frequently create a palpable mass.

The passage of the testicle through the abdominal wall during the embryonic stage weakens and enlarges the myopectineal orifice above the inguinal ligament, predisposing males to indirect and direct inguinal hernias. In females, the increased diameter of the true pelvis proportionally widens the femoral canal and probably predisposes females to femoral herniation.

Etiology Inguinal hernias can be congenital or acquired. All indirect inguinal hernias are congenital and result from a patent processus vaginalis, with which the patient is born. A patent processus vaginalis is found in 80 percent of newborns and in 50 percent of 1-year-olds. The incidence of a patent processus vaginalis in adults is 20 percent. Having the potential for a hernia does not mean a hernia will develop. Other factors must be present to cause failure of the transversalis fascia to retain the visceral sac in the myopectineal orifice. These factors include (1) the erect stance of human beings, (2) muscle deficiency, and (3) destruction of connective tissue from smoking, aging, or systemic illnesses.

Inguinal hernias of all types occur equally in sedentary and physically active individuals. Vigorous physical activity per se is not a cause of inguinal herniation.

Basics of Groin Hernia Repair The object of groin hernioplasty is to prevent peritoneal protrusion through the myopectineal orifice. Integrity is restored in two fundamentally different ways: (1) aponeurotic closure of the myopectineal orifice to the extent necessary and (2) replacement of the defective transversalis fascia with a large synthetic prosthesis. The two methods occasionally are combined.

Hernias are repaired anteriorly through a groin incision or posteriorly through an abdominal incision. The anterior approach is the most popular incision for inguinal hernioplasty. Posterior hernia repairs are called *properitoneal hernioplasties.*

Tension is the principal cause of failure of all hernioplasties that close the myopectineal orifice by aponeurotic approximation. Assiduous efforts to prevent suture-line tension are essential. Permanent monofilament synthetic sutures are preferable.

Synthetic mesh prostheses have a major role in the management of hernias of the groin. Mesh prostheses are used to patch or plug the myopectineal orifice, to reinforce a classic repair, and to replace the transversalis fascia.

Anterior Classic Groin Hernioplasty Three anterior classic hernioplasties are used: the Marcy simple ring closure, the Bassini operation, and the McVay-Lotheissen Cooper ligament repair. All produce equally satisfactory results in primary hernias when correctly indicated and are easily performed with local anesthesia in adults. Recurrent inguinal hernias are fixed by prosthetic techniques because the results are distinctly better. Classic hernioplasty has three parts: dissection of the inguinal canal, repair of the myopectineal orifice, and closure of the inguinal canal.

The Marcy repair of the myopectineal orifice consists of tightening an enlarged deep ring only. It is commonly called *simple ring closure* and is indicated in males and females with only minimal damage to the deep ring. The operation restores the anatomy of the deep ring by placing one or two sutures in the transverse aponeurotic arch and the iliopubic tract just medial to the spermatic cord or the round ligament.

The Bassini-Shouldice hernioplasty repairs the myopectineal orifice superior to the inguinal ligament, i.e., the deep ring and Hesselbach's triangle, and is indicated in all direct and indirect inguinal hernias. The Bassini repair consists of high ligation of the sac and approximation of the conjoined tendon and the internal oblique abdominal muscle to the shelving edge of the inguinal ligament. The McVay-Lotheissen Cooper ligament hernioplasty repairs the three areas most vulnerable to herniation in the myopectineal orifice, i.e., the deep ring, Hesselbach's triangle, and the

femoral canal. In the McVay-Lotheissen repair the transverse aponeurotic arch is sutured to Cooper's ligament medially and to the femoral sheath laterally. Relaxing incisions are mandatory because otherwise there is too much tension on the suture line.

Femoral hernias with small orifices in females only are repaired from below the inguinal ligament with a few sutures or corked with a cylindrical plug of Marlex because they rarely are associated with hernias above the inguinal ligament. Large femoral hernias in females and all femoral hernias in males are repaired by the McVay-Lotheissen Cooper ligament repair or by a properitoneal prothesis. Strangulated femoral hernias are preferably accessed properitoneally because this provides direct access to the constricting femoral hernial orifice, easy release of the entrapped bowel by incision of the iliopubic tract and lacunar ligament, and ample room for bowel resection. Strangulated inguinal hernias are managed easily through a groin incision.

In indirect hernias in infants, children, and some young males, the myopectineal orifice and transversalis are not damaged, and classic repair is unnecessary; merely eliminating the sac cures the hernia.

In young males, exploration of the contralateral groin commonly is performed up to age 3 years, especially if a unilateral hernia is present on the left. This avoids a second hernioplasty later.

Prosthetic Material for Hernioplasty Synthetic mesh prostheses for hernia repair include Marlex, Prolene, Trelex, Surgipro, Mersilene, and Gore-Tex. Marlex, Trelex, and Prolene mesh are composed of knitted monofilament fibers of polypropylene and resemble each other. All are porous, slightly elastic, semirigid, and contain plastic memory. Surgipro mesh is composed of knitted braided strands of polypropylene. Its physical characteristics closely resemble knitted meshes of monofilament polypropylene. Mersilene is an open-knitted mesh composed of braided fibers of the polyester Dacron. It is porous, soft, supple, elastic, and without plastic memory and has a grainy texture to prevent slippage.

Tension-Free Hernioplasties Prosthetic soft tissue patches have been used to reinforce classic repairs but without significantly improving results. When the prosthesis is implanted without a formal repair, obviating tension, results improve dramatically. Lichtenstein developed a tension-free repair for femoral and recurrent inguinal hernias when the defect is fibrous, circumscribed, and not too large. The technique consists of a prosthetic plug that stoppers the aponeurotic defect. Tension-free hernioplasties may not be appropriate for repair of most recurrent groin hernias in

males because they require redissection of the spermatic cord, a paramount cause of testicular atrophy. Tension-free hernioplasties are easy to perform, even with local anesthesia; recovery is quick; and results are superb. Tension-free hernioplasties are suited to the management of simple primary hernias in males but are not the procedures of choice for complex groin hernias or those with complications.

Properitoneal Groin Hernioplasty The properitoneal space is the logical site to implant a prosthesis. The prosthesis is held in place by intraabdominal pressure and is relatively immune to superficial infection. The hernia defect can be patched or plugged and hernioplasties buttressed with a prosthesis from the posterior approach just as they can be from the interior. The properitoneal prosthetic technique to eliminate hernias of the groin with a large nonresorbable prosthesis that functionally replaces the transversalis fascia was introduced by Stoppa. The prosthesis adheres to the visceral sac and renders the peritoneum inextensible so that the peritoneum cannot protrude through the myopectineal orifice or adjacent areas of weakness; repair of the defect in the abdominal wall is unnecessary. The operation is technically known as *giant prosthetic reinforcement of the visceral sac* (GPRVS) but is commonly called the *Stoppa procedure.* GPRVS is an efficient, anatomic, and tension-free repair. When done correctly, it cures all hernias of the groin with rapid recovery and minimal discomfort.

Laparoscopic Repair There is no question that laparoscopic hernioplasty can be done successfully in experienced hands and that in some patients produces less postoperative pain. It is inherently riskier than open hernioplasty. Data from the most experienced laparoscopic hernia surgeons have been compared with those of surgeons who have specialized in open hernioplasty. The results showed that with the exception of wound infection, the morbidity, mortality, and recurrence rates after laparoscopic hernioplasty are significantly higher than those after open hernioplasty. The degree of postoperative discomfort should never be the motivating factor in selecting the type of operation. Open hernioplasty, preferably tension-free, with local anesthesia, when possible, is the procedure of choice for most patients.

Complications Ischemic orchitis, with its sequela of testicular atrophy, and residual neuralgia are two important but uncommon complications unique to groin hernioplasty. They occur more frequently after anterior groin hernioplasty because the nerves and

spermatic cord are necessarily dissected and mobilized. Recurrences also are rightfully a complication of groin hernioplasty.

Classic repairs obtain recurrence rates in the range of 1–3 percent in a 10-year follow-up. Recurrences are caused by excessive tension on the repair, deficient tissues, inadequate hernioplasty, and overlooked hernias. Recurrences, predictably, are more common in patients with direct hernias, especially bilateral direct inguinal hernias. Indirect recurrences result from insufficient excision of the proximal end of the sac, insufficient repair of the deep ring, and continued atrophy of the shutter mechanism. Most recurrences are direct and usually are in the region of the pubic tubercle, where suture-line tension is the greatest. Repairing bilateral inguinal hernias simultaneously does not increase suture-line tension and is not a cause of recurrence. Recurrent hernias require a prosthesis for successful repair. Recurrences after anterior prosthetic hernioplasty are managed properitoneally with a second prosthesis or anteriorly with a prosthetic plug.

UMBILICAL HERNIA

The umbilicus is a common site of herniation. Umbilical hernias occur more frequently in females. Obesity and repeated pregnancies are common precursors. Strangulation of the colon and omentum is common. Umbilical hernias are common in infants and close spontaneously without special treatment if the aponeurotic defect is 1.5 cm or less. Repair is indicated in infants with hernial defects greater than 2.0 cm in diameter and in all children with umbilical hernia still present by the age of 3 or 4.

Umbilical hernias with a small parietal defect are merely closed by polypropylene suture, and those with large parietal defects are managed with a prosthesis.

EPIGASTRIC HERNIA

Epigastric hernia is a protrusion of properitoneal fat and peritoneum through the decussating fibers of the rectus sheath in the midline (linea alba) between the xiphoid and the umbilicus. Epigastric hernias often are irreducible, invariably have small aponeurotic defects, sometimes are multiple, and often produce discomfort out of proportion to their size. Repair is similar to that of umbilical hernias.

SPIGELIAN HERNIA

Spigelian hernias are ventral hernias occurring along the subumbilical portion of Spieghel's semilunar line and through Spieghel's fascia. Spigelian hernias are rare and, unless large, are difficult to diagnose because they are interparietal and contained by the aponeurosis of the external oblique muscle. Ultrasound and CT scans often reveal symptomatic spigelian hernias too small to detect clinically. Spigelian hernias are most common in the area between the umbilicus and the line connecting the anterosuperior iliac spines and in the area beneath the arcuate line and above the inferior epigastric vessels. Small spigelian hernias are simply closed, but large spigelian hernias that are in the muscles require a prosthesis.

PARASTOMAL HERNIA

Parastomal hernias interfere with colostomy irrigations and the adhesion of stomal appliances. Paracolostomy hernias are more common than paraileostomy hernias, and both are more likely to occur when the stoma emerges through the semilunar line rather than the rectus sheath. Parastomal hernias usually are lateral to the ostomy. Moving the stoma to a new location is preferred to local repair. Local repair often fails because the belt muscles lateral to the ostomy lack sufficient aponeurosis. Among the prosthetic repairs, the preferred technique consists of closing the parietal defect lateral to the stoma and implanting a large piece of Mersilene slit to accommodate the stoma.

INCISIONAL HERNIAS

Incisional hernias are serious surgical problems. Obesity and infection are the two principal causes of this condition. The weight of the panniculus pulls apart the surgical incision, and infection hampers wound healing. A large incisional hernia produces paradoxical respiratory abdominal motion similar to a flail chest. Diaphragmatic function becomes inefficient. The diaphragm no longer contracts against the abdominal viscera and instead forces them into the hernia sac. Appraisal of respiratory function and blood gases is essential. The viscera lose their right of domain in the abdomen in long-standing large incisional hernias. In this instance the reduction of the viscera at operation can cause death by compression of the inferior vena cava and by respiratory failure from forced elevation and immobilization of the diaphragm.

Progressive pneumoperitoneum is a useful technique to prepare patients for incisional hernioplasty because it overcomes some of the disorders of eventration disease. Pneumoperitoneum stretches the abdominal wall and intraabdominal adhesions, facilitates return of the viscera to the abdomen, and improves diaphragmatic function. Most small incisional hernias are managed by simple closure of the aponeurotic defect. Large incisional hernias with aponeurotic defects greater than 10 cm have recurrence rates as high as 50 percent. Consequently, most incisional hernias and all recurrent incisional hernias require a prosthesis for a successful repair. The Stoppa hernioplasty is preferred; it is applicable to all types of abdominal incisional hernias, including postnephrectomy lumbar hernias.

In the Stoppa hernioplasty, a very large Mersilene prosthesis is implanted deep to the muscles of the abdominal wall on top of the posterior rectus sheath or peritoneum. The prosthesis extends far beyond the borders of the myoaponeurotic defects and is firmly held in place by intraabdominal pressure and later by fibrous ingrowth. The prosthesis prevents peritoneal eventration by rendering the visceral sac indistensible and by solidly uniting and consolidating the abdominal wall.

Aponeurotic closure of the parietal defect is important. The midline closure can withstand greater tension because the prosthesis, not the suture line, ultimately unites the abdomen. When necessary, tension can be reduced by vertical relaxing incisions in the rectus sheath. Aponeurotic approximation is usually achievable, but when it is not, a second absorbable or nonabsorbable prosthesis inlaid in the aponeurotic defect will ensure stability of the abdominal wall during the healing process. Dead space created by large prostheses always requires closed-suction drainage to prevent seromas and hematomas and to allow quick fibrous incorporation of the prosthesis in the abdominal wall.

Infection Infection is a serious complication and occurs in as many as 10 percent of patients. Early infection is managed by prompt and complete exposure of the prosthesis. With intense local and systemic antimicrobial therapy, complete integration of the prosthesis can be anticipated. When delayed infections occur, reintegration of the infected prosthesis usually does not occur, and removal of the sequestered portion of the prosthesis becomes necessary. In these patients, removal of the integrated remaining prosthesis is unnecessary.

For a more detailed discussion, see Wantz GE: Abdominal Wall Hernias, chap. 34 in *Principles of Surgery,* 7th ed.

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CHAPTER

35

PITUITARY AND ADRENAL

PITUITARY

Anatomy

MACROSCOPIC ANATOMY

The pituitary gland is surrounded by the *sella turcica,* covered superiorly by the *diaphragma sellae,* through which the pituitary stalk passes. The optic chiasm lies superior and anterior to the stalk. The hypothalamus lies directly above. The cavernous sinuses border the lateral walls of the sella. The pituitary weighs 500 mg in the adult male and 600 mg in the adult female.

The gland is composed of the anterior pituitary, or *adenohypophysis* (*pars distalis,* which is the major portion; *pars intermedia,* which is rudimentary; and *pars tuberalis,* which extends the pars distalis along and around the stalk), and the posterior pituitary, or *neurohypophysis* (median *eminence,* or infundibulum, in the hypothalamus; infundibular stem, which is the neural portion of the stalk; and *neural lobe,* or *infundibular process,* the inferior portion of the neurohypophysis).

MICROSCOPIC ANATOMY

Vascular Anatomy The anterior pituitary has the highest blood flow of any organ (0.8 mL/g/min). The superior hypophyseal arteries from the internal carotid form a portal venous system that carries stimulatory and inhibitory hypothalamic hormones to the anterior pituitary. The posterior pituitary is perfused by short portal veins from the lower infundibular stem. Pituitary hormones are released into the surrounding dural sinuses. Low pressure in the portal system makes the pituitary vulnerable to ischemic injury.

ADENOHYPOPHYSIS

Immunohistochemistry has allowed description of pituitary cells according to their secretory function.

Growth Hormone (GH)–Producing Cells (Somatotropes) These are located in the lateral aspect of the adenohypophysis. GH

effects growth of bone, muscle, and visceral organs. It is released in surges six to eight times daily. Growth hormone-releasing hormone (GHRH) stimulates secretion; somatostatin limits it.

Prolactin-Producing Cells (Mammotropes), Lateral Aspect Prolactin facilitates the development of breast tissue to ensure lactation. Hypothalamic control is maintained through prolactin-inhibiting factor (dopamine) and prolactin-releasing factor (thyrotropin-releasing hormone, TRH). Pregnancy, lactation, stress, and exercise are associated with high levels.

Adrenocorticotropic Hormone–Producing Cells (Corticotropes), Mediolateral Aspect Adrenocorticotropic hormone (ACTH) promotes growth of the adrenal cortex and synthesis of adrenal steroid hormones and also is melanotropic. Normal secretion is stimulated by corticotropin-releasing hormone (CRH) from the hypothalamus, following the circadian rhythm—highest late in sleep period. Inhibition of release is by negative feedback of cortisol on corticotrope and release of CRH.

Thyroid-Stimulating Hormone (TSH)–Producing Cells (Thyrotropes), Anteromedial Aspect TSH increases thyroid growth and synthesis of thyroid hormones. Hypothalamic control is through thyrotropin-releasing hormone (TRH). Triiodothyronine (T_3) and thyroxine (T_4) inhibit TSH release: cold and stress increase release.

Gonadotrophic Hormone–Producing Cells (Gonadotropes) *Follicle-Stimulating Hormone (FSH)* FSH is responsible for growth and maturation of ovarian follicles or testicular growth and spermatogenesis.

Luteinizing Hormone (LH) LH promotes development of the corpus luteum and enhances ovarian estrogen and progesterone production or stimulates the testes to produce testosterone. Hypothalamic influence is mediated via gonadotropin-releasing hormone (GnRH).

NEUROHYPOPHYSIS

The posterior pituitary has no blood-brain barrier. It consists of hypothalamic neuronal axons and terminals, specialized glial cells, and blood vessels.

Regulation of the Hypothalamic-Pituitary Axis This is mediated by parvocellular and magnocellular neuronal systems.

Parvocellular Small neurons originate in cell groups that produce the hypothalamic-pituitary hormones and end in the median eminence, where these hormones are released and regulate adenohypophyseal release of hormones via the portal circulation.

Magnocellular Large-body neurones contain oxytocin (uterine contraction) and vasopressin (antidiuretic hormone, ADH) and end in the posterior lobe, where hormones are stored and released. ADH is regulated through osmoreceptors in the hypothalamus and by baroreceptors.

Diagnostic Studies

NEUROENDOCRINE EVALUATION

Anterior Pituitary Patient presents with signs or symptoms of single or multiple hormonal deficits, hyperprolactinemia, hyperthyroidism, diabetes insipidus, a hypothalamic disorder, or any sellar or suprasellar lesion.

TSH Deficiency Measure simultaneous basal serum TSH and thyroid hormone levels; low T_4 with low TSH suggests central cause. TRH test differentiates hypothalamic from pituitary defect.

ACTH Deficiency Dynamic testing is required (A.M. cortisol level is low only when the ACTH deficiency is very severe). With the CRH test, no ACTH response means corticotrope deficiency. An ACTH stimulation test measures the capacity of the adrenals to secrete cortisol.

Gonadotropin Deficiency Measure simultaneous basal serum FSH and LH levels as well as gonadal steroids (estradiol or testosterone). High FSH and LH levels mean primary gonadal failure. The GnRH stimulation test measures gonadotrope function.

GH Deficiency Plasma level of insulin-like growth factor-1 (IGF-1) reflects 24-h secretion of GH.

Posterior Pituitary *Central Diabetes Insipidus (DI)* This results from the insufficient secretion of vasopressin (not renal DI, in which the kidney fails to respond to elevated vasopressin levels). Diagnosis is made by the water deprivation test with development of abnormally concentrated plasma (osmolality $>$ 300 mOsm/kg) and dilute urine (osmolality $<$ 270 mOsm/kg), which is not reduced in volume as much as expected. Administration of vasopressin will correct these abnormalities (not in renal DI).

RADIOGRAPHIC EVALUATION

Provides information about the bony anatomy of the sella and surroundings and intrasellar contents. Lateral skull radiographs may show enlargement of sella in intrasellar tumors. For a more precise evaluation, use computed tomography (CT) with special "windows" to enhance bony detail.

For soft tissue detail, magnetic resonance imaging (MRI) is the first choice. High-field thin-section MRI appears to be the most sensitive method for preoperative localization of pituitary adenomas. CT may be used if MRI is not available (and may provide supplemental information about bony landmarks and lesion calcification).

Anterior Pituitary Disorders

POSTPARTUM PITUITARY ISCHEMIA

Postpartum Infarction and Necrosis (Sheehan Syndrome) The pathogenesis of this syndrome is debatable but hypovolemic shock and portal venous thrombosis from diffuse intravascular coagulation are suggested. Hypopituitarism may be total or partial, delayed or acute. Clinical features include failure to lactate, amenorrhea, and progressive indications of adrenal and thyroid insufficiency.

PITUITARY ADENOMAS

Benign Tumors These may originate from any of the above-described pituitary cell types. Microadenomas (<10 mm in diameter) may be present in 10–20 percent of the older population. Macroadenomas (>10 mm) are quite rare. They are classified according to their secretory product, if any.

Null-Cell Adenomas Most common; these are without function, so they are more likely to reach macro size and produce symptoms by displacement or pressure such as headache, visual failure, or hypopituitarism. They may be misdiagnosed as prolactinoma because pressure can lead to stalk compression, causing loss of dopaminergic inhibition of tonic prolactin release.

Therapy Objectives: (1) relief of signs and symptoms from mass effect and (2) correction of endocrine abnormalities. For nonfunctioning tumors, primary prescription is surgical, with radiation therapy second.

Prolactinomas These are the most common functional adenomas, with equal frequency in men and women. Their clinical significance is greater in women, in whom secondary amenorrhea is

the presenting symptom and only half have galactorrhea. In men, decreased libido and impotence usually are attributed to aging, so the diagnosis is missed until mass effect is present.

Treatment Surgery is the first choice for microadenomas; cure is frequent. Long-term surgical cure is less frequent with large or invasive tumors. Bromocriptine should reduce both the size and prolactin secretion and should be used first; surgery is reserved for patients intolerant of side effects to reduce the required dose. Radiation therapy also can bring residual tumor under control.

Cushing's Disease Cushing's disease is characterized by hypersecretion of ACTH by corticotrope adenomas in 90 percent of patients (or diffuse corticotrope hyperplasia from hypersecretion of hypothalamic CRH in the remainder). Cushing's disease affects women eight times more frequently than men.

Clinical Manifestations (1) Those resulting from glucocorticoid excess: central obesity, "moon" facies, dorsocervical and supraclavicular fat pads, proximal muscle wasting, thin skin with ecchymoses, and violaceous striae, cataracts, osteoporosis, amenorrhea, diabetes mellitus, growth retardation in children, and immunosuppression with fungal infections, and (2) those resulting from peripheral androgen excess: hirsutism and acne.

Diagnosis (1) Increased basal plasma cortisol level with loss of diurnal variation, (2) elevated 24-h urinary free cortisol excretion (>100 mg/24 h), and (3) failure of the serum cortisol to suppress with *low-dose dexamethasone suppression test* (1 mg dexamethasone at 11 P.M.; 8 A.M. plasma cortisol >4 mg/dL).

Therapy Most patients have microadenomas that can be excised completely. Macroadenomas frequently invade adjacent dura and bone and so defy chemical cure by surgery alone. If medical therapy fails, adrenalectomy will palliate.

Acromegaly and Gigantism Excess GH produces acromegaly. Before epiphyses fuse, it produces gigantism, with growth to more than 7 ft. Soft tissue changes in acromegaly include coarsening of facial features, vocal enlargement, goiter, thick heel pads, acanthosis nigrans, cardiomegaly, and hepatomegaly. Bony changes include facial prognathism, enlargement of the mandible, and bony enlargements of hands and feet. Metabolic changes include associated hypertension, diabetes mellitus, and cardiomyopathy. These disorders affect males and females with equal frequency.

Diagnosis Diagnosis is by physical examination and assessment of GH secretion (basal fasting GH level >10 ng/mL in 90 percent of acromegalics). Confirmation is by the glucose suppression test (100 g of glucose PO fails to suppress GH level to <5 ng/mL at 60 min). Serum IGF-1 levels are elevated in acromegalics. MRI and/or CT demonstrates a pituitary adenoma in more than 90 percent of patients.

Treatment Treatment should be expedient because of associated metabolic problems. Complete surgical removal of pituitary adenomas that secrete GH controls the elevated GH level and may be curative. Lesions that are not completely resectable may be helped by parenteral octreotide or radiation therapy.

Surgery for Pituitary Adenomas *Preoperative Evaluation* An adequate endocrine evaluation is necessary to minimize the potential for catastrophe because of inadequate pituitary reserve. Most important are cortisol and thyroid levels. Cortisol replacement prevents adrenal insufficiency. Reestablishment of euthyroidism requires a week of treatment. Electrolyte status defines marginal DI.

Transsphenoidal Approach Transnasal transsphenoidal approach is the procedure of choice for surgical access to sellar lesions. In microadenomas, the transsphenoidal approach has resulted in greater than 90 percent tumor control. In larger tumors, control has been only 50–85 percent with surgery alone. Operative mortality is less than 1 percent. Morbidity includes DI (1.8–17 percent), postoperative cerebrospinal fluid (CSF) fistulas (1–4.4 percent), stroke, visual loss, vascular injury, meningitis, CSF rhinorrhea, and cranial nerve palsy (3.5 percent). Relative contraindications include extensive lateral tumor, ectatic carotid arteries (*transcranial approach* may be used), or acute sinusitis.

Perioperative Management Glucocorticoids are given to all patients. Serial visual field testing is used to monitor visual and neurologic condition. Any loss of vision postoperatively may indicate hemorrhage. CT scanning further defines this. Urine volume and serum glucose levels are followed along with sodium levels to detect DI. The A.M. fasting cortisol level before discharge determines the need for cortisol replacement. Thyroid function is tested at 3–4 weeks.

Primary Radiation Therapy With radiation therapy, there is a significant risk of worsening preexisting hypopituitarism; it also increases the rate of atherogenesis and can cause visual impairment.

It should be reserved for patients with major operative risk factors. *Stereotactic radiosurgery* may prove a safer and more effective method for pituitary adenomas. *Postoperative radiotherapy* to reduce the incidence of recurrence is used for large tumors and those with cavernous sinus invasion.

OTHER LESIONS

The differential diagnosis of mass lesions that can affect pituitary function includes *benign cysts, meningiomas, craniopharyngiomas* (characteristic appearance on skull radiograph or CT scan: calcification within or above sella; primary treatment is surgical, but the results are disappointing), *optic chiasm* or *hypothalamic glioma* (associated with neurofibromatosis, but sporadic cases are more frequent and defy surgical cure, so surgery is used to establish the diagnosis), *sellar metastases* (present as progressive hypopituitarism), and *empty sella syndrome* (herniation of arachnoid and subarachnoid space of suprasellar cistern through an incompetent diaphragma sellae; may be primary or follow surgery or radiation therapy).

Trauma

The pituitary stalk is susceptible to transection in basilar skull fracture. Most pituitary and hypothalamic damage results from increased intracranial pressure (ICP).

Posterior Pituitary Disorders

Diabetes insipidus involves impaired H_2O conservation; one-third of cases are idiopathic. Other causes include tumors, granulomatous disease, or trauma that destroys the hypothalamus, pituitary stalk, or posterior pituitary. The *syndrome of inappropriate secretion of antidiuretic hormone* (SIADH), which occurs in 15 percent of hospitalized patients, leads to impaired water excretion.

ADRENAL

Embryology

The cortex and medulla arise separately. The primitive cortex develops from the coelomic mesoderm. The medulla and sympathetic nervous system develop together from primitive neural crest cells. One group migrates along the adrenal vein, invades, and becomes surrounded by cortex. Preganglionic sympathetic fibers synapse directly with these medullary cells. A second group forms the organs

of Zuckerkandl lateral to the aorta near the inferior mesenteric artery. They usually atrophy in childhood but are a frequent location of extraadrenal chromaffin tumors (Fig. 35-1).

Anatomy

The adrenal glands are bilateral, located near the upper pole of each kidney, and each weighs 3–5 g and is bright yellow in color. Each is supplied by numerous small arteries from the inferior phrenic artery, the aorta, and the renal artery. The right adrenal vein enters the posterior aspect of the vena cava; the left adrenal vein enters the left renal vein. There are three cortical zones: the outer glomerulosa, (aldosterone), the reticularis (sex steroids), and the fasciculata (cortisol). There is also a central medulla (catecholamines).

Adrenal Cortex

PHYSIOLOGY

Aldosterone This causes sodium retention by renal tubules. It is regulated by the *renin-angiotensis system*, with potassium concentration, atrial natruretic hormone, and dopamine making contributions, to maintain extracellular fluid volume, extracellular potassium concentration, and blood pressure.

Cortisol Glucocorticoids are essential for life. Secretion occurs in a circadian pattern, with the peak before awakening in the morning. Secretion is mediated through ACTH and stimulated by stress, antidiuretic hormone (ADH), and epinephrine. Most important is CRH. Plasma cortisol levels exert negative feedback on ACTH at the pituitary and CRH at the hypothalamus.

Sex Steroids During normal sexual development, *adrenarche* marked by secretion of dehydroepiandrosterone (DHA).

PATHOLOGY

Hyperplasia This is an increased number of cells. In Cushing's disease, hyperplasia is caused by increased pituitary secretion of ACTH.

Adrenal Cortical Adenoma This is a benign neoplasm of the cortex. It may cause symptoms by unregulated production of hormone. Adenomas do not exceed 5 cm in diameter. Cells usually look bland, but pleomorphism and necrosis may be seen.

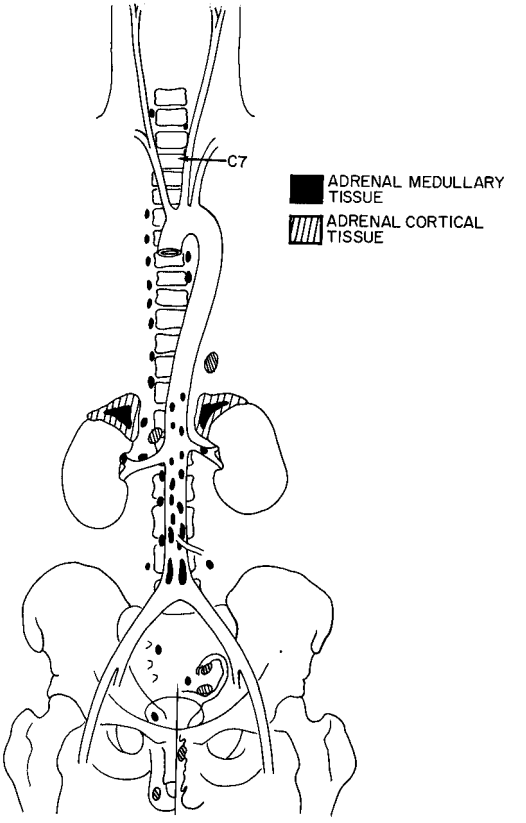

FIGURE 35-1 Location of ectopic adrenal tissue. The location of ectopic adrenal medullary tissue is shown in black; cortical tissue is shown in the shaded areas. The incidence of extraadrenal medullary tissue is very high compared to the incidence of extraadrenal cortical tissue, and while functioning extraadrenal medullary tissue occurs in about 1 in 8 cases of medullary hyperfunction, it occurs in fewer than 1 in 1000 cases of adrenocortical hyperfunction.

Adrenal Cortical Carcinoma This is a malignant neoplasm of cortical cells. It is rare, having a bimodal peak occurrence at less than 5 years and during the fifth decade. These carcinomas are larger than 6 cm. Vascular invasion, desmoplastic bands, and mitoses are suggestive of the diagnosis. Nodal or distant metastasis is the only reliable criterion.

CUSHING'S SYNDROME

Cushing's syndrome is endogenous hypercortisolism caused by secretion of ACTH by a pituitary tumor (Cushing's disease), secretion of cortisol by an adrenal tumor, or ectopic secretion of ACTH by a nonadrenal tumor.

Clinical Manifestations Clinical manifestations include truncal obesity, thinning of the extremities due to muscle wasting, "buffalo hump," "moon" facies, mildly increased blood pressure, purple striae along the flank, hirsutism with excessive fine hair on the face, upper back, and arms, mild hyperglycemia, muscle weakness, menstrual irregularity, impotence, ruddy facial appearance, mental changes from mild depression to severe psychosis, impaired immune function leading to opportunistic infections, and arrest of normal growth.

Diagnosis The diagnosis depends on recognizing the different signs and symptoms. Three steps: First, establish the presence of hypercortisolism. The best screen is a 24-h urinary free cortisol test; another is the single-dose dexamethasone suppression test. Normal individuals given 1 mg dexamethasone PO at 11 P.M. have plasma cortisol levels below 5 μg/dL at 8 A.M. In hypercortisolism, the level will be higher. Second, determine if the hypercortisolism is pituitary dependent. The plasma ACTH level is undetectable or low with a primary adrenal tumor, intermediate with a pituitary tumor, and very high with an ectopic ACTH-producing tumor. Third, determine the exact cause. With the CRH test, 1 μg/kg CRH increases the plasma ACTH and cortisol levels in pituitary tumor but not in ectopic ACTH syndrome. The dexamethasone suppression test (see above) also can be used. In addition, metyrapone stimulates ACTH release in pituitary disease.

Radiographic Evaluation CT and MRI of the sella turcica detect tumor only in a small percentage of patients. Bilateral petrosal sinus sampling is best for differentiating a pituitary from an ectopic ACTH-secreting tumor. Sampling of blood from both the inferior petrosal sinuses and peripheral veins before and after CRH administration produces a ratio of more than 3:1 in Cushing's disease,

which helps with lateral localization. An adrenal CT scan can distinguish cortical hyperplasia from tumor with more than 95 percent sensitivity. A T_2-weighted MRI adds specificity and may distinguish adenoma from carcinoma. Pheochromocytoma is particularly bright. Radioisotope imaging with labeled iodocholesterol may differentiate hyperplasia (bilateral) from adenoma (unilateral) or carcinoma (usually cold).

ADRENAL INSUFFICIENCY (ADDISON'S DISEASE)

Primary adrenal insufficiency is caused by autoimmune adrenalitis, tuberculosis, adrenomyeloneuropathy, fungal infections, the acquired immune-deficiency syndrome (AIDS), metastatic carcinoma, adrenal hemorrhage, familial deficiency, or adrenal surgery. Secondary adrenal insufficiency is caused by an abnormality of the pituitary or hypothalamus. Most commonly it is iatrogenic from long-term glucocorticoid administration. It may lead to an adrenal crisis perioperatively.

Clinical Manifestations Clinical manifestations include weakness and fatigue, weight loss and anorexia, and dehydration. In adrenal crisis, poorly defined upper abdominal or flank pain, fever, nausea, lethargy, disorientation and confusion, hypotension, hypoglycemia, hyperkalemia, leukocytosis with eosinophilia, and prerenal azotemia may be seen. These signs with or without cardiovascular collapse in any perioperative or critically ill patient should raise the question of insufficiency.

Diagnostic Testing The plasma cortisol level is often depressed, and the ACTH level is often elevated. The capacity to respond to ACTH stimulation is measured to assess the stress response. Cortisol is measured before and 60 min after administration of 250 μg ACTH. Function is normal if the basal level is 20 μg/dL and there is an increment of more than 7 μg/dL over basal levels at 60 min.

Treatment If the clinical condition is rapidly deteriorating, a blood sample for plasma ACTH and cortisol, glucose, Na, K, blood urea nitrogen (BUN), and creatinine determination and a complete blood count (CBC) should be drawn, and 200 mg of a water-soluble corticosteroid should be administered. After the initial intravenous bolus, 100–200 mg of corticosteroid should be administered over the next 24 h. Fluid and electrolyte imbalances are corrected with intravenous replacement fluids, and the underlying cause is sought. High-dose replacement should be continued for several days and then tapered.

Perioperative Treatment Patients currently taking steroids or who have taken them within 2 years should be treated perioperatively with hydrocortisone. If there is a question, a cosyntropin stimulation test may be done. The amount of perioperative steroid treatment will depend on the magnitude of the surgical procedure. Patients undergoing major procedures (e.g., Whipple procedure, coronary artery bypass grafting) need 100–150 mg IV on-call to the operating room, 50 mg IV every 8 h for 2 days, 25 mg every 8 h for 3 days, and then maintenance. For smaller operations, lower doses are sufficient. For surgical treatment of endogenous hypercortisolism, glucocorticoid replacement is required after removal of the cause.

PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)

Diagnosis This is one of the few surgically curable causes of hypertension. The causes include adrenocortical adenoma (80 percent), hyperplasia of the zona glomerulosa, and (rarely) adrenocortical carcinoma.

Hypertension (predominantly diastolic), spontaneous hypokalemia, high plasma levels of aldosterone, and low plasma levels of renin are characteristic. Patients may be asymptomatic or have weakness, muscle cramps, polyuria, and polydipsia. It is important to rule out essential hypertension treated with potassium-wasting diuretics. Stop all diuretics and measure 24-h excretion of potassium (>30 mEq/24 h is suggestive).

The ratio of plasma aldosterone to renin is usually greater than 30. An inability to reduce the plasma aldosterone level to less than 15 ng/dL and raise plasma renin activity after administration of captopril is confirmatory.

Localization High-resolution CT scanning (75–90 percent accurate) of the contralateral adrenal cortex should show it to be atrophic. Tumors of less than 1 cm may be missed. Radioactive iodocholesterol scanning may be helpful Selective venous sampling for aldosterone is indicated when these tests fail.

Treatment *Adenoma* Laparoscopic adrenalectomy is the treatment of choice.

Hyperplasia Medical management is attempted with spironolactone, nifedipine, and/or amiloride plus other antihypertensive drugs.

HYPOALDOSTERONISM

Hypoaldosteronism may be genetic or autoimmune. It may follow excision of an aldosteronoma. It is treated with fludrocortisone (0.1–0.2 mg/day) for months.

ADRENOGENITAL SYNDROME

Adrenogenital syndrome is associated with congenital adrenal hyperplasia, a group of inherited diseases caused by defects in one of five enzymes that contribute to synthesis of cortisol from cholesterol resulting in a decrease in cortisol and an increase in precursors. Hyperplasia is driven by ACTH. An associated finding is ambiguous external genitalia as a result of a deficiency or excess of adrenal androgens. Treatment is glucocorticoid replacement and may include surgical correction of genitalia.

Postnatal children and adults may preset with signs or symptoms of excess sex hormone secretion, almost always caused by tumors of the adrenal, usually carcinoma.

ADRENAL MASS

This is an unexpected finding in 0.6 percent of abdominal CT scans. Most are usually benign, nonfunctional adenomas (autopsy incidence 10 percent). The surgeon should obtain a careful history and physical examination, a stool guaiac test, a Pap smear and hematocrit, and determinations of the 24-h urine for free cortisol level (Cushing's syndrome), vanillylmandelic acid (VMA), and catecholamines (pheochromocytoma). Aldosterone and renin should be measured in any patient with hypertension or hypokalemia. Even if nonfunctional, a mass larger than 5 cm may be carcinoma and should be resected. Smaller masses should be remeasured by CT in 6 months and resected if larger or left alone if unchanged. If pheochromocytoma is excluded and metastatic disease is suspected, a fine-needle aspiration (FNA) may be helpful (Fig. 35-2).

Treatment of Adrenal Cortical Neoplasms *Adenoma* Treatment involves complete resection of the involved adrenal gland using laparoscopic technique with postoperative glucocorticoid supplementation.

Carcinoma Stage I is a tumor smaller than 5 cm without local invasion. Stage II is the same but larger than 5 cm. Stage III shows local invasion or positive nodes. Stage IV shows distant metastases. CT scan or MRI should include the chest to assess extent of tumor. A venacavagram is necessary if the vena cava appears to be involved. A contrast study is needed to document contralateral function if nephrectomy is needed. En bloc resection of the tumor and involved adjacent organs provides the best chance for cure and may require a thoracoabdominal approach. Even debulking will help by reducing the amount of hormone-secreting tissue. Cure is likely only in stage I or II disease. The 5-year survival is 10–35 percent. Recurrent or metastatic disease is usually treated with mitotane,

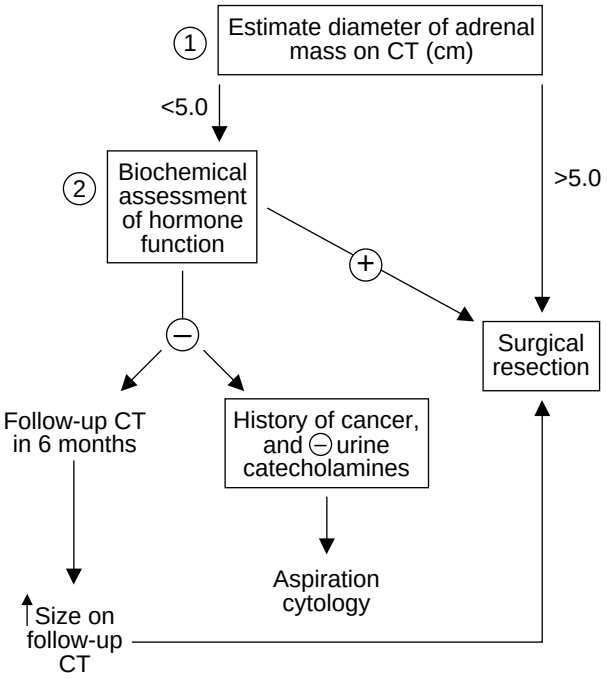

FIGURE 35-2 Flow diagram for the management of an incidentaloma.

which affects steroid metabolism and can reduce symptoms of hypercortisolism.

ECTOPIC ACTH SYNDROME

The diagnosis requires Cushing's syndrome and bilateral adrenal hyperplasia but no evidence of pituitary tumor. Ectopic ACTH-producing tumors include oat cell or small cell lung cancer, bronchial or thymic carcinoid, pancreatic islet cell tumor, medullary thyroid cancer, pheochromocytoma, midgut carcinoid, and others. Workup should screen for and localize these tumors. A suspicious finding is confirmed by FNA and radioimmunoassay for ACTH on aspirate. Treatment is resection or debulking of tu-

mor or medical control of metabolic abnormalities. Bilateral adrenalectomy may be indicated.

Adrenal Medulla

PHYSIOLOGY

The sympathoadrenal system consists of a sympathetic neuronal component that uses norepinephrine as the main neurotransmitter and adrenomedullary secretory hormone, epinephrine, the main hormone secreted into the bloodstream. The system influences cardiovascular, metabolic, and visceral activity, and its typical effects are observed during severe stress. Release of norepinephrine at sympathetic nerve endings is critical for maintenance of normal blood pressure, especially during upright posture. Epinephrine metabolites (e.g., normetanephrine, metanephrine, and VMA) are excreted with catecholamines in the urine.

PHEOCHROMOCYTOMA

Pheochromocytomas arise from chromaffin cells that are associated with sympathetic ganglia in fetal life and are concentrated in the adrenal medulla after birth. Between 85 and 90 percent of pheochromocytomas arise in the adrenal medulla, but they can arise wherever there is a sympathetic ganglion, including the carotid body, the heart, along the thoracic or abdominal aorta, and in the renal hilum or urinary bladder. The most common extraadrenal site is the organ of Zuckerkandl near the origin of the inferior mesenteric artery. Pheochromocytomas are usually 3–5 cm in diameter and weigh about 100 g. Ten percent or more are malignant, and these tend to be larger. The only absolute criteria are the presence of secondary tumors where chromaffin cells are not found and identification of visceral metastases.

Associated Syndromes Ten percent of pheochromocytomas occur as part of an inherited condition. Bilateral medullary pheochromocytomas are components of multiple endocrine neoplasia (MEN) types IIA and IIB. They can occur in families without other manifestations of MEN syndromes. They occur in 25 percent of patients with von Hippel–Lindau's disease and in less than 1 percent of patients with neurofibromatosis and von Recklinghausen's disease.

Clinical Manifestations Pheochromocytomas can cause anxiety attacks and episodic or sustained hypertension. Patients classically describes "spells" of paroxysmal headaches, pallor, palpitations, hypertension, and diaphoresis. Some have mild hypertension;

others suffer sudden death from myocardial infarction or cerebrovascular accident. They may have chronic hypovolemia or lactic acidosis. Most patients have mild weight loss.

Diagnosis Diagnosis is based on a 24-h urine collection for catecholamine, metanephrine, and VMA determinations. Plasma levels may be measured but are not as sensitive. Elevated levels of norepinephrine occur with extraadrenal pheochromocytomas. The clonidine suppression test may be supplemental. Clonidine suppresses plasma levels in normal individuals, not in those with pheochromocytomas.

Localization Studies CT and MRI detect tumors greater than 1 cm diameter. Each has advantages. Nuclear medicine scanning with ^{131}I-labeled metaiodobenzylguanidine (MIBG) is 78–91 percent sensitive and 98–100 percent specific.

Treatment *Preoperative Preparation* Treatment starts with alpha-adrenergic blockade with phenoxybenzamine, 10–20 mg PO 2–3 times a day, increasing to 20 mg/day until the blood pressure is stabilized. Tachycardia of more than 130 beats per minute is treated with beta-adrenergic blockade (propranolol). Extra volume is required.

Intraoperative Management Right-sided heart catheter monitoring, an arterial catheter, and peripheral intravenous catheters are placed. Manipulation of the tumor causes changes in blood pressure. Nitroprusside and Levophed are used to titrate the blood pressure quickly and effectively. A transabdominal approach with a long midline or bilateral subcostal incision is used. The entire abdomen is visualized and palpated. A laparoscopic approach can be used for precisely localized tumors but is still considered experimental. Family members require yearly physical examinations and screening for elevated catecholamines, calcitonin, and serum calcium.

Malignant Pheochromocytoma Metastases may not develop for years. The basic principle is to resect recurrences of metastases whenever possible and to treat hypertension with appropriate blockade. Painful bony metastases respond to radiotherapy. Chemotherapy with cyclophosphamide, vincristine, and dacarbazine has been beneficial. Five-year survival is 36–60 percent.

NEUROBLASTOMA

This is the fourth most common pediatric malignancy. Median age at diagnosis is 2 years. Neuroblastomas may be associated with genetic diseases, including neurofibromatosis, Beckwith-Weidemann

syndrome, and trisomy 18. They may spontaneously differentiate and regress. Neuroblastomas are thought to arise from the embryonic neural crest. They may be difficult to distinguish from other small, round blue cell tumors of childhood. Look for tumor markers in the serum or urine. Elevated 24-h urine levels of homovanillic acid and VMA are detected in 65 and 90 percent, respectively. Neuroblastomas can occur anywhere along the sympathetic nervous system. Metastases (50 percent in infants and 67 percent in older children) usually involve lymph nodes, bone marrow, bone, liver, and subcutaneous tissue.

Clinical Manifestations The most common presenting symptom is an abdominal or flank mass. Thoracic neuroblastoma presents as a posterior mediastinal mass on chest radiograph and may cause respiratory distress or cord compression. Neck tumor presents with a cervical mass. Pelvic tumor usually involves the organ of Zuckerkandl.

Radiology and Staging CT is the best imaging study for patients with neuroblastoma and should be performed to determine the extent of disease. Useful nuclear medicine studies include a technetium bone scan and a ^{131}I-MIBG scan.

Treatment Treatment depends on the stage of disease. Stage I and II tumors can be resected. Most abdominal tumors involve major vessels. Unresectable abdominal tumors are biopsied, treated with radiation or chemotherapy, and then removed if possible. Radiation therapy is useful in nodal disease and in infants with spinal cord compression. Neuroblastomas are highly chemoresponsive.

Adrenalectomy

Adrenalectomy may be done using a posterior approach through the bed of the twelfth rib or laparoscopically using a lateral approach. The laparoscopic approach is suited for small aldosteronomas or cortisol-secreting adenomas or hyperplastic adrenal glands. It is not recommended for pheochromocytoma because of the need for tumor manipulation and because the adrenal vein cannot be controlled early.

For a more detailed discussion, see Couldwell WT, Simard MF, Weiss MH, and Norton JA: Pituitary and Adrenal, chap. 35 in *Principles of Surgery*, 7th ed.

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CHAPTER

36

THYROID AND PARATHYROID

THYROID

Anatomy

Gross Normal adult thyroid gland weighs 15–20 g. It consists of two lateral lobes that extend along the sides of trachea to the level of the middle thyroid cartilage and is connected centrally by an isthmus. A pyramidal lobe is present in 80 percent; it extends left of the midline upward from the isthmus along the anterior surface of the thyroid cartilage. It is a remnant of embryonic thyroglossal duct. Four parathyroid glands are found on the posterolateral surface of the lobes. Arterial supply is superior from the external carotid and inferior from the thyrocervical trunk of the subclavian arteries.

Microscopic The thyroid is divided into lobes that contain 20–40 follicles, which are spherical and average 30 μm in diameter. Follicles contain a central store of colloid secreted from epithelial cells that are influenced by thyroid-stimulating hormone (TSH). C cells or parafollicular cells contain and secrete the hormone calcitonin; they are part of the amine-containing precursor uptake decarboxylase (APUD) series.

Recurrent Laryngeal Nerves These originate in the vagus nerves; on the right, the recurrent nerve loops under the subclavian artery to ascend obliquely and enter the larynx at the level of the cricoid cartilage. On the left, it loops posteriorly around the ligamentum arteriosus and ascends medially in the tracheoesophageal groove to enter the larynx. The right recurrent nerve is in the tracheoesophageal groove in 64 percent of people and in the left in 77 percent; it is lateral to the trachea on the right in 28 percent and on the left in 17 percent. Rarely, it is anterolateral to the trachea (right 8 percent and left 6 percent). The recurrent nerves run behind the inferior thyroid artery in 53 percent on the right and 69 percent on the left; in others it is anterior to the artery on the right in 37 percent and on the left in 24 percent and between the branches of the

artery on the right in 7 percent and on the left in 6 percent. In 1 percent is it nonrecurrent almost always on the right because of a vascular anomaly of the right subclavian artery; when on the left, the nerve arises from the vagus to run directly to the larynx close to the superior thyroid vessels and can be at risk when these vessels are transected. Injury to nerves results in vocal cord paralysis.

Superior Laryngeal Nerve Most often the nerve is in close proximity to the superior pole vessels; it can be at significant risk if not identified at operation. To avoid injury, the superior pole vessels should be individually ligated and divided low on the thyroid gland and dissected laterally to the cricothyroid muscle.

Anomalies

The median thyroid anlage can fail to develop, resulting in athyreosis, or it may fail to descend, resulting in lingual thyroid, and this occurs more often in females. It can present as a mass in the region of foramen cecum at the base of the tongue; if it enlarges, it can cause dysphagia, dysphonia, or dyspnea. Treatment should be suppression with thyroxine or ablation with radioactive iodine. Surgery is indicated for hemorrhage, degeneration, and necrosis or threatened airway.

Physiology

Through release of thyroxine (T_4) and triiodothyronine (T_3), the thyroid gland influences the metabolic rate of all tissues. Release of T_4 and T_3 is stimulated by the TSH, which can be suppressed by T_4 and T_3. TSH is also stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH). Increased secretion in thyroid hormone increases metabolic rate; the rate decreases when secretion is decreased. Calcitonin is produced by C cells. It has use in the treatment of hypercalcemia and Paget's disease of bone and as a tumor marker for medullary carcinoma.

Iodine Metabolism Formation of thyroid hormones depends on exogenous iodine, which is found in dietary sources. It is rapidly converted to iodides in the gut and distributed into extracellular space; it is then concentrated in the thyroid (90 percent) or excreted in urine.

Hormone Synthesis Steps in the synthesis are

1. Active transport of iodine from plasma into thyroid cells, gradient 50:1 or more. Influenced by TSH inversely with glandular iodine content.

2. Rapid oxidation of iodides to iodine.
3. Tyrosine radicals iodinated to 3-monoiodotyrosine (MIT) and 3–5-diiodotyrosine (DIT). TSH-sensitive.
4. Coupling to form hormonally active iodothyronines; T_4 from two DIT molecules and T_3 from one DIT and one MIT molecule.

Storage, Secretion, and Metabolism of Thyroid Hormone T_4 and T_3 are bound to thyroglobulin and stored in the colloid of the thyroid follicles. Release of active hormones is by endocytosis; hydrolysis results in production of all component parts. Through deiodination, most iodide is released and reused in the follicle; the iodothyronines are secreted. The steps are TSH-dependent.

Active thyroid hormones circulate in plasma attached to plasma proteins: thyroid hormone–binding globulin (TBG), thyroid hormone–binding prealbumin (TBPA), and albumin. T_4:T_3 ratio is 10–20:1. T_3 is three to four times more active than T_4 and has a half-life of 3 days. T_4 has a half-life of 7–8 days.

Regulation of Thyroid Activity TRH is produced by the hypothalamus and stimulates anterior pituitary cells to secrete TSH, which in turn stimulates all processes leading to synthesis of thyroid hormone. TSH regulation is the direct feedback exerted on the pituitary by the level of thyroid hormone in the blood.

Assessment of Patients with Thyroid Disease

History There are two types of thyroid disease: problems relating to function (hyperthyroidism/hypothyroidism) and thyroid masses. Symptoms such as dysphagia, dysphonia, dyspnea, or a choking sensation are frequent. Pain is uncommon, but localized pain may suggest malignancy; pain radiating to the arm is suggestive of thyroiditis or hemorrhage within the thyroid gland. Change in the character of the voice may suggest involvement of the recurrent laryngeal nerves. Past exposure to radiation, family history of thyroid disease, and iodine deficiency or ingestion of goitrogenic drugs are significant.

Examination Most masses are visible. Look for retrosternal goiter arising from beneath the sternum and clavicles. Palpation of a seated patient is usually from the back with the neck slightly extended; palpate for size and consistency and regional lymph nodes. Listen for a bruit.

Fine-Needle Aspiration Cytology (FNAC) Slides are made from cellular material aspirated from a nodule with a 23-gauge needle.

Skilled cytopathologists can accurately diagnose most thyroid diseases. This is less accurate for patients with thyroid nodules, familial nonmedullary thyroid cancer, or exposure to low-dose therapeutic radiation.

Thyroid Function Tests Normal values are

Serum TSH	0.15–4.2 mIU/L
Total T_4	55–150 nmol/L
Free T_4	12–28 pmol/L
Total T_3	1.5–3.5 nmol/L
Free T_3	3–9 pmol/L

Thyrotoxicosis

Thyrotoxicosis results when excessive levels of active thyroid hormone are secreted. There are two predominate causes: Graves' disease (diffuse toxic goiter) and toxic solitary or multinodular goiter (Plummer's disease).

GRAVES' DISEASE

This is an autoimmune disease; thyroid-stimulating antibodies are directed at TSH receptors on follicular cells. This stimulates the receptors and results in excess thyroid hormone production.

Macroscopically, the thyroid gland is diffuse and smoothly enlarged with increased vascularity. Microscopically, it is hyperplastic with columnar epithelium and minimal colloid.

Clinical Features Common to All Forms of Thyrotoxicosis
Symptoms There are manifestations of increased caloric turnover, heat intolerance, thirst, sweating, weight loss despite adequate intake, amenorrhea, tachycardia or atrial fibrillation, and congestive heart failure (CHF). Adrenergic stimuli may include fatigue, agitation and excitability, disturbed sleep pattern, emotional lability, hyperkinesis, tremor, and diarrhea. Patients with extreme involvement may exhibit psychosis.

Physical Examination The examination may disclose weight loss, flushing, warm and moist skin, inappropriate sweating, tachycardia, widening of pulse pressure, fine tremor, muscle wasting, and hyperactive tendon reflexes.

The Graves' disease triad is goiter including the pyramidal lobe, thyrotoxicosis, and exophthalmos. Patients may have pretibial myxedema, gynecomastia, or an audible bruit over the gland. Eye signs include (1) spasm of the upper lid with retraction and lid lag,

(2) external ophthalmoplegia, (3) exophthalmos with proptosis, (4) supraorbital and infraorbital swelling, and (5) congestion and edema.

Autonomous thyroid function is characterized by decreased or undetectable levels of TSH, elevated circulating T_3/T_4 levels, or raised levels of circulating thyroid autoantibodies. Radioactive iodine (RAI) scan shows diffuse uptake through the gland of 45–90 percent.

Treatment of Graves' Disease *Antithyroid Drugs* Beta blockers (propranolol) are used to alleviate peripheral adrenergic effects. Main antithyroid drugs are propylthiouracil (PTU) and methimazole (Tapazole), which inhibit organic binding of iodine and the coupling of iodotyrosines. They have no effect on the underlying cause of the disease. T_4/T_3 levels help in assessing response to treatment. It is hoped that natural remission will occur after the patient is rendered euthyroid. The relapse rate is 50 percent after 12–18 months; recurrent hyperthyroidism requires definitive treatment with RAI or surgery.

Radioactive Iodine Therapy (^{131}I) Most patients in the United States undergo radioiodine treatment. Patients should be euthyroid and have stopped all antithyroid drugs 2–3 weeks before treatment. The initial dose of ^{131}I is about 8500 cGy; 20 percent require a second dose. Patients under age 35 usually are treated with thyroidectomy and older patients with ^{131}I. It is contraindicated in pregnant or nursing females. Complications of ^{131}I therapy include exacerbation of thyrotoxicosis with arrhythmias, overt thyroid storm, hypothyroidism, increased ophthalmopathy, and hyperparathyroidism.

Surgery Surgery is advised when RAI is contraindicated. It is preferred for young patients with severe thyrotoxicosis and large goiters. Toxic adenoma should be excised. Patients should be euthyroid with antithyroid drugs continued to the day of surgery or Lugol's iodine solution 3 drops bid for 10 days preoperatively. Some prefer 5–7-day preparation with propranolol. Iodine reduces the vascularity of the gland.

Advantages of thyroidectomy are immediate cure, decreased long-term incidence of hypothyroidism, simultaneous removal of coexisting carcinomas, and possible relief of ophthalmopathy. The disadvantages are recurrent laryngeal nerve injury (1 percent) and hypoparathyroidism (transient 13 percent, permanent 1 percent).

TOXIC MULTINODULAR GOITER

Also known as *Plummer's disease*, this is the result of one or more thyroid nodules trapping and organifying more iodine and secreting

more thyroid hormone independent of TSH control. Hyperthyroidism is milder than Graves' disease and without extrathyroidal manifestations of ophthalmopathy. Antithyroid antibodies usually are absent. ^{131}I uptake is localized to autonomous toxic nodules, and the remaining thyroid tissue is suppressed. Surgical excision is the preferred treatment.

THYROID STORM

This is life-threatening, but it is rare during surgery. It usually is precipitated by infection, labor, administration of iodine, or after ^{131}I treatment. Symptoms are similar to those of severe thyrotoxicosis with profound tachycardia, fever, confusion, dehydration from nausea, vomiting, and fever, and eventual coma. The best management is prevention. Patients should be euthyroid before operation. The acute phase is managed with fluid replacement, antithyroid drugs, beta blockers, sodium iodate solution, steroids, and a cooling blanket.

Hypothyroidism

This occurs because of a deficiency in the circulating levels of thyroid hormone. It is cretinism in neonates and is characterized by neurologic impairment and mental retardation. Early treatment lessens the neurologic deficits. It may be associated Pendred's syndrome and Turner's syndrome. Juvenile hypothyroidism appears at a younger age and can result in abdominal distention, umbilical hernia, and rectal prolapse. In adults, symptoms are insidious, and patients may be unaware. Principal causes in the United States are autoimmune thyroiditis and iatrogenic (e.g., thyroidectomy, RAI treatment, or medications).

Clinical Manifestations Hypothyroidism secondary to autoimmune thyroiditis is more common in females (80 percent). In adults, symptoms are nonspecific: tiredness, weight gain, cold intolerance, constipation, and menorrhagia. Severe hypothyroidism (*myxedema*) is characterized by facial and periorbital puffiness, rough, dry, yellow-tinged skin, hair loss with the remainder dry and brittle, and slowed speech. Other indications include an enlarged tongue, dementia, bradycardia, cardiomegaly, and pericardial or pleural effusions.

Laboratory Findings Low circulating T_4 and T_3 levels with raised TSH levels are evidenced in primary failure, in secondary (pituitary) failure, TSH levels are low. Thyroid autoantibodies may be present. Other findings are anemia and flattened T waves.

Treatment Thyroxine is given in doses of 50–200 μg/day. The dosage is titrated against TSH levels. For severe disease in the elderly, the dose is started lower and increased slowly. Myxedema coma requires emergency treatment with large doses of intravenous thyroxine.

Thyroiditis

HASHIMOTO'S DISEASE

This is an autoimmune disease; it is more common at ages 30–60 years; the female-to-male ratio is 10:1. It can be familial and is autosomal dominant.

Pathology The gland is firm, granular, and mildly enlarged, and the enlargement is symmetric. There is follicular and Hürthle cell hyperplasia with lymphocyte and plasma cell infiltration and formation of lymphoid follicles. Epithelial cell degeneration and fragmentation of the basement membrane occur. It can lead to fibrosis.

Clinical Manifestations Twenty percent present with hypothyroidism, and a few present with hyperthyroidism. Most are euthyroid. Common symptom is tightness in the throat with painless, nontender enlargement of the thyroid gland.

Diagnostic Findings Tests are biphasic with early signs of hyperfunction, later hypofunction, and then normalization. Diagnosis is confirmed by circulating antithyroid antibodies. FNAC may confirm the diagnosis or document cancer.

Treatment This disorder is best treated with thyroid hormone for goiter and long-term monitoring of TSH. Surgery is indicated for obstructive symptoms or cosmesis for a markedly enlarged gland.

SUBACUTE THYROIDITIS (DEQUERVAIN'S THYROIDITIS)

This is granulomatous or giant cell thyroiditis, an uncommon acute inflammatory disease that might be precipitated by viral infection. Patients present with fever, malaise, and unilateral or bilateral thyroid pain; they may have a recent history of upper respiratory tract infection. The gland is tender and firm, with one or both lobes enlarged.

Acute inflammation and degenerative follicles with giant cell granulomas may show on FNAC. Laboratory findings indicate an elevated erythrocyte sedimentation rate (ESR) with neutrophilia; also, there usually are elevated thyroid function tests. RAI uptake is low.

Treatment Nonsteroidal anti-inflammatory drugs (NSAIDS) are used for pain relief, and beta blockers are used for thyrotoxicosis. In more severe cases it may be necessary to prescribe steroids for short periods. The disease usually lasts 1–6 weeks and resolves spontaneously. Some patients can alternate between bouts of exacerbation and remission.

REIDEL'S THYROIDITIS

This is a rare disease characterized by dense, invasive fibrosis that may extend beyond the thyroid capsule and involve surrounding structures. It can lead to hypothyroidism. Symptoms include hoarseness, stridor, and dyspnea. The gland feels woody and is nontender.

Treatment Treatment is with tamoxifen or steroids. Isthmectomy to relieve compressive symptoms or establish diagnosis may be necessary.

ACUTE SUPPURATIVE THYROIDITIS

This is a rare disease of childhood or adolescence and is associated with upper respiratory tract infection. Symptoms are manifest as acute thyroid pain and dysphagia, fever, and occasionally, rigors. Most common bacterial agents are streptococci, staphylococci, and pneumococci. Treatment is with intravenous antibiotics and drainage.

Goiter

Goiter is an enlargement of the thyroid gland in a euthyroid patient.

Familial Goiter Familial goiter is caused by an inherited enzyme defect; it is usually autosomal recessive.

Endemic Goiter This is defined as thyroid enlargement affecting a significant number of people of a particular locale. The most important factor is iodine deficiency and ingestion of goitrogens. Prophylactic iodination in the form of table salt is successful in reducing the incidence.

Sporadic Goiter This is goiter for which no definitive causes can be established.

Pathology The thyroid gland may be diffusely enlarged and smooth or grossly nodular. Early hyperplasia is reversible. Nodules are filled with gelatinous, colloid-rich substance interspersed with normal tissue.

Clinical Manifestations Most patients are asymptomatic, but patients may present with pressure in the neck and a mass. Dysphagia or tracheal compression occurs with respiratory distress, particularly with substernal extension. Sudden pain with rapid expansion is caused by hemorrhage. The gland may feel soft and diffusely enlarged or may evidence multiple nodules of varying size and firmness. FNAC accurately defines a colloid nodule.

Treatment Diffuse goiter and familial goiter respond to thyroxine. Surgical indications include cosmesis, compressive symptoms, substernal goiter, or malignancy on FNAC.

Solitary or Dominant Thyroid Nodule

Four percent of population have palpable thyroid nodules; 40 per million will be malignant. There are two high-risk groups for cancer. The first group consists of those with a family history of thyroid cancer. Medullary cancer is autosomal dominant (RET point mutation); 6 percent of papillary cancers have family history. The second group consists of those with a history of low-dose irradiation to the head and neck, which was used to treat "enlarged thymus," tonsils, and acne vulgaris. There is a linear increase in risk from 6.5–2000 cGy. The cancer tends to be papillary and multifocal.

Clinical Manifestations *History* Forty percent of nodules with a history of irradiation are malignant. Important criteria are the time of onset (recent or growing), age and gender (nodule in a child or adolescent or new nodule in male over 40 or a female over 50 is likely to be malignant), rapid enlargement, husky voice (recurrent nerve involvement), and dyspnea or dysphagia (indicating compression).

Physical Examination Most nodules are benign (colloid nodules or adenomas). Fifteen percent of solitary nodules are malignant; those which are firm or hard and fixed are two to three times more likely to be malignant. Lymph node enlargement suggets malignancy.

Diagnostic Studies *Fine-Needle Aspiration for Cytology* This is the procedure of choice for evaluating thyroid nodules. Nodules can be categorized as benign (65 percent), suspicious (15 percent), malignant (5 percent), and nondiagnostic (15 percent). Incidence of false-positive results is 1 percent and false-negative is 5 percent. Ultrasound differentiates solid from cystic and monitors size. Computed tomography (CT) and magnetic resonance imaging (MRI)

are unnecessary except for very large or substernal lesions. Thyroid isotope scanning indicates functional activity. It is useful only in follicular lesions.

Thyroid function tests usually are not useful. Thyroglobulin levels are used to follow post-total thyroidectomy patients for cancer. Serum calcitonin levels are measured in anyone with a family history of medullary cancer or multiple endocrine neoplasia type II (MEN II). Those who are RET oncogene positive need a 24-h urine collection for determination of vanillylmandelic acid (VMA), metanephrine, and catecholamine levels.

Treatment Colloid nodule is operated on for cosmesis or symptoms. Lesions are measured with ultrasound. A baseline thyroglobulin level is determined, and a repeat FNAC is performed in 6 months if the lesion enlarges. Thyroid lobectomy is indicated for nodules enlarging on suppressive doses of thyroxine, cysts recurrent after three aspirations or complex on ultrasound, or symptoms. Patients who have had previous irradiation should be considered for thyroidectomy.

Malignant Tumors

Tyroid cancer occurs in about 40 per million persons per year; 90–95 percent are differentiated (papillary, follicular, or Hürthle cell), 6 percent are medullary, and of those, 30 percent are familial.

Molecular Basis of Thyroid Tumors Oncogenes contribute directly to tumor genesis. Several oncogenes are involved in thyroid tumor genesis.

PAPILLARY CARCINOMA

Papillary carcinoma is the most common of thyroid cancers (80 percent). There is a 2:1 female-to-male ratio, and the mean age at presentation is 35 years.

Pathology Tumors are hard and whitish. Macroscopic calcification, necrosis, or cystic change may be apparent. Histologically, papillary carcinomas may be pure follicular with intranuclear inclusions or a mixed pattern. Cells are cuboidal with abundant cytoplasm, crowded nuclei and intranuclear cytoplasmic inclusions (Orphan Annie cells), and calcium deposits (psammoma bodies). Bewteen 30 and 87.5 percent are multifocal. Commonly, there is lymphatic spread within the gland and to local nodes, but the tumor may invade adjacent structures (e.g., trachea, esophagus, and recurrent laryngeal nerves).

Tumors are classified as *minimal or occult* (less than 1 cm and without local invasion or nodal spread), *intrathyroidal* (more than than 1 cm and confined to the thyroid gland), and *extrathyroidal* (locally advanced with invasion into adjacent structures). Other types are tall cell, columnar, Hürthle cell, and poorly differentiated variants that are more aggressive.

Clinical Manifestations Most patients are euthyroid and present with a slowly growing, painless mass in neck. Ipsilateral lymphadenopathy may be present and is most common in children, as are lung metastases.

Prognostic Indicators Prognosis is determined by use of the AGES scale (*a*ge, *g*rade, *e*xtent, and *s*ize), the MACIS scale [*m*etastases, *a*ge at presentation (40 or less), *c*ompleteness of resection, extrathyroidal *i*nvasion, and *s*ize], and DNA ploidy. Distant metastases are most grave. Local invasion increases mortality tenfold.

Surgical Treatment For patients with minimal disease, lobectomy with isthmectomy usually is sufficient. In all others, total or near-total thyroidectomy is preferred, which will manage multifocal disease (4.2–26 percent), decrease the incidence of local recurrence (disease related mortality 30–50 percent), reduce the risk of anaplastic transformation (1 percent in residual disease), and facilitate the diagnosis of unsuspected metastases by radioiodine scanning (metastases identified and ablation with RAI). Lymph node metastases are treated with modified radical neck dissection.

FOLLICULAR CARCINOMA

This represents 10 percent of thyroid cancers; it occurs more often in females at a ratio of 3:1, and the mean age at presentation is 50 years.

Pathology It is usually solitary, and 90 percent are encapsulated. Vascular invasion and hematogenous spread to bone, lung, and liver are more common than lymphatic spread. Histologically, follicles are present; colloid may be absent. Categories include *minimally invasive* and *frankly invasive.*

Clinical Manifestations Usually presents as a solitary nodule and a recent change in long-standing goiter. One percent are hyperfunctioning. Diagnosis is by FNAC.

Surgical Treatment and Prognosis Follicular neoplasm diagnosed on FNAC should undergo lobectomy, including the isthmus

and pyramidal lobe. Intraoperative frozen sections should be performed when there is evidence of capsular or vascular invasion. Total thyroidectomy is indicated for carcinoma, except in patients with minimally invasive follicular cancers. Total thyroidectomy enables ^{131}I detection and ablation of metastatic disease. Mortality is 15 percent at 10 years and 30 percent at 20 years, but the long-term prognosis is worse when the age of presentation is over age 50.

HÜRTHLE CELL CARCINOMA

These represent 3 percent of thyroid cancers and are considered by the World Health Organization (WHO) to be a variant of follicular neoplasm. Tumors contain sheets of eosinophilic cells. Tumors possess TSH receptors and produce thyroglobulin. Only 10 percent trap RAI. They often are multifocal and bilateral and are more likely to metastasize to local nodes (25 percent). Hürthle cell neoplasm is diagnosed by FNAC; 20 percent are malignant. Treatment is similar to that of follicular cancer. When malignancy is confirmed on frozen or permanent section, total thyroidectomy with central node dissection is appropriate. With palpable nodes, modified radical neck dissection should be performed and the patient treated with T_4 postoperatively.

MEDULLARY CARCINOMA

These represent 5 percent of thyroid malignancies and arise from C cells or parafollicular cells, which secrete calcitonin. These cells are neuroectodermal and originate from the ultimobranchial bodies and then join the thyroid gland proper and are concentrated mainly in the superior poles laterally. They are part of the APUD complex.

Pathology Tumors are located in the middle to upper poles of the thyroid and are 75 percent unilateral. Familial cases are more likely multicentric with premalignant C-cell hyperplasia; 90 percent are bilateral. Microscopically, sheets of cells are separated by areas of collagen and amyloid; cells may be polyhedral and resemble carcinoid or spindle cells. The tumor spreads to regional nodes in the neck and superior mediastinum and then distally. These tumors stain positively for calcitonin peptide (CGRP), carcinoembryonic antigen (CEA), and histaminase.

Clinical Manifestations Patients usually present with a neck mass; 15–20 percent have palpable nodes. Local pain is more common, and local invasion may produce symptoms of dysphagia, dyspnea, or dysphonia. The female-to-male ratio is 1.5:1. Age at presentation is 50–60 years, except in familial cases, which present at a younger age. Tumors may secrete a variety of peptides. Debilitating diarrhea is a late symptom.

Diagnosis Diagnosis is established by history, mass on examination, raised serum calcitonin or CEA level, and FNAC. New patients should be screened for RET point mutations and pheochromocytoma.

Medullary thyroid carcinoma (MTC) is sporadic (70 percent) or familial (30 percent), which occurs as MEN IIA and MEN IIB syndrome. *MEN IIA* consists of MTC, pheochromocytoma or medullary hyperplasia, and hyperparathyroidism. C-cell hyperplasia is present in all. Bilateral pheochromocytomas are detectable in 50 percent. Patients may have Hirshsprung's disease and cutaneous amyloidosis.

MEN IIB patients are found with MTC, bilateral pheochromocytomas, and mucosal ganglioneuromas. Patients display a thickened tongue and lips. Marfanoid features, slipped epiphyses, and pectus excavatum also may occur.

Treatment Total thyroidectomy is the treatment of choice because of the high incidence of multicentricity and more aggressive course. More than 60 percent have positive nodes. Neck dissection is necessary if nodes are involved or for tumors larger than 2 cm. Debulking ameliorates APUD effects. Pheochromocytomas should be operated on before thyroidectomy; laparoscopic removal is favored. Abnormal parathyroids are removed; normal parathyroid should be preserved. When a normal parathyroid cannot be maintained on a vascular pedicle, it should be removed and then autotransplanted to the nondominant forearm.

Postoperative Follow-Up and Prognosis Patients should have periodic examinations with levels of serum calcitonin and CEA monitored. For suspected recurrence, CT, MRI of the neck and mediastinum, ultrasound, and selective venous catheterization can be used, as well as hepatic vein and jugular sampling after pentagastrin stimulation. Survival is 80 percent at 10 years and 45 percent with nodal metastases. With positive genetic screening, prophylactic thyroidectomy for C-cell hyperplasia is performed before age 5 years to prevent MTC.

ANAPLASTIC CARCINOMA

This is the most aggressive of thyroid cancers. Few survive 6 months after diagnosis. Most anaplastic carcinomas arise from differentiated cancers during the seventh and eighth decades.

Pathology Growth is extremely rapid. Tumors are unencapsulated with invasion of surrounding tissues. Sheets of cells are seen with marked heterogeneity. Cells may be spindle-shaped, polygonal, or multinucleated giant cells.

Clinical Manifestations Long-term masses enlarge rapidly and become painful. Dysphonia, dysphagia, and dyspnea are common. The mass is hard and fixed. Diagnosis is by FNAC.

Treatment All forms of treatment are disappointing. A combination of radiation therapy with doxorubicin and debulking may have some effect.

LYMPHOMA

One percent of thyroid malignancies are lymphomas. Diagnosis is by FNAC with biopsy for definitive diagnosis, if necessary. Patients usually respond rapidly to chemotherapy; a combined treatment with radiation therapy and chemotherapy often is recommended. Thyroidectomy and nodal resection are used to alleviate symptoms of airway obstruction in those who do not respond quickly to initial treatment.

METASTATIC CARCINOMA

Between 2 and 4 percent of patients dying of malignant disease have metastases in the thyroid. Kidney, lung, breast, and melanoma are the most likely sources.

Surgery of the Thyroid

Operative Technique Endotracheal anesthesia is used. The neck is extended. An equilateral low collar incision is made in a skin crease. The upper flap is raised to the upper border of the thyroid cartilage. The lower flap is mobilized to the suprasternal notch. The cervical fascia is incised in the midline. The sternothyroid and sternohyoid muscles are retracted or, if the gland is large, divided. This lobe is rotated medially, and the middle thyroid veins are divided. The cricothyroid space is opened. The external branch of the superior laryngeal nerve to the inferior pharyngeal constrictor and cricothyroid muscles is identified and preserved. Upper pole vessels are ligated separately, close to the lobe. The lobe is retracted medially, and branches of the inferior thyroid artery are ligated and divided near the capsule to preserve blood supply to the parathyroids. The recurrent laryngeal nerve is unroofed gently. In the operation for Graves' disease, 2–4 g of posterior thyroid tissue is left and secured to the lateral tracheal fascia, or the lobe may be removed totally. Parathyroids should be identified and preserved with their blood supply or autotransplanted. The isthmus is separated from the anterior trachea leaving no remnant. The wound is closed in layers.

Intrathoracic goiter usually represents an extension of cervical thyroid tissue into the chest, which usually can be removed through a cervical incision. Occasionally, transsternal resection is necessary.

Complications Mortality is very low; serious morbidity occurs in less than 2 percent.

Recurrent Laryngeal Nerve Injury This is relatively uncommon (1 percent of thyroid operations). It is more likely with large, invasive, or recurrent tumors. It may be temporary (6–12 months) or permanent. With abductor laryngeal palsy, the vocal cord assumes a medial position. The voice is husky and hoarse. Bilateral vocal cord paralysis can compromise the airway. It is wise to evaluate vocal cord function preoperatively.

Hypoparathyroidism This occurs 0.5–2 percent of patients. The incidence varies with size and invasion of the tumor, pathology, extent of the procedure, and experience of the surgeon. It rarely results from removal of all glands. Hypoparathyroidism results from parathyroid ischemia as a consequence of disruption of the blood supply. Risk can be minimized by dissection along the thyroid capsule and gently teasing the parathyroid gland on a broad plane of tissue away from the thyroid gland in a posterolateral direction. Devascularized gland may be minced and implanted in pockets in the sternomastoid or the arm.

Hypoparathyroidism is manifest within days of operation with signs of circumoral numbness, tingling of fingertips, and anxiety. Chvostek sign occurs early, followed by Trousseau's sign and carpopedal spasm. This may lead to tetany. The serum calcium level is reduced, and the phosphorus level is increased. Symptoms may be transient and resolve in a few days or be permanent.

Treatment is with 1 g calcium by mouth every 4 h. If calcium remains low, intravenous calcium (1–10 ampules of calcium gluconate) is given over several hours. For permanent hypoparathyroidism, vitamin D (Rocaltrol 0.25–1.0 μg/d) is given in addition to calcium.

Postoperative Management of Differentiated Thyroid Cancer Postoperatively, patients should be placed on thyroxine as replacement hormone and to suppress TSH. Thyroglobulin levels in patients who have undergone total thyroidectomy should be below 2 ng/dL when the patient is taking thyroxine and below 3 ng/mL when the patients is not taking thyroxine. A thyroglobulin level above 3 ng/mL is highly suggestive of metastatic disease.

Radioiodine Therapy Metastatic differentiated thyroid cancer can be detected and treated by RAI in 75 percent of patients. Treatment is facilitated by removal of all normal thyroid tissue, which effectively competes for uptake of iodine. Thyroxine replacement should be withheld long enough for TSH to rise. A

screening dose of 2 mCi ^{131}I is administered, and the uptake is measured at 24 h. Hot spots are treated with a larger dose; then thyroxine is restarted. The maximum lifetime dose is 1000 mCi.

External-beam radiotherapy occasionally is required to control unresectable disease. Taxol has been reported recently to have some value.

PARATHYROID

Anatomy

The superior parathyroid glands arise from the fourth branchial pouch with ultimobranchial bodies so as to remain close to the posterior portion of the upper thyroid lobes near the cricothyroid membrane entrance of the recurrent laryngeal nerve. When enlarged, they descend into or along the tracheoesophageal groove and stay in a posterior plane; they may be found in the posterior or middle mediastinum. The inferior parathyroids arise from the third branchial pouch with the thymus. Ectopic sites are more common and more widely distributed; these sites range from an intrathymic gland in the anterosuperior mediastinum to an undescended interior parathyroid gland located superior to the superior parathyroid gland. Inferior parathyroids are found most commonly within 2 cm of the lower pole of the thyroid (60 percent). Most of the remainder are found in the thymic tongue. A normal parathyroid usually weighs less than 50 mg and measures $3 \times 3 \times 3$ mm. They are browner than fat and opalescent.

Pathology

Primary hyperparathyroidism is due to parathyroid adenomas (90 percent), hyperplasia, or rarely, carcinoma. Double adenomas occur in 2 percent. Hyperplasia occurs in 8 percent with sporadic disease and is almost universal in familial disease. Hyperplasia is seldom symmetric. Normal glands primarily contain chief cells with occasional oxyphil cells. Adenoma is composed of sheets of either or both. Macroscopic appearance is the most accurate means of identifying parathyroid pathology.

Physiology of Calcium Homeostasis

Parathyroid Hormone (PTH) PTH is a single-chain polypeptide. The *N*-terminal portion is biologically active with a half-life 2 min. The hormone increases osteoclast and osteoblast activity. It increases the rate of production of the active form of vitamin D,

which increases absorption of calcium from the gut. There is increased excretion of bicarbonate and of phosphate by the kidney, lowering the serum phosphate level.

Calcium Calcium is the principal regulator of PTH release through receptors on parathyroid cells. Calcium is essential for most physiologic functions. The body contains about 1000 g calcium. Total calcium level must be considered in its relationship to plasma protein levels.

Vitamin D Vitamin D is vital to calcium hemostasis. Vitamin D is absorbed from the GI tract and synthesized in the skin. It is converted by the liver to 25-hydroxycholecalciferol, which is converted to its active form (1,25-dihydroxycholecalciferol) in the kidneys. Vitamin D_3 increases absorption of calcium and promotes phosphate retention; it elevates serum calcium and phosphate levels and enhances the mineralization of bone. In the presence of PTH, when serum calcium and phosphorus levels are low, synthesis of 1,25-$(OH)_2$ D_3 is increased. This mechanism is feedback controlled.

Primary Hyperparathyroidism (PTH)

Hypercalcemia is a result of overproduction of PTH by one or more parathyroid glands. It occurs in 1 in 700 persons (the female-to-male ratio is 3:1) and 1 in 200 postmenopausal women.

Etiology The exact cause is unknown. Typically, it is caused by benign enlargement of one (90 percent) or two (2 percent) parathyroid glands; the condition is referred to as *benign adenoma(s).* Multigland enlargement accounts for 8 percent. Parathyroid carcinoma is a rare cause (<1 percent).

Clinical Manifestations Before serum calcium levels were measured routinely, patients typically presented with renal stones (64 percent), bone disease (20 percent), peptic ulcer (12 percent), and hypertension (4 percent). After successful surgical management, nearly all patients realize that they had been symptomatic.

Evaluation Diagnosis is commonly one of exclusion. Differential diagnosis includes a history of the use of thiazide diuretics, lithium, excessive vitamin A or D, extraordinary amounts of milk or antacids (milk-alkali syndrome), granulomatous disease (sarcoidosis, tuberculosis, histoplasmosis, etc.), malignancy (renal cell carcinoma, multiple myeloma, squamous or small cell lung cancer that can

produce a parathyroid hormone-like polypeptide), and metastatic malignancy (commonly prostate or breast). A family history of MEN or benign familial hypocalciuric hypercalcemia (low urinary calcium excretion) may be an indication. Physical examination rarely is helpful (neck mass, voice abnormality, or hoarseness could indicate parathyroid cancer). Adenomas, regardless of size, rarely are palpable. A single serum calcium determination is cost-effective and sufficient. Diagnosis is virtually certain if PTH is inappropriately high; it should be near zero. Serum phosphorous level should be low.

Imaging Radiologic studies are unnecessary unless previous neck operations have been undertaken. With reoperation, in those in whom dissection is more hazardous, ultrasound of the neck with FNAC of any suspicious cervical mass is useful. If equivocal, technetium-99m sestamibi scanning has great sensitivity in identifying missed parathyroid tissue. CT, MRI, and venous sampling are expensive and less accurate.

Treatment The indication for surgical intervention is the diagnosis of primary hyperparathyroidism. Expected success rate is 98 percent, and there is negligible mortality and minimal morbidity. For recurrent or persistent hyperparathyroidism, repeat exploration is indicated if the offending gland is localized in imaging studies. Expected success rate is 90 percent. For a solitary adenoma, excision without biopsy of the other glands is sufficient. Double adenomas should both be removed. For multigland hyperplasia, three and one-half gland parathyroidectomy or total parathyroidectomy with reimplantation of 50 mg in the neck or forearm is an option. Normocalcemia within 24–72 h can be expected. Transient hypocalcemia is common; the cause is bone hunger (low serum phosphate and normal PTH levels) or hypoparathyroidism (elevated phosphate and abnormally low PTH levels). Hospitalization is overnight while calcium levels are checked and stabilized before discharge. Calcium is checked at 1–2 months and then yearly.

Technique A 10-cm collar incision 2 fingerbreadths above the sternal notch is made. The operative technique should be gentle and unhurried with a bloodless field. The strap muscles are retracted or divided, and the thyroid is elevated anteriorly, superiorly, and then medially. Superior parathyroids usually are found close to the posterolateral aspect of the upper pole. Takedown of the upper pole seldom is necessary. Inferior glands are intimately involved with the lower pole and the thyrothymic tongue of fat that extends inferiorly toward the mediastinum. They are often subscapular. Glands

may be found as high as the angle of the mandible or as low as in thymus, in the anterior mediastinum, or in the aortopulmonary window in the posterior mediastinum. If the superior gland is not found, the tracheoesophageal groove below the inferior artery and lower gland should be investigated. Other possible sites are in the thymus, buried within the thyroid, in the carotid sheath, or lateral to the carotid sheath. Bilateral exploration is recommended.

PERSISTENT AND RECURRENT HYPERPARATHYROIDISM (FIG. 36-1)

An improperly performed primary operation is the cause for the majority of patients with persistent (elevated serum calcium levels that do not return to normal after surgery) or recurrent hyperparathyroidism. The possibility of benign familial hypocalciuric hypercalcemia in which 24-h urine calcium excretion is less than 100 mg must be excluded. Reoperative cure rates of 80–90 percent are reported. Postoperative recurrent laryngeal nerve palsy or permanent hypoparathyroidism occurs in 3–5 percent. Nonoperative alternatives (angiographic embolization or, preferably, ultrasound-guided alcohol ablation) should be considered. The surgeon should review the prior operative report, and the pathologist should review previously excised tissue. The radiologist should be consulted about localizing with technetium-99m sestamibi and ultrasound (with FNAC). Localization allows focused exploration (unilateral or lateral cervical approach, thoracoscopy, or mediastinal exploration). If all localizing modalities are negative, blind exploration should not be performed.

Secondary Hyperparathyroidism

This is uncommon. There is appropriate parathyroid hyperplasia with elevation of PTH secretion in patients with chronic renal failure causing hyperphosphatemia and decreased vitamin D production with calcium maintained in normal range or intestinal malabsorption (calcium and vitamin D absorption diminished to the point of hypocalcemia).

Clinical Manifestations Symptoms include bone pain or fractures, renal osteodystrophy or soft-tissue calcifications (calciphylaxis), and pruritus.

Treatment Treatment is nonsurgical dietary restriction of phosphate and oral phosphate binders, oral calcium, and vitamin D. Surgery is performed for hyperplasia involving all glands and uncontrollable symptoms.

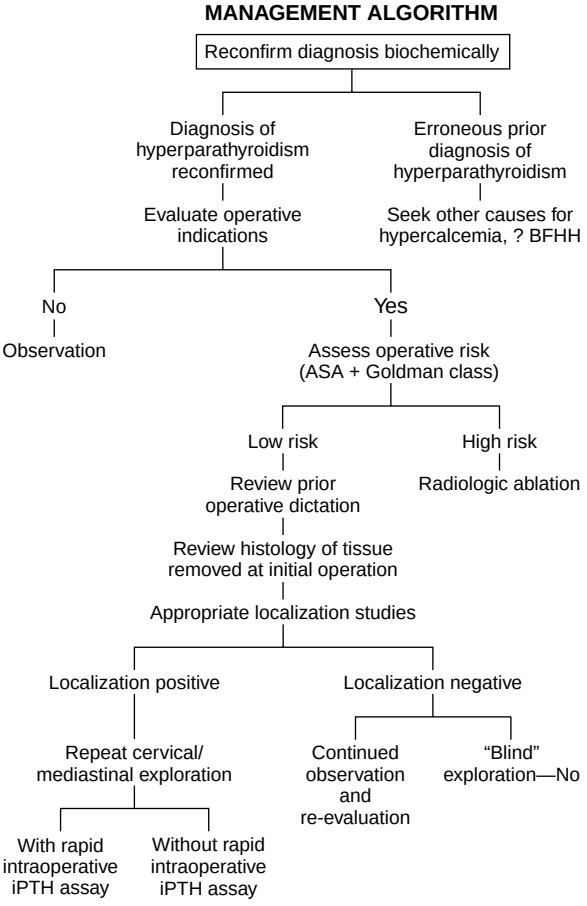

FIGURE 36-1 Algorithm of the approach to the patient with persistent/recurrent hyperparathyroidism.

Tertiary Hyperparathyroidism

This is the continuation of secondary hyperparathyroidism. PTH secretion becomes autonomous, and the serum calcium level becomes elevated. It is observed most commonly in patients with long-standing renal dysfunction who undergo renal transplantation. With restored renal function, PTH levels usually return to normal. Surgery is indicated for persistent disease.

Multiple Endochrine Neoplasia and Hyperparathyroidism

Multiple endocrine neoplasia (MEN) has an autosomal dominant pattern of inheritance. The hallmark is multicentricity and bilaterality.

MEN type I includes pituitary (15–50 percent), parathyroid (100 percent), or pancreatic (30–80 percent) neoplasms. MEN type IIA (Sipple's syndrome) includes C-cell hyperplasia and, subsequently, medullary thyroid carcinoma if total thyroidectomy is not done prophylactically, adrenal medullary hyperplasia/pheochromocytoma (50 percent), and parathyroid abnormality (10–25 percent). MEN type IIB patients can develop medullary thyroid cancer and adrenal neoplasms with marfanoid habitus and mucosal neuromas. Parathyroid chief cell hyperplasia is uncommon. Malignancy shortens life if prophylaxis is not undertaken.

Clinical Manifestations Seventy-five percent of patients have a family history of endocrine abnormalities. With time patients present with visual changes, kidney stones, ulcer pain or diabetes (MEN I), neck masses and hypertension (MEN IIA), or buccal and lingual nodules, hypertension, neck masses, and marfanoid habitus (MEN IIB). Patients should have serologic surveillance of appropriate markers.

Testing for the RET proto-oncogene is indicated for those with a family history of medullary cancer, and prophylactic thyroidectomy is performed if the history is positive. Parathyroid surgery is performed to prevent the ravages of primary hyperparathyroidism. It is not uncommon for these patients to have 5–6 parathyroid glands. Exploration should be thorough and should include transcervical thymectomy. Treatment includes removal of all but 50 mg parathyroid tissue or total parathyroidectomy with autotransplant of heterotopic tissue.

Hypercalcemic Crisis

This life-threatening systemic condition is accompanied by an elevation of serum calcium to 13 mg/dL or higher. Symptoms vary from neuromuscular changes with mild fatigue and irritability to

coma. Dehydration is common. GI manifestations include anorexia, nausea, vomiting, and weight loss. Cardiac dysrhythmias may be lethal. Cancer cachexia may be evident with skeletal metastases. A palpable neck mass with hypercalcemic crisis is parathyroid carcinoma until proved otherwise. Differential diagnosis includes all causes of hypercalcemia. Ninety percent of patients will either have advanced malignancy or hyperparathyroidism.

Treatment Intravenous saline is advanced to achieve a diuresis of 100 mL/h or higher. About 4–5 L is required to overcome dehydration. Once hydrated, the patient should receive loop diuretics to stimulate natruresis and subsequent calciuresis. Cardiac dysrhythmias are treated with standard agents. When hypercalcemia persists, treatment with mithramycin, phosphate binders, vitamin D, estrogen, calcitonin, or steroids may help. Vocal cord function should be checked. Ultrasound may identify a large adenoma and allow focused exploration. Even with coma or hemodynamic instability, operation should not be delayed.

Parathyroid Carcinoma

This occurs in less than 1 percent of cases of hyperparathyroidism.

Preoperative Findings Findings are (1) palpable neck mass, (2) markedly abnormal biochemistry, calcium usually higher than 13 mg/dL, PTH elevated tenfold, and alkaline phosphatase elevated threefold, and (3) complications of hyperparathyroidism.

Intraoperative Findings There is evidence of a parathyroid mass, which is firmer than the usual. The gland is not the normal bean-shaped kidney color but irregular, pale white, and adherent to surrounding structures.

Pathology Most masses weigh more than 2 g and are composed of a thick fibrous capsule, with fibrous septa interdigitating throughout the tumor, and enlargement, hyperchromasia, and variation in nuclear size are seen. Capsular and local tissue invasion usually is found.

Treatment En bloc resection of the tumor and involved surrounding structures is performed, usually by thyroid lobectomy. If lymph nodes are involved, appropriate resection is needed. Radiation and chemotherapy are of limited usefulness. Symptomatic hypercalcemia is treated with mithramycin and biophosphonates. Recurrence is at least 66 percent. Surgical debulking may be needed

to control hypercalcemia. Five-year survival is 69 percent. Death often is related to the consequences of hypercalcemia.

For a more detailed discussion, see Sadler GP, Clark OH, van Heerden JA, and Farley DR: Thyroid and Parathyroid, chap. 36 in *Principles of Surgery,* 7th ed.

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CHAPTER

37

PEDIATRIC SURGERY

GENERAL CONSIDERATIONS

Fluid and Electrolyte Balance Initial intravenous fluids in a newborn should consist of 10% dextrose and water with a volume of 65–100 mL/kg/day. After the first 10 days of life, maintenance fluid is 100 mL/kg/day, and the solution should consist of 5% dextrose and quarter-normal saline. Daily potassium needs are met by 2 mEq/kg potassium chloride. Additional fluid losses are replaced with an equal volume of fluid containing electrolytes equivalent to those lost. Maintenance fluid requirement for children weighing more than 10 kg consists of 50 mL/kg for the next 10 kg and 25 mL/kg thereafter. Hyperosmotic fluids may cause intracranial hemorrhage in the neonate and should be used with extreme caution.

Acid-Base Equilibrium Arterial blood gases permit monitoring of the alveolar ventilation and acid-base equilibrium. Acute metabolic acidosis implies inadequate tissue perfusion, and its etiology must be investigated. A rising PCO_2 usually indicates the need for assisted ventilation, and a falling PaO2 may indicate compromised ventilation-perfusion secondary to parenchymal disease or a right-to-left shunt. In addition, the respiratory or metabolic nature of the imbalance is determined. Correction is made by adjusting ventilation and the possible infusion of sodium bicarbonate.

Blood Volume and Blood Replacement The estimated blood volume of the newborn is 85 mL/kg of body weight. However, the premature infant has a relatively larger blood volume than does the full-term infant. The transfusion requirement of packed red blood cells is 10 mL/kg. The use of fresh frozen plasma (20 mL/kg) and platelet transfusions (1 unit/5 kg) should be considered when transfusion exceeds 30 mL/kg.

Hyperalimentation and Nutrition Parenteral hyperalimentation will meet caloric needs for growth and recovery from illness if the

alimentary tract cannot. Protein, carbohydrate, and fat, plus minerals and vitamins, may be administered by either a central or a peripheral intravenous route. The latter carries less risk. (The former is used when peripheral access no longer exists or the infusate is highly concentrated.) Prolonged hyperalimentation may lead to intrahepatic cholestasis. Jaundice and cirrhosis may develop, which can be irreversible and lead to death of the infant. Enteral nutrition continues to be the preferred route.

Venous Access Most infants requiring short-term intravenous medications and nutrition can be managed by peripheral intravenous catheter placement. For long-term access, Silastic central venous catheters are used. Catheters may be inserted by cutdown (external jugular vein, facial vein, or proximal saphenous vein) or percutaneously (subclavian or internal jugular veins). Chest x-ray confirms central location. Catheter-related sepsis occurs in about 10 percent of patients.

Thermoregulation Cold stresses the infant because of impaired thermogenesis and causes increased glucose and oxygen requirements to meet metabolic needs. The use of overhead radiant warmers regulated by servo controls and the appropriate wrapping of infants during transport and surgery will help protect the infant.

Pain Control It is now generally accepted that all children, including neonates, experience pain after surgery. Proper doses of intravenous narcotics should not cause respiratory depression. Different methods of pain control have been shown to be effective in infants and children, and these include patient-controlled analgesia (PCA), epidural catheters, and caudal blocks. Regional blocks such as those given for hernia repairs appear to be effective.

LESIONS OF THE NECK

Cystic Hygroma (Lymphangioma)

Etiology and Pathology The lesion results from sequestration or obstruction of lymphatic vessels most frequently in the posterior triangle of the neck, axilla, groin, and mediastinum. Adjacent tissues may show lymphatic infiltration and also nests of vascular tissue. Lesions at the thoracic inlet may cause airway obstruction. Sudden enlargement due to infection caused by streptococcal or staphylococcal organisms also may cause airway obstruction. These

may be detected by prenatal ultrasound and are associated with abnormal karyotypes and hydrops fetalis.

Treatment Total excision is the treatment of choice. Radical excision is avoided in this benign lesion. Needle aspiration is worthless because of lack of communication between the cysts. Injection by sclerosing agents has not proved effective.

Thyroglossal Duct Remnants

Pathology and Clinical Manifestations The thyroglossal duct descends from the foramen cecum in conjunction with the development of the hyoid bone. Remnants from the duct will develop into a cyst, which may become apparent at about age 2–4 years. The cyst is located in the midline, over or inferior to the hyoid bone, and moves with swallowing. Occasionally the cyst may become infected, but this usually clears with penicillin therapy. The differential diagnosis includes lymphadenopathy, a dermoid cyst, or rarely, ectopic thyroid.

Treatment Infection should be controlled first with drainage and antibiotics. Total excision involves removal of the cyst, the central portion of the hyoid bone, and the tract to the foramen cecum (the Sistrunk procedure).

Branchial Cleft Anomalies

Branchial cleft sinuses and cysts represent remnants from embryologic structures. The most common are from the second branchial cleft. Complete sinuses extend from a fistulous opening in the skin anterior to the sternocleidomastoid muscle and pass superiorly through the bifurcation of the carotid artery to enter into the pharynx anterior and inferior to the tonsillar fossa. Other remnants may contain cartilage. Sinuses drain a mucoid material and occasionally may become infected. Total excision is necessary to prevent recurrence.

Torticollis

Fibrosis of the sternocleidomastoid muscle shortens the muscle, rotating the head to the contralateral side. About 20 percent require surgical transection of the muscle, but most resolve spontaneously or respond to physical therapy.

RESPIRATORY SYSTEM

Congenital Diaphragmatic Hernia (Bochdalek)

Pathology The pleuroperitoneal canal in the posterolateral portion of the hemidiaphragm is the last portion to close during embryonic development. The bowel returning from the umbilical cord to the abdominal cavity herniates into the chest when the canal fails to close. This usually involves the left side of the chest. The result is failure of development of the lung on the ipsilateral side by the encroaching intestine and on the contralateral side by the mediastinal shift. The abdomen is scaphoid, and the heart tones are shifted away from the side of herniation. A chest radiograph reveals gas-filled loops of bowel in the chest. An antenatal ultrasound will demonstrate the lesion. Symptoms at birth are respiratory distress and cyanosis. The underlying pathophysiology is increased pulmonary vascular resistance and pulmonary artery hypertension, which can lead to a persistent fetal circulation with a right-to-left shunt.

Treatment Surgical closure via the abdomen is accomplished after the infant is stabilized by endotracheal intubation and ventilation. Sodium bicarbonate may be given intravenously once the PCO_2 is reduced to further correct a metabolic acidosis. At operation, the posterior rim of the diaphragm must be dissected from overlying peritoneum, and a two-layer closure is achieved. Rarely, insufficient diaphragm exists, and a synthetic patch is necessary for closure. The need for a patch or the inability to achieve a PaO_2 greater than 100 mmHg and a PCO_2 less than 40 mmHg after correction is a bad prognosis. Pulmonary vasodilators have little therapeutic effect. The use of high-frequency ventilation and extracorporeal membrane oxygenation (ECMO) has resulted in increased survival of these severely compromised infants. These may be used preoperatively and occasionally continued intraoperatively.

Congenital Lobar Emphysema

The right middle and upper lobes and the left upper lobe are the most frequently involved. Sudden expansion of the involved lobe can lead to respiratory distress and cyanosis because of compression of the remaining lung. Emergent surgical excision of the involved lobe may be needed to relieve the distress. Lobar emphysema developing more slowly may resolve gradually, and judicious observation is warranted. Cardiac anomalies may coexist. It is

caused by intrinsic bronchial obstruction from poor cartilage development.

Congenital Adenomatoid Malformation

This is frequently confused with a diaphragmatic hernia because of the cystic proliferation of the terminal airways, most frequently located in the left lower lobe. This results in an expanding lesion that by chest radiography may have a similar appearance to a congenital diaphragmatic hernia. Treatment is an urgent resection done through a thoracotomy on the affected side and is curative.

Pulmonary Sequestration

This lesion consists of a mass of nonfunctioning lung tissue usually in or adjacent to the left lower lobe. There is no bronchial communication to the respiratory tree, and the arterial supply is usually systemic, frequently coming from the aorta below the diaphragm. The condition is revealed as a shadow on the chest radiograph. Air may be seen in the intralobar variety if there is communication with adjacent lung alveoli. The latter may present clinically with cough, hemoptysis, and recurrent pulmonary infections. These are classified as extralobular or intralobular depending on their location.

Bronchogenic Cysts

These can present at any age and occur anywhere along the respiratory tract. Treatment is resection and may be needed emergently if airway compression occurs. Histologically, the cysts are hamartomatous lesions, usually a single cyst lined with respiratory epithelium with cartilage and smooth muscle.

Bronchiectasis

Bronchiectasis is an abnormal dilatation of the bronchi and bronchioles associated with chronic infection. This is usually associated with an underlying congenital pulmonary anomaly, cystic fibrosis, a foreign body, or immunodeficiency. Symptoms include chronic cough, purulent secretions, recurrent pulmonary infections, and hemoptysis. The diagnosis is made by computed tomography (CT). Treatment is medical, with antibiotic therapy and postural drainage. Lobectomy is indicated for localized disease not responding to medical management.

Foreign Bodies

Airway These are found most frequently in the airways of toddlers. Peanuts or small parts of toys may be aspirated, and the child presents with cough and unilateral wheezing. A radiograph of the chest will show atelectasis of the involved lobe and the foreign body if it is radiopaque. Occasionally, a clinical diagnosis of asthma eventually will be found to be caused by an unrecognized foreign body in the airway. Bronchoscopy and extraction of the body are the treatment.

Esophagus Swallowed coins are the most common foreign body to lodge in the esophagus. The most frequent locations for foreign bodies to become trapped are the cricopharyngeus, the aortic arch, and the gastroesophageal junction. Symptoms vary from an inability to swallow saliva to respiratory distress because of tracheal compression. Treatment is esophagoscopy and removal of the foreign body. Occasionally, foreign bodies are advanced to the stomach, where one would expect them to pass through the rest of the gastrointestinal tract without difficulty.

ESOPHAGUS

Tracheoesophageal Fistula and Esophageal Atresia

Clinical Manifestations Between 85 and 90 percent of these lesions are made of a blind upper pouch with a tracheal communication to the lower esophagus (Fig. 37-1). An isolated tracheoesophageal fistula occurs in 2–4 percent of such children. There are frequently associated congenital anomalies that affect the outcome. Imperforate anus and/or congenital cardiac disease occurs in 10–12 percent of these infants. Excess salivation and attempted feedings result in choking and cyanosis. The diagnosis is made by the inability to pass a Replogle tube into the stomach. Instillation of air will prove the diagnosis on a chest x-ray. A radiograph of the infant will reveal air in the intestinal tract if a fistula coexists.

Treatment Sump suction via the Replogle tube is applied to the upper pouch, and broad-spectrum antibiotics are begun.

Primary Surgical Correction The operation is performed via a posterolateral thoracotomy using a retropleural approach. The fis-

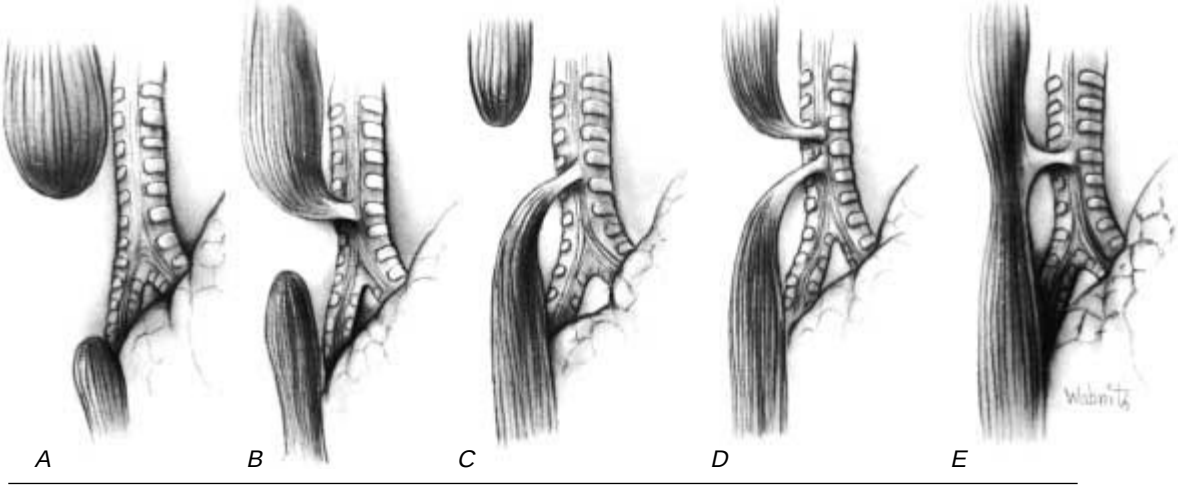


FIGURE 37-1 Five major varieties of esopageal atresia and tracheoesophageal fistula. *A.* Esophageal atresia without associated fistula. *B.* Esophageal atresia with tracheoesophageal fistula between proximal segment of esophagus and trachea. *C.* Esophageal atresia with tracheoesophageal fistula between distal esophagus and trachea. *D.* Esophageal atresia with fistula between both proximal and distal ends of esophagus and trachea. *E.* Tracheoesophageal fistula without esophageal atresia (H-type fistula).

tula is ligated and transected at the trachea. The esophagus is repaired using a single-layer anastomosis.

Delayed or Staged Repair For infants that are extremely premature or have serious coexisting anomalies, a gastrostomy is placed and repair delayed. Once the infant has been stabilized, pulmonary infection cleared, and other anomalies assessed, total correction should be performed. If the gap is too great to anastomose the two ends, additional length in the upper pouch may be achieved by a circular myotomy. A colon interposition can bridge a gap too long to permit a primary anastomosis. This is performed as a delayed procedure when the child is larger and has greater reserve.

Postoperative Complications Anastomotic leaks are not infrequent, and most heal spontaneously. Between 10 and 20 percent develop strictures that usually present as choking and gagging. A contrast esophagogram is confirmatory, and simple dilatation is corrective. Gastroesophageal reflux is common. Most children respond favorably to medical management, but about a third require an antireflux procedure.

Esophageal Atresia (Associated Abnormalities)

There are several associated abnormalities known to occur with esophageal atresia. These have come to be known as the VATER syndrome. This is to remind one that the *V* stands for vertebral abnormalities and also the fact the most common cardiac abnormality is the ventricular septal defect (VSD). The *A* stands for the atresias, especially imperforate anus or duodenal atresias. The *TE* stands for tracheal and esophageal abnormalities. This should serve to remind one that if one is faced with a child with an imperforate anus, the child should be checked for esophageal and tracheal abnormalities. The *R* stands for abnormalities of the renal system and also to remind one that there can be abnormalities of the radial aspect of the forearms.

ISOLATED ESOPHAGEAL ATRESIA

This is diagnosed by a plain film demonstrating a nasogastric tube coiled in the blind upper pouch and no air in the intestinal tract. A cervical esophagostomy may be performed, and a feeding gastrostomy will permit feeding the infant. When the child is older, the defect is bridged by a colon interposition or a reversed gastric tube.

ISOLATED (H-TYPE) TRACHEOESOPHAGEAL FISTULA

The symptoms may be delayed and confusing. There is usually choking on feeding, especially with liquids. Gaseous abdominal distention develops, and frequently there is a history of repeated aspiration pneumonia. The diagnosis is made by a careful contrast study via the esophagus or, more safely, by bronchoesophagoscopy. Surgical division of the fistula, usually through the neck, is curative.

LARYNGOTRACHEOESOPHAGEAL CLEFT

This rare anomaly is frequently present in association with esophageal atresia. It is another type of an abnormal separation of the trachea from the esophagus. In this situation, there is an open cleft from the larynx to the vocal cords and occasionally extending down to the carina. Surgical correction, while certainly possible, frequently requires a tracheostomy, gastrostomy, and extensive surgical intervention.

Corrosive Injury of the Esophagus

This type of injury is caused by ingestion of strong alkaline or acid substances. All children suspected of swallowing a corrosive agent should have esophagoscopy within 24 h of the injury. The scope is passed only to the first evidence of injury; further insertion may lead to perforation of the injured esophagus. If the injury is circumferential, a string is passed for future guidance during dilatations, and a gastrostomy is performed. Steroids are generally not used. Antibiotics are administered for 3 weeks. Dilatation is started after 3 weeks and continued as needed until any stricture has resolved.

Esophageal Substitution

There are two indications for this procedure: unrelenting stricture of the esophagus and a large defect in esophageal atresia. The connection is achieved with either colon based on the middle colic vessels or a reversed gastric tube fashioned from the greater curvature of the stomach or a free jejunal graft. The conduits are usually placed in the native esophageal bed but can be brought up behind the lung root in the left chest or substernally.

Gastroesophageal Reflux (GER)

GER occurs to some degree in all children. However, it is pathologic when children manifest failure to thrive, esophagitis, esophageal stricture, or repeated aspiration pneumonias.

Clinical Manifestations These children usually have a history of repeated vomiting. There may be symptoms of asthma. Esophagitis can lead to chronic blood loss and anemia. A barium swallow will reveal the anatomy of the esophagus but may not reveal reflux. A pH probe placed in the distal esophagus should reveal the reflux. Esophagoscopy and biopsy may reveal esophagitis.

Treatment Most children respond to medical therapy, propping, and thickened feedings. Drugs such as ranitidine (an H_2 blocker) or cisapride (a prokinetic agent) may relieve the reflux. If medical therapy fails and the reflux is life-threatening or causing esophagitis and stricture, surgical correction is indicated. The most frequently used procedures are the complete (Nissen) or partial (Thal) fundic wrap around the distal esophagus.

GASTROINTESTINAL TRACT

Pyloric Stenosis

Clinical Manifestations Vomiting, progressing to explosive (projectile), begins after the first 2–3 weeks of life. The vomitus is nonbilious. Most infants are males, and the disease is hereditary, although penetrance is low. A metabolic alkalosis develops with depressed serum chloride and potassium levels and an elevated sodium bicarbonate level. Most tumors are palpable in the right upper quadrant and may be demonstrated by ultrasonography or a contrast study.

Treatment Metabolic alkalosis is corrected by intravenous 5% dextrose and half-normal saline with 30 mEq/L of potassium chloride at two times maintenance until the urine specific gravity is less than 1.010, the chloride level is greater than 95 mEq/L, and the bicarbonate is less than 30 mEq/L. A Fredet-Ramstedt pyloromyotomy is then performed. Before operation, a nasogastric tube is passed to empty the stomach and prevent vomiting during induction of anesthesia. Small, frequent feedings of an electrolyte solution are begun 4 h after operation; the volume is gradually increased to maintenance, and then formula is given. Discharge is usually 24–36 h postoperatively.

Intestinal Obstruction in the Newborn

Bilious vomiting in the newborn means intestinal obstruction until another cause is proved. An abdominal radiograph will help

determine the level of obstruction. If there is a proximal incomplete obstruction, an upper gastrointestinal series is required to diagnose malrotation with possible midgut volvulus. A barium enema is useful to look for malrotation, a microcolon signifying ileal obstruction, colonic atresia, Hirschsprung's disease, meconium ileus, meconium plug, or small left colon syndrome.

DUODENAL MALFORMATIONS

Obstruction may be complete, as in atresia, or partial, as in annular pancreas, stenosis, or bands associated with malrotation. The abdominal radiograph classically shows the "double bubble" of air in a distended stomach and duodenum. Intrinsic obstructions are managed by a side-to-side duodenoduodenotomy. If obstruction is secondary to volvulus from a malrotation, timely surgery is needed to prevent infarction of the midgut secondary to occlusion of the superior mesenteric vessels. Duodenal webs usually contain the common bile duct and must be approached with extreme caution. One-third of all such infants have Down syndrome (trisomy 21).

INTESTINAL ATRESIA

This condition is believed to be due to an antenatal vascular accident or volvulus. There may be simple atresias or loss of considerable amounts of intestine with a deep cleft in the mesentery and resulting short-gut syndrome. Multiple atresias exist in about 10 percent of such patients. A radiograph usually will determine the level of atresia, and a barium enema will detail the rotation of the colon and its caliber. The disparity in caliber of the two atretic ends can be managed by an end-to-oblique anastomosis using a single layer of nonabsorbable sutures. A complementary gastrostomy aids greatly in the management of these children, who may have a prolonged period before enteric function is restored. About 10 percent will have cystic fibrosis. All should have a sweat test. The "apple peel" or "Christmas tree" deformity is a type of jejunal atresia resulting from occlusion of the superior mesenteric artery distal to the middle colic artery. The small bowel distal to the occlusion is short and spirals about a longitudinal vessel supplied by the middle colic and marginal vasculature of the colon.

MALROTATION AND MIDGUT VOLVULUS

During the sixth week of fetal development, the midgut herniates into the umbilical cord and begins its return to the abdominal cavity in the tenth week. During its return, the midgut undergoes a 270-degree counterclockwise rotation around the superior mesenteric artery. This results in the ligament of Treitz being in the left upper quadrant and the cecum in the right lower quadrant. If

this does not occur, peritoneal attachment between the ascending colon and right abdominal wall are elongated and create Ladd bands that are able to obstruct the second portion of the duodenum. The resulting stalklike mesentery containing the superior mesenteric artery results in the potential for a volvulus of the intestine around the superior mesenteric vessels that can result in a midgut strangulation. If this occurs, rapid third-space fluid loss occurs in the midgut. Bilious vomiting, abdominal distention, and resulting abdominal tenderness are pertinent manifestations. Urgent laparotomy is required, with a counterclockwise derotation of the volvulus and division of the peritoneal bands. A Ladd's procedure that results in the duodenojejunal junction being in the right abdominal gutter and the entire colon being on the left side will, it is hoped, create enough adhesions to avoid a recurrence. An incidental appendectomy is also done routinely. If this operation is done emergently, massive resection of ischemic small bowel may be avoided.

MECONIUM ILEUS

Infants born with this condition almost always have cystic fibrosis. Inspissated meconium caused by a lack of pancreatic enzymes and viscid mucus obstructs the distal ileum. The infant presents with late bilious vomiting, palpable loops of bowel with maleable meconium, a low small bowel obstruction on the radiograph, and a microcolon on contrast enema. Antenatal perforation of the intestine will be revealed by calcific densities noted on the abdominal radiograph. Uncomplicated obstruction can be relieved by a detergent in Gastrografin enema with fluoroscopic control. The hyperosmolality of the solution must be diluted to prevent diarrhea and dehydration. Complicated conditions are managed surgically by the creation of temporary ileostomies and irrigation of the obstructed bowel with acetyl cysteine (Mucomyst).

NECROTIZING ENTEROCOLITIS (NEC)

This condition almost exclusively affects the stressed premature infant. There is a breakdown of the mucosal barrier, and endogenous bacteria invade the bowel wall. This causes vomiting, abdominal distention, and bloody stools. Sepsis, metabolic acidosis, and third spacing soon follow. There is a left shift in the white blood cell count, and the platelet count falls. The diagnosis is made by palpation of tender loops of bowel on abdominal examination and demonstration of pneumatosis intestinalis on an abdominal radiograph. Gas also may be noted in the hepatic portal veins.

The disease may be corrected in most infants by medical therapy: decompression of the intestinal tract by a nasogastric tube, giving adequate amounts of intravenous fluids (both electrolyte and

colloid) to restore circulating volume, and the administration of broad-spectrum antibiotics to treat the sepsis. Frequent observation and abdominal radiographic examination are needed to document improvement or progression of the disease, which then requires surgical management. Free air on the abdominal radiograph is a specific indication for surgery. Necrotic bowel is excised and enterostomies fashioned. The latter are closed after the child recovers. Thought may be given to primary anastomosis of the small bowel to prevent the large caustic fluid losses that occur with small bowel fistulas. Postoperative parenteral hyperalimentation is needed to provide adequate calories for healing and continued growth of the infant. Occasionally, intestinal strictures may develop with signs of obstruction in infants recovering on medical management. This condition requires surgical correction.

INTUSSUSCEPTION

This is a common cause of intestinal obstruction in the infant. The usual age range is 3 months to 3 years. The lead point may be a hypertrophied Peyer's patch in the terminal ileum, which then intussuscepts into the cecum and ascending colon. If intussusception occurs in the child over age 5 years, a different cause must be suspected that may include malignant disease. Such lead points include polyps, Meckel's diverticulum, and non-Hodgkin's lymphoma.

Clinical Manifestations The onset is sudden and consists of severe, crampy abdominal pain lasting a minute. There is usually marked pallor, suggesting shock. A period of ease follows, only to have the brief episode of pain recur. Vomiting usually follows, and during a period of relaxation, a soft elongated mass can be felt in the right upper quadrant. The absence of bowel in the right lower quadrant (Dance's sign) may be noted. A bloody mucoid stool may be passed ("currant jelly" stool), and a guaiac test of the smear from a rectal glove is usually positive. A barium enema will reveal the "coiled-spring" appearance of the intussuscepted bowel.

Treatment Air enema is the preferred method of diagnosis and treatment. Air pressure should not exceed 120 mmHg. If successful, air will reflux into the small bowel. The child is hydrated with intravenous fluids and observed for 4–6 h. If all symptoms are relieved, oral fluids are begun and the child is discharged. If reduction is not achieved, it must be accomplished by celiotomy. The intussusceptum is gently milked out of the intussuscipiens by distal pressure until reduction is complete. An incidental appendectomy is usually performed. If the serosa of the intussuscipiens begins to split during reduction, resection of the intussuscepted bowel is

carried out with primary anastomosis. The recurrence rate is about 3 percent for both hydrostatic and operative reduction.

Appendicitis

The incidence of perforation rises as the age of the patient decreases (25 percent of adolescents, 80 percent children less than 5 years of age). Vomiting, right lower quadrant pain and tenderness, and leukocytosis are common findings. Plain abdominal films, sonography, and abdominal CT scans with enteric contrast material may aid in the diagnosis. Definitive management is appendectomy.

DUPLICATIONS, MECKEL'S DIVERTICULUM, AND MESENTERIC CYSTS

Duplications

These may occur anywhere in the intestinal tract but are usually in the ileum. They are usually cystic masses but also may be long tubular structures. They lie in the leaves of the mesentery and share a common wall with the adjacent bowel. They usually present as a palpable, movable mass or as an acute abdomen if torsion and infarction occur. If the duplication communicates with the intestinal tract and contains gastric mucosa, gastrointestinal bleeding may be the presenting sign. Diagnosis is made by sonography or a technetium pertechnetate scan. The lesion should be excised with the adjacent bowel if it is short. Longer lesions may be treated with multiple enterotomies in the duplication with mucosal stripping or the creation of a distal connecting anastomosis if no ectopic gastric mucosa exists.

Meckel's Diverticulum

This is a persistent portion of the omphalomesenteric duct and occurs in about 2 percent of the population 2–3 ft from the ileocecal valve on the antemesenteric border of the ileum. It is usually asymptomatic but may present as appendicitis, intestinal obstruction, or most commonly, intestinal hemorrhage. The latter occurs if there is aberrant gastric mucosa within the diverticulum. The stools are maroon, and the hematocrit drops appreciably. Diagnosis may be made by technetium scan. The treatment is surgical excision.

Mesenteric Cysts

These also lie in the leaves of the mesentery but, unlike duplication cysts, contain no mucosa or muscular wall. They are believed to re-

sult from obstructed lymphatic channels. They present as a palpable, movable mass and may cause intestinal obstruction. The diagnosis is suspected by sonography. Excision is the treatment, and adjacent bowel may need to be resected. If the lesion is large, marsupialization to the peritoneal cavity is indicated.

HIRSCHSPRUNG'S DISEASE

This usually is a disease of male infants and consists of the absence of ganglion cells with hypertrophied nerve fibers in the rectum and sigmoid colon. Longer segments may be involved, and in the long-segment disease, the sex incidence is equal. There is an increased incidence in children with Down syndrome. The aganglionic segment is spastic and causes obstruction. This presents as distal obstruction in the newborn with abdominal distention and vomiting. Occasionally, it may present with diarrhea and toxicity from an enterocolitis that carries a serious mortality rate when fully developed. Chronic constipation with poor nutrition may occur in the older child.

Diagnosis A barium enema usually shows a megacolon in the innervated bowel, and the distal aganglionic colon has a more normal caliber. This may not be apparent during the first 2–3 weeks of life. Definitive diagnosis is made by a biopsy of the distal rectum to search for the presence or absence of ganglion cells. This can be a suction biopsy of the mucosa and submucosa or a full-thickness biopsy of the rectal wall as a surgical procedure.

Treatment Initially, a colostomy is performed through ganglionated bowel (Fig. 37-2). A pull-through procedure is accomplished when the child weighs 10 kg. If the child is older and has a megacolon, pull-through is delayed until the bowel has returned to normal caliber. The colostomy may be closed at the time of the pull-through or as a third stage depending on the surgeon's judgment. The various procedures used are a Swenson, Duhamel, and Soave endorectal pull-through.

IMPERFORATE ANUS

This congenital anomaly occurs equally in both sexes in up to 1 in 5000 births. It results from the failure of normal development of the urorectal septum, which divides the cloaca and separates the urinary from the hindgut systems. The lesion is considered "high" when the rectal pouch ends above the levator ani muscles and "low"

when it ends below. High lesions usually have fistulas to the vagina in the female and to the prostatic urethra in the male. Low lesions usually have fistulas to the perineum or male urethra. There are frequently associated anomalies involving other systems, which is known as the VATER syndrome.

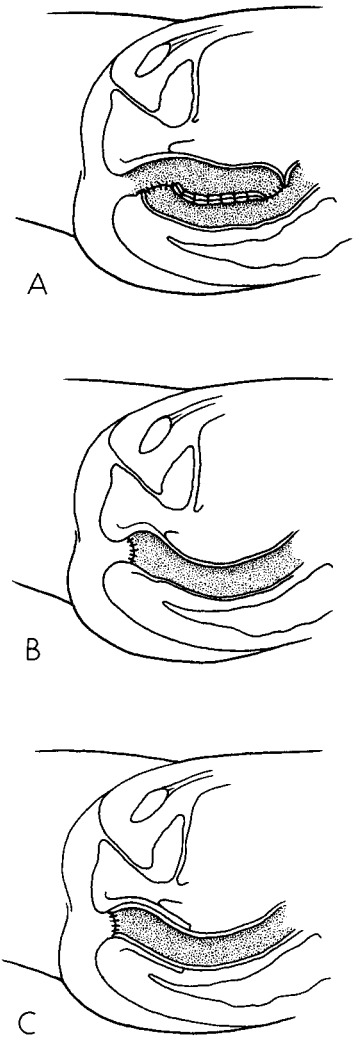
Diagnosis The diagnosis is determined by physical examination. The level is determined either by a fistulogram or by a perineal injection of contrast material into the blind pouch under fluoroscopic control. A cystourethrogram should be performed to look for an associated fistula or ureteral reflux. "Inverted" radiographs are not reliable.

Treatment Initially, a sigmoid colostomy is performed if the lesion is high. If the lesion is low, a perineal proctoplasty may be attempted in the newborn. High lesions are best managed by a posterior sagittal anoproctoplasty, as described by Pena, using a muscle stimulator to identify the anal sphincters, vertical fibers, and the levator ani muscles. The rectum is detached from the fistula without sacrificing any of its distal length and placed precisely through the above muscle complex. The colostomy is closed several months later following complete healing of the pull-through. The caliber of the cutaneous anastomosis is maintained during the healing phase with the daily insertion of Hegar dilators.

BILIARY ATRESIA

Neonatal jaundice is usually physiologic. It becomes abnormal if it persists beyond 2 weeks, especially if the direct fraction of bilirubin is elevated. Biliary atresia affects both the extrahepatic biliary tree and the liver.

FIGURE 37-2 The three basic operations for surgical correction of Hirschsprung's disease. *A.* The Duhamel procedure leaves the rectum in place and brings ganglionic bowel into the retrorectal space. The common wall, indicated by lines, is crushed to eliminate the septum.
B. Classic Swenson operation (1948) is a resection with end-to-end anastomosis performed by exteriorizing bowel ends through the anus.
C. The Soave operation is performed by endorectal dissection and removal of mucosa from the aganglionic distal segment and bringing the ganglionic bowel down to the anus within the seromuscular tunnel.


A
B
C

Etiology and Pathology The cause is unknown, but an infectious etiology is suspected. Atresia or hypoplasia may involve all or part of the extrahepatic biliary ducts and also the intrahepatic ducts.

Clinical Manifestations Jaundice is present from birth but may not be marked until after the first several weeks. The urine becomes dark and stools acholic. The abdomen may gradually become distended by the enlarging liver or ascites. Eventually, the spleen enlarges also.

Diagnosis The serum bilirubin level gradually rises, and the direct fraction is at least half the total. After a month of observation, a nuclear scan using technetium-99m IDA (DISIDA) is performed after pretreatment with phenobarbital. If there is no excretion of the radionuclide into the intestinal tract, atresia is virtually ensured. A sample of duodenal contents may be assayed for the presence of bile. An ultrasound may reveal a choledochal duct cyst. The intrahepatic ducts are never dilated in biliary atresia. Screening tests for infectious and metabolic causes should be negative. Percutaneous needle biopsy of the liver will establish the diagnosis with a high degree of certainty.

Differential Diagnosis The differential diagnosis includes physiologic jaundice, total parenteral nutrition–induced jaundice, hemolytic disease, sepsis, neonatal hepatitis (a probable variant of biliary atresia), alpha-trypsin deficiency, the inspissated bile syndrome, biliary hypoplasia, infection with different viruses, or metabolic defects.

Treatment Surgical exploration should be performed, and if possible, a cholecystogram should be obtained. If no ductal system is found, a dissection of the porta hepatis is carried out to see if any proximal duct is present. If there is none, the porta hepatis is excised between the right and left hepatic arteries, and a portoenterostomy, Roux-en-Y, is performed. If a duct is present, it is anastomosed to a Roux-en-Y loop of jejunum. If the operation is performed prior to the third month of life and the diameter of the bile ducts in the resected porta hepatis is greater than 100 μm, there is an excellent chance for prolonged bile excretion into the intestinal tract. Inflammation of the liver may continue, with the development of fibrosis and portal hypertension. If portoenterostomy fails, liver transplantation becomes an option.

Choledochal Duct Cyst

There are a variety of such cysts according to Alonso-Lej. The most common type is the fusiform dilatation of the common bile duct with the cystic duct opening into it. The female-male ratio is 4:1. The classic symptom triad consists of pain, a palpable mass, and jaundice.

Diagnosis This is accomplished by ultrasound or CT. Occasionally, endoscopic retrograde cholangiopancreatography (ERCP) will be required.

Treatment Surgical excision and anastomosis of the proximal duct to a defunctionalized Roux-en-Y loop of jejunum is the treatment of choice. If the cyst lining is not resected, there is a risk of malignant degeneration.

DEFORMITIES OF THE ABDOMINAL WALL

Embryology

Four separate embryologic folds contribute to the formation of the abdominal wall: cephalic, caudal, and right and left lateral folds. These coalesce at the umbilical ring surrounding the two arteries and left umbilical vein. The developing gut herniates into the umbilical cord during the fourth through the eighth weeks of gestation and returns to the enlarging abdominal cavity from the ninth to the tenth week. Failure of the cephalic fold to close results in sternal defects and the pentalogy of Cantrell. Caudal fold abnormalities include extrophy of the bladder or the cloaca. Lateral fold defects result in omphalocele. Gastroschisis results from an antenatal herniation of the gut to the right of the cord.

Umbilical Hernia

These hernias result from failure of closure of the umbilical ring. They frequently are small, less than 1 cm, and will close spontaneously. Larger ones may not close and sometimes are so disfiguring that early closure is justified. Supraumbilical hernias produce a protrusion of the umbilical skin, but the defect is adjacent and superior to the umbilicus. The pigmented portion of the skin points inferiorly. These defects do not close spontaneously, and early repair is justified. Repair of an umbilical hernia is done through a skinfold incision around the navel; the navel may be excised. Incarceration is extremely rare.

Patent Urachus

During development of the abdominal cavity, the bladder communicates to the umbilical cord through the urachus. If this tract persists, urine will be observed emanating from the navel. Incomplete closure may result in a urachal cyst, demonstrated by sonography. These are rare abnormalities and are treated by surgical excision.

Patent Omphalomesenteric Duct

During fetal life, this duct connects the ileum to the yolk sac via the umbilical cord. Normally, the duct involutes, but a portion may persist as a Meckel's diverticulum seen in about 2 percent of the population. If the entire duct persists, ileal contents will spill from the umbilicus. The diagnosis is made by stool observed at the umbilicus or intubation of the duct and instillation of contrast material. A radiograph will reveal the material flowing into the terminal ileum. Complete excision is the definitive treatment.

Omphalocele

These present at birth as herniation of abdominal contents into the umbilical cord. They may be small and contain only a small amount of intestine or large and contain liver in addition to intestine. There may be rupture of the cord and herniation of the contents into the amniotic cavity. Associated anomalies are noted in about two-thirds of these children. Primary closure of the abdominal wall is the surgical goal. If the mass of the contents is small, closure is easy. In large omphaloceles, the intestine and liver have lost the "right of domain," and primary closure is frequently not possible. If other life-threatening anomalies are present, escharification of the cord may be accomplished using silvadene, pigskin, or povidone-iodine solution. This will allow epithelialization over the defect. If the child's condition will permit closure, this can be accomplished as a staged repair. A pouch of prosthetic material is sutured to the medial borders of the recti and covers the herniated viscera. The size of the pouch is decreased by taking multiple tucks within 7 days. This returns the contents to the enlarging abdominal cavity. Once reduction is complete, the pouch is removed and a primary repair accomplished. Severe associated anomalies account for the 20–30 percent mortality in this malformation.

Gastroschisis

This condition was once thought to represent a ruptured omphalocele but now is believed to represent rupture of the umbilical cord

at the site of the resorbed right umbilical vein. The intestine herniates through a small defect to the right of the umbilical cord. The fallopian tube also may herniate. Intestinal atresia is the only associated abnormality and occurs infrequently. The intestine may appear normal but more frequently is covered by a thickened peel. Often primary closure is possible by manually stretching the abdominal wall. This will require intubation and mechanical ventilation for several days following surgery to allow the abdominal cavity to stretch and relieve the subdiaphragmatic pressure. If pressures are too great, staged closure with a prosthetic pouch is accomplished as in giant omphalocele. There may be considerable delay in return of intestinal function, and central venous hyperalimentation should be initiated early.

Exstrophy of the Cloaca (Vesicointestinal Fissure)

This is a severe congenital malformation involving the inferior abdominal wall. Included are omphalocele, exstrophy of the bladder, separation of the symphysis pubis, foreshortened colon, imperforate anus, prolapse of the distal ileum through the bifid bladder, and epispadias in the male. Many of these children do not survive. The operation involves a proximal colostomy, closure of the omphalocele, and preferably closure of the bladder or creation of a bowel loop with transplanted ureters.

Congenital Deficiency of the Abdominal Musculature (Eagle-Barrett Syndrome, Prune-Belly Syndrome)

This is a rare syndrome affecting males almost exclusively. There is usually minimal muscular development in the abdominal wall. In addition, there are undescended testes and hydroureters and a megacysticus. Treatment involves antibiotics to prevent or treat urinary tract infections. An operation involves reductive abdominoplasty. Orchidopexy is performed at 6–12 months of age. Urinary diversion should be avoided unless obstruction occurs.

Inguinal Hernia

Indirect inguinal hernias result from failure of closure of the processus vaginalis, which usually occurs by 2–3 months of age. Incarceration is particularly likely in young infants, and surgical

correction is recommended early after diagnosis. Gentle maneuver reduction by manual compression usually is successful. If this maneuver is unsuccessful, immediate surgery is necessary to prevent necrosis of intestine or the gonad. A hydrocele of the cord may mimic an incarcerated hernia, but there is no pain and no vomiting because intestinal obstruction does not exist. Hydroceles of the tunica vaginalis may herald an associated hernia and in children over age 2 usually does. In infant females, an ovary may incarcerate in the hernia sac. These usually are associated with sliding hernias, and at surgery, the sac must be opened in all such patients to prevent ligating the fallopian tube.

Treatment involves a high ligation of the sac. No repair of the floor of the inguinal canal is indicated unless the internal ring is so stretched that the transversalis fascia is incompetent. If the hernia is a slider, the sac is ligated distal to the sliding component. A purse-string suture is placed at the base of the sac, and following excision of the sac, the stump is inverted and the purse-string tied.

There is controversy over repairing the opposite, asymptomatic side. Many advocate repair if the child is under 1 year of age or if the presenting hernia is on the left side.

GENITALIA

Cryptorchidism

The testes develop from the urogenital ridge and by the seventh month of gestation lie in the pelvis. They then begin their descent along with the developing processus vaginalis into the scrotum. The undescended testis may lie in the abdominal cavity or the inguinal canal. An ectopic testis that has passed through the external ring may lie in the superficial inguinal pouch, the thigh, or the perineum. There is increased risk of malignancy in the gonads of the patient with an undescended testis, probably due to the character of the testes themselves rather than to their position. Histology of the undescended testis reveals decreasing spermatogonia after 2 years of age. Therefore, orchidopexy is recommended before that age. The rationale for orchidopexy is to protect spermatogenesis, place the testis in a less vulnerable position, make early detection of malignancy possible, and most important, make the child feel the equal of his peers.

Vaginal Anomalies

Anomalies range from imperforate hymen to vaginal agenesis. Diagnosis is made by physical examination. Vaginal obstruction

leads to hydrocolpos and may present as a large abdominal mass. Ultrasound may help delineate the anatomy. Surgical reconstruction depends on the extent of pathology.

Ambiguous Genitalia (Intersex Syndromes)

Normal sexual differentation of the gonad occurs in the sixth fetal week and depends on a gene located on the Y chromosome. Wolffian (male) and müllerian (female) ducts exist in the embryo until sexual differentation. The fetal testis secretes testosterone and müllerian-inhibiting substance. Testosterone stimulates maturation of wolffian duct structures into epididymis, vas deferens, and seminal vesicles. Müllerian-inhibiting substance produces regression of the female structures. In the absence of the fetal testis, the müllerian system proceeds to full maturation. Any disruption of the orderly steps of sex differentiation may present as an intersex problem. These may be classified as a true hermaphrodite, a male pseudohermaphrodite, a female pseudohermaphrodite, or mixed gonadal dysgenesis. Most of these patients present with ambiguous external genitalia.

The true hermaphrodite is the rarest and usually has an XX karyotype. They usually have an ovary and a testis or an ovotestis. The male pseudohermaphrodite has bilateral testes, but there is a persistence of müllerian duct structures due to a defect in androsynthesis or müllerian-inhibiting substance. Female pseudohermaphrodites usually have a defect in adrenal cortisol synthesis, resulting in adrenal hyperplasia and increased adrenocorticotropic hormone (ACTH) production. The latter stimulates the production of adrenal androgens and masculinization of the developing female infant. Mixed gonadal dysgenesis may result in malignant degeneration of the gonad. Determination of the sex of rearing must be made early. This involves studies of urinary and serum biochemical factors, physical and radiologic examinations, chromosomal studies, and occasionally, celiotomy and study of the gonads with biopsy.

The appearance of the external genital abnormalities may be surgically modified by reducing and recessing an enlarged clitoris, repairing and elongating the penile hypospadias, vaginoplasty, or insertion of testicular prostheses.

It is important to remember that the external appearance of the genitalia is a major influence on the determination of the assigned gender. Infants with two X chromosomes should be assigned the female gender. Infants with an X and Y chromosome should be raised as males only if a sufficient phallus exists to be functional as a

male. In addition, abnormal development of the vagina may cause a variety of abnormalities. These range from an imperforate hymen to vaginal agenesis. Physical examination is usually sufficient for diagnosis, although ultrasound occasionally is necessary. Surgical repair depends on the defect. Imperforate hymen requires a simple incision of the hymen, whereas vaginal agenesis requires a complex reconstruction either from skin flaps or using intestine to create a neovagina.

Ovarian Cysts and Tumors

Infrequently females develop ovarian cysts and tumors that may be either neoplastic or nonneoplastic. Nonneoplastic cysts are usually simple, follicular, inclusion, paraovarian, or corpus luteum. Additionally, they may be solid, such as those seen in endometriosis, or inflammatory lesions. Neoplastic lesions are classified on the primordial cell layers, those being mesenchymal, germinal, and germ cell. Most commonly, children complain of abdominal pain, with obstruction of the urinary tract or intestine being common, along with endocrine imbalances. On physical examination, a mass is not uncommon, although ascites and abdominal distention are not common. With increasing frequency, ultrasound in the prenatal period has become diagnostic, with surgical excision being recommended for lesions greater than 5 cm in diameter. This is especially true of complex lesions, although resolution of simple cysts is not unusual. Laparoscopic or percutaneous drainage has been reported.

NEOPLASTIC DISEASE

Cancer is the second leading cause of death after trauma in children 1–14 years of age. Improved survival over the past two decades is due to several factors: better diagnostic imaging, new chemotherapeutic drugs, collaboration between surgeons, chemotherapists, and radiation therapists, and multi-institutional studies that evaluate new treatments and protocols.

Wilms' Tumor

Wilms' tumor is an embryonal neoplasm of the kidney that usually presents as an asymptomatic mass in the flank and upper abdomen. The peak age of incidence is 1–3 years. Associated conditions include familial aniridia, Beckwith-Wiedemann syndrome, urinary tract defects, hemihypertrophy, and chromosomal deletion, suggesting genetic influences. Bilateral involvement occurs in 5–10 percent of series.

Genes specific for the Wilms' tumor have been discovered that actually may be responsible for the development of this tumor. These include suppressor genes that have been cloned (WT1 and WT2), along with mutations and deletions.

Evaluation consists of CT scans to study the tumor-containing kidney, the status of the contralateral kidney, and the rest of the abdominal viscera. CT scan of the chest will reveal any pulmonary metastases, the most likely site of the metastic disease. Ultrasound examination of the abdomen will reveal any tumor extension into the renal vein or vena cava. The role of magnetic resonance imaging (MRI) is yet to be defined.

Treatment Surgical excision is performed through a wide transabdominal incision. The entire kidney and tumor are removed, along with the attached ureter. Invasion of the tumor into adjacent viscera is treated by excision of the involved tissue in continuity with the tumor. Paraaortic nodes are sampled for staging, biopsies of any suspicious areas are taken, and the opposite kidney is evaluated for tumor. Chemotherapy is given to all children; the mainstays are actinomycin-D and vincristine. Doxorubicin (Adriamycin) is added for children with more advanced disease, as is radiation therapy.

If the tumor is of "favorable" histology and all the tumor is removed at surgery, cure rate approaches 97 percent. A small percentage of tumors are of "unfavorable" histology, and their cure rates are diminished. Preoperative chemotherapy reduces massive tumors, making resection safer and possible. One must follow patients for development of second malignancies.

Neuroblastoma

Following central nervous system tumors and lymphomas, neuroblastoma is the next most common solid neoplasm in children. Therapy has not been nearly so successful as in Wilms' tumor. Neuroblastomas arise from neural crest cells and are seen most frequently in the adrenal medulla. Less frequently noted sites include the posterior mediastinum, neck, and pelvis. Over 90 percent of children present before age 9 years, and 60 percent are younger than age 5. Two-thirds will present with asymptomatic abdominal masses, and the majority will have metastases at diagnosis. The most frequently noted site of metastasis is bone. Prognosis is age-related. About 85 percent of children under 1 year of age will be cured even with metastatic disease to skin, liver, or bone marrow. Only 15 percent of children over age 2 are cured.

Evaluation consists of CT scans of the involved body cavity plus bone marrow examination and bone scans. Catecholamines

and their metabolites will be elevated in serum and urine. Serum ferritin and neuron specific emolase levels correlate with poor prognosis. Tumor DNA and N-*myc* are also prognostic indicators.

Treatment Total surgical excision in children over 1 year of age is the only hope of cure. This may include laminectomy, especially in posterior mediastinal tumors, where extension may occur through the vertebral foramina. The tumor may be radiosensitive and responsive to chemotherapy, but these adjunctive treatments have not altered the dismal prognosis associated with metastatic disease in patients over age 2. Bone marrow transplantation offers a promising outcome.

Rhabdomyosarcoma

This is an embryonic tumor arising from a variety of mesenchymal tissues. Common sites of origin are the head and neck, extremities, and the genitourinary tract. Diagnosis is made by incisional or excisional biopsy. Sites of metastasis include the lung, regional lymph nodes, liver, brain, and bone marrow. Extent of disease is determined by MRI, CT scans, and bone marrow biopsy.

Wide local excision, sparing mutilating surgery, is accompanied by radiation therapy and chemotherapy. Commonly used drugs include actinomycin-D, vincristine, and cyclophosphamide.

Prognosis is affected by site of origin and the pathologic type. Embryonal pathology is more favorable than alveolar histology. A 60 percent 5-year survival can be anticipated. The best prognosis is with total surgical excision.

Teratoma

These tumors are composed of all three embryonic germ layers. They are usually benign but can harbor malignant elements. Sites are varied, with the most frequently noted site being the sacrococcygeal area (40 percent). Other sites include the anterior mediastinum, ovary, retroperitoneum, testis, and neck. Therapy involves total surgical excision. Newer chemotherapeutic agents including *cis*-platinum have improved the outlook in higher-staged malignant disease. Radiation is used without proven effect on survival.

Liver Tumors

More than two-thirds of all liver tumors in children are malignant. Hepatoblastoma is the most common malignant tumor of the liver; 65 percent of these are diagnosed before age 4 years. Hepatocellular

carcinoma is the next most common lesion, with a peak incidence between ages 10 and 15. Most present with an upper abdominal mass. There may be weight loss, fever, and anorexia. Alpha-fetoprotein levels are elevated in 90 percent of children with hepatoblastoma and serve as a good marker for follow-up evaluation. Double-contrast CT scan of the abdomen and chest and celiac axis angiography are required for adequate evaluation of the tumor.

Preoperative chemotherapy to debulk massive tumors along with complete surgical extirpation results in cure of most hepatoblastomas. Half these tumors are completely resectable, and 80 percent are curable with adjunct chemotherapy. Children with hepatocellular carcinoma have a more dismal prognosis because fewer are completely resectable. Their survival is only 15 percent.

TRAUMA

Injuries account for 46 percent of all pediatric deaths, more than cancer, congenital anomalies, pneumonia, heart disease, homicide, and meningitis combined. Motor vehicle crashes account for 20 percent, drowning 8 percent, burns 5 percent, and firearms 1 percent of all trauma deaths. The establishment of major trauma centers skilled in the management of child trauma has improved survival statistics. Most fatal cases have associated head trauma, and the management of these injuries affects survival rates. By virtue of their soft, pliable skeletons, growing bodies, and immature emotional development, children constitute special trauma patients whose injuries and management differ markedly from those in the adult.

For a more detailed discussion, see Guzzetta PC, Anderson KD, Altman P, Newman KD, and Schnitzer JJ: Pediatric Surgery, chap. 37 in *Principles of Surgery,* 7th ed.

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CHAPTER

38

UROLOGY

ANATOMY

Kidney The kidneys are paired organs that lie in the retroperitoneum, enveloped in Gerota's fascia and variable amounts of fat. Dorsally, the lower ribs, the quadratus lumborum, and the psoas muscle are in close proximity. Ventral relationships of the right kidney include adrenal, liver, colon, and ileum; those of the left kidney include adrenal, stomach, spleen, pancreas, colon, and ileum.

The renal arteries arise from the aorta, and approximately two-thirds of kidneys will have a single renal artery. The main renal artery divides into five major branches, which represent an end artery supplying a renal segment. Thus occlusion of the renal artery branches will cause infarction of the renal segment. The renal veins empty into the inferior vena cava. The renal lymphatics empty into the hilar trunks, and the capsular lymphatics empty into infradiaphragmatic periaortic nodes. The renal nerves contain vasomotor and pain fibers and receive their contributions from T4–T12 segments. The renal pelvis lies dorsal to the renal vessels and has transitional epithelium.

Ureter The ureters are muscular tubes that travel through the retroperitoneum and connect the renal pelvis to the bladder. The normal adult ureter is 28–30 cm long and about 5 mm in diameter. The ureter transmits urine from the renal pelvis to the bladder by active peristalsis. The blood supply of the ureters originates from the renal, aortic, iliac, mesenteric, gonadal, vasal, and vesical arteries. Pain fibers transmit stimuli to the T12–L2 segments. The ureter can be deviated medially in retroperitoneal fibrosis and laterally by retroperitoneal tumor or aortic aneurysm.

Bladder The urinary bladder is a muscular organ located in the bony pelvis. The blood supply originates from the superior, middle, and inferior branches of the hypogastric arteries. The lymphatics drain into the perivesical, hypogastric, and periaortic nodes. The autonomic nervous system enters via the sacral cord and the presacral and epigastric plexus.

Prostate and Seminal Vesicles The prostate encases the proximal urethra and is attached to the bladder neck and the symphysis pubis. Distally, the prostate sits on the pelvic diaphragm, which contains the voluntary urinary sphincter. The blood supply is derived from inferior vesical, middle hemorrhoidal, and internal pudendal arteries. The prostate receives secretory and motor (parasympathetic) innervation from S3 and S4 and vasomotor (sympathetic) fibers from the hypogastric plexus. The lymphatics drain into the obturator nodes and the external, internal, and common iliac nodes. The seminal vesicles are situated behind the bladder, lateral to the ampullae of the vasa deferentia.

Penis and the Urethra The penis is composed of two erectile bodies called *corpora cavernosa* and a single body through which the urethra travels called the *corpus spongiosum*. The latter terminates with the glans penis, which is also erectile. The urethra in the male is divided into pendulous, bulbous, membranous, and prostatic segments. The female urethra corresponds to the prostatic and membranous urethra in males.

Testis and Epididymis The testes are ovoid, firm organs that are found in the scrotum. They are covered by the tunica albuginea. The epididymis and the vascular pedicle lie posteriorly. The epididymis is a crescent-shaped structure located around the dorsal portion of the testis. The vas deferens is a tubular structure that originates from the inferior portion of the epididymis. The arterial blood supply of the testis originates from the aorta. The venous drainage of the left testis is into the left renal vein; the right testis blood drains into the inferior vena cava.

DIAGNOSIS

Gross Hematuria Any amount of gross blood in the urine warrants further evaluation. The common causes are inflammation, tumors, calculi, and trauma. In young patients gross hematuria is more likely to be the result of infection, whereas in older patients it is more likely to be the result of tumor or prostate disease. It also is important to determine if the hematuria is initial, terminal, or total. This may help to localize the exact site of the pathology.

Acute Postrenal Retention of Urine This term reflects an inability to empty the bladder. A variety of afflictions can cause this condition.

Benign prostatic hypertrophy is the most common cause of acute retention in men. There usually is a long-standing history of

difficulty in voiding. In carcinoma of the prostate, the symptoms are more acute. Carcinoma of the prostate usually coexists with benign prostatic hypertrophy. In young males, prostatic inflammation may lead to acute urinary retention. This usually is a result of urethritis and/or prostatitis. Acute urinary retention also may be the result of a urethral stricture that occurs because of urethritis or trauma.

Neurogenic bladder dysfunction may lead to an increase in residual urine and to complete urinary retention. This may be the first indication of spinal cord disease. Other causes of neurogenic retention include trauma, pelvic surgery, general anesthesia, and drugs that influence the innervation of the bladder and the sphincter mechanism. Acute urinary retention in females usually is a result of neurogenic and psychogenic factors or urethral obstruction.

Incontinence True incontinence is a situation in which a patient is not aware of the loss of urine. Enuresis is nocturnal bed wetting, usually affecting children. Urgency occurs when the sensation of urination cannot be controlled before reaching a bathroom. Certain urinary cutaneous or urinary genital fistulas can lead to incontinence. Stress incontinence results from ineffective sphincter muscle tone. Overflow incontinence represents a small amount of urine leakage from a bladder carrying a large amount of residual urine.

Ureteral Colic This is related to a sudden increase in the hydrostatic pressure of the upper urinary tract. Typically, there is a sudden, increasing pain at the costovertebral angle. This may be associated with nausea or vomiting.

Frequency This refers to voiding an excessive number of times, whereas *polyuria* refers to an excessive amount of voiding. Frequency may be related to reduction in bladder capacity or to reduction in the effective bladder capacity that is seen with high residual urine. Frequency also may be a symptom of psychological stress.

Nocturia This may be caused by excessive fluid intake, generalized restlessness, cardiac decompensation, diuretic intake, and prostatic hypertrophy.

Urgency This symptom is a result of bladder or bladder outlet inflammation.

Dysuria This is difficult or painful urination. It usually is described as a burning sensation. Severe pain at the termination of urination is called *strangury. Hesitancy* indicates delay in voiding after mental command. *Intermittency* is involuntary stopping or starting of the stream.

Urinary Stream Lack of force of the urinary stream may reflect obstructive uropathy.

Erectile and Ejaculatory Dysfunction The cause may be endocrinologic, vasculogenic, or neurogenic. Certain drugs can lead to erectile and ejaculatory disturbances. In some instances, the problem may be situational or psychogenic. When anatomic abnormalities are found, they can be corrected. When directly injected into the corpora cavernosa, certain pharmacologic agents such as papaverine can result in adequate erections. In selected patients, insertion of penile prosthesis may be indicated.

Physical Examination

Renal Areas The renal areas are first examined with the patient in the upright position. Attention should be paid to bulging or asymmetry of the costovertebral region. Gentle palpation of the costovertebral region is followed by sharp percussion. Palpation is performed by bimanual examination of the area below the rib cage.

Ureters Because of their location in the retroperitoneum, the ureters cannot be palpated.

Bladder The bladder is examined with the patient in the supine position, and when empty, it cannot be palpated. With high residual urine the bladder can present as a lower abdominal mass.

Penis The penis can be examined with the patient in the upright or supine position. If the patient is not circumcised, the foreskin should be retracted. The urethral meatus, foreskin, and glans should be examined.

Scrotum Examination of the scrotum is carried out in conjunction with examination of the penis. The use of a flashlight to transilluminate lesions may help in diagnosis.

Epididymitis Acute epididymitis is a result of retrograde infection from the prostate, urethra, or bladder. The scrotum is very tender; the overlying skin is red and erythematous. There may be a mass in the scrotum. Nonspecific chronic epididymitis represents an incompletely resolved acute epididymitis. There may be an indurated scrotal mass that can be tender. Tuberculous epididymitis is nontender, stony hard, and associated with an indurated vas deferens. A sterile or chemical epididymitis can occur with retrograde extravasation of urine into the epididymis secondary to abdominal strain.

Varicocele This is more common on the left side because the left spermatic vein drains into the left renal vein, which usually is higher. Characteristically, there is a "bag of worms" appearance to the scrotum. The acute onset of a varicocele after the age of 40 may be a result of an invasive kidney tumor. If the patient is being evaluated for infertility, the finding of a varicocele may be significant. These patients may have a low sperm count with reduced motility and change in the sperm morphology.

Hydrocele Primary hydrocele may be unilateral or bilateral, which represents fluid between the tunica vaginalis. It presents as a nontender, fluid-filled scrotal mass. Secondary hydrocele is the consequence of serous effusions in the vicinity of a disease process. Acute hydrocele may be a result of testicular tumor. A communicating hydrocele is present in a patient with a patent processus vaginalis.

Spermatocele This is a cyst of an efferent ductule of the rete testis. It is located at the head of the epididymis as a cystic mass.

Testis Tumor A nodule within the testis is a malignant tumor unless proved otherwise. These usually are firm and nontender. Ultrasound examination can help define the lesion. Prompt surgical management is indicated.

Mumps Orchitis This lesion occurs after acute parotitis. Marked testicular swelling without scrotal edema is noted.

Torsion of the Testis and Appendages Torsion of the testis refers to torsion of the spermatic cord. The patient presents with sudden onset of pain associated with scrotal swelling and edema. The testis is elevated in the scrotum and is very tender to palpation. The cremasteric reflex usually is absent. This may be confused with acute epididymitis; isotopic testicular scanning may aid diagnosis. Detorsion and bilateral orchidopexy should be performed as soon as possible. Appendix testis, which is an embryologic remnant above the testis, also can undergo torsion. It can be detected as a black dot on transillumination.

Prostate The prostate is examined transrectally by digital palpation or ultrasonography. This could be done with the patient in a lateral recumbent or standing flexed position. The normal prostate is two finger breadths wide with a sulcus in between two lobes. The consistency of the normal prostate and benign hypertrophy is similar to that of the thenar eminence. In contrast, carcinoma of the

prostate feels stony hard. Crepitations are a result of prostatic calculi. Acute inflammation of the prostate is accompanied by tenderness or fluctuations that require gentle examination.

Female Urethra Pelvic examination of the female is necessary to evaluate the lower urinary tract. The presence of urethral lesions, cystocele, or urethrocele can be determined. A urethral diverticulum can be detected by expressing purulent material by pressure.

Urinalysis

Optimal urine collection from males is a fresh two-glass specimen and in females a catheterized collection. However, carefully obtained midstream urine in both sexes usually is satisfactory. The specimen should be examined while fresh.

Cloudy urine is not normal. This may be because of phosphaturia, which will clear with acetic acid. Certain foods and drugs can alter the color of urine. The degree and the origin of bleeding can be determined by gross inspection of urine. Screening examination includes tests for the presence of blood, albumin, sugar, acetone, and pH. With microscopic examination of the centrifuged urinary sediment, one can detect casts, crystals, epithelial cells, white blood cells, red blood cells, and bacteria. Cytologic examination of the exfoliated cells may help in detecting malignancy in the urinary tract. Flow cystometry may give additional information about malignancy.

Genital Secretions

Urethral Discharge The discharge is collected on a glass slide before the patient urinates. Gonococcal urethritis is diagnosed by the presence of gram-negative intracellular diplococci. A wet specimen is adequate for the diagnosis of *Trichomonas* infections. Noninfected secretions usually are whitish and opalescent; infected secretions are purulent.

Prostatic Secretions The specimen is obtained by gentle massage. Normal prostatic fluid contains 3–5 white blood cells per high-power field. In the presence of infection, secretions become granular and contain large amounts of white blood cells.

Semen Analysis The semen specimen should be obtained by masturbation. After 1 h, the semen will liquefy and should contain more than 20 million spermatozoa per milliliter, with 80 percent motility and 60 percent normal morphology.

Instrumentation

Insertion of any instrument into the urethra carries a risk of trauma, introduction of infection, sepsis, stricture formation, and exacerbation of the preexisting condition.

Cystourethroscopy This can be performed in the office with local anesthetics with either flexible or rigid instruments. Not only can very small lesions be detected but also small calculi, ureteral orifices, prostate size, urethral strictures or valves, and other lesions can be seen.

Ureteropyeloscopy The entire upper urinary tract can be visualized with flexible or rigid ureteroscopes. Certain procedures can be performed with these instruments.

Therapeutic Instrumentation An indwelling catheter allows temporary relief of obstruction. If the catheter is left in for over 3 days, there is associated infection. Bladder drainage also can be obtained with suprapubic tap and insertion of a polyethylene tube. Drainage of an obstructed upper urinary tract can be accomplished by percutaneous nephrostomy tube or a retrograde ureteral catheter placement.

Therapeutic instrumentation may be applied in the endoscopic removal of calculi or foreign bodies, biopsy or excision of tumors, drainage of prostatic abscesses, dilatation or incision of urethral strictures or valves, and transurethral removal of prostatic obstruction.

Special Diagnostic Studies

Excretory Urography Certain intravenously administered organic molecules are excreted and concentrated by the kidneys. When they are rendered opaque by iodinization, renal parenchyma and the collecting system can be visualized radiographically. Because these agents are hyperosmotic, they can lead to diuresis and dehydration. These agents also can cause severe allergic reactions.

The adult male kidney is about 13 by 6.2 cm on pyelography. The female kidney is approximately 5 mm smaller. The right kidney is about a half vertebral body lower than the left. The longitudinal axis of the kidneys follows the lateral margin of the psoas muscle, and any deviation may indicate a pathologic condition. The calyces and the infundibulae should be delicate. The pelvis and the ureter should be smooth without redundancy.

Nephrotomography A more detailed visualization of the kidney is obtained by taking slices posteriorly and advancing anteriorly.

Retrograde Pyelourethrography This is indicated to further evaluate the pyelocalyceal system. This study requires cystoscopy, insertion of ureteral catheters, and injection of contrast material.

Antegrade Pyelography Percutaneous insertion of a small catheter into the pelvocalyceal system may be both therapeutic and diagnostic. An infected and obstructed kidney can be drained, whereas injection of contrast material allows the collecting system to be visualized. After percutaneous access to the kidney, stones can be fragmented (nephrolithotripsy), strictures dilated or incised, and lesions biopsied using nephroscopes.

Renal Arteriography Transfemoral renal arteriography is useful in the evaluation of renal vascular hypertension and therapeutic dilatation of narrow arteries (angioplasty). This also is useful in evaluating renal masses and renal vascular anatomy.

Digital Subtraction Angiography After intravenous or intraarterial injection of contrast material, a computerized subtraction system provides clear visualization of the renal vasculature.

Vena Cavography The inferior vena cava can be visualized by injection of contrast material through a catheter placed from the femoral vein. This is especially helpful in evaluating renal or testicular neoplasms.

Lymphangiography Pedal lymphangiography may provide information regarding lymph node involvement in certain genitourinary cancers.

Renography and Renal Perfusion Scan The iodine-131 (^{131}I) hippurate renogram provides information regarding function and drainage of the kidneys. The use of different isotopes may provide additional information about renal perfusion, drainage, morphology, and differential renal function.

Ultrasound Using this noninvasive test, cystic renal lesions can be differentiated from solid lesions. Hydronephrosis also can be determined with this technique. Transrectal ultrasound also can aid in the detection of prostate cancer. Using ultrasound as a guide, biopsies and cyst aspirations can be performed.

Computed Tomography (CT) This is one of the most useful and accurate means of evaluating intraabdominal pathology, and in some instances it has replaced other tests. It can be performed with or without contrast material. Along with detailed anatomy, the extent and size of the tumors can be detected.

Cystometrics, Urethral Pressure Profiles, and Sphincter Electromyography These studies are useful in evaluating micturition dysfunction resulting from a variety of clinical problems.

Percutaneous Renal Cyst Puncture Aspiration of fluid from a renal mass may aid in differentiation of cysts from tumor.

Biochemical and Radioimmunoassay (RIA) Evaluation of renal function, hypertension, electrolyte disturbances, calculus disease, impotence, and genitourinary neoplasms requires the use of biochemistry and radioimmunoassay.

BLADDER FUNCTION AND DISORDERS

Physiology of Micturition Gradual bladder filling under normal circumstances is accompanied by a voiding reflex at a certain volume. This can be inhibited by cortical centers. If the conditions are socially acceptable, voiding results by contraction of the detrusor and relaxation of the sphincter. In patients with bladder outlet obstruction, the pressure required to empty the bladder exceeds normal, and detrusor hypertrophy ensues. In long-standing obstruction, muscle fibers may decompensate and result in atonia, which can be accompanied by high residual urine.

Bladder Innervation Sensations are mediated by sensory fibers accompanying the sympathetic and parasympathetic nerves. They arise from T9–L2 segments of the spinal cord. Motor pathways originate in the S2–S4 segments and reach the bladder via the pelvic nerves. Parasympathetics are responsible for reflex contractions of the detrusor. The external sphincter is innervated with motor nerves from the S2–S4 segments via the pudendal nerve. Sympathetic nerves have an important role in detrusor function and outlet resistance.

Motor pathways can be evaluated by bulbocavernosus reflex. Cystometry is the best method for evaluating motor function. This is performed by installation of either gas or water at a certain rate into the bladder and recording pressure changes. Intravesicle pressure rarely exceeds 20 cmH_2O.

Neurogenic Bladder Dysfunction

Uninhibited Neurogenic Bladder This condition presents as urgent voiding that is without voluntary control. Cerebral vascular accidents and multiple sclerosis are classic causes. Treatment is with parasympatholytic drugs.

Reflex (Automatic) Neurogenic Bladder A well-functioning reflex bladder results if the spinal cord is transected. The lesion must be between T7 and C7. With rehabilitation, the bladder can provide adequate emptying.

Centrally Denervated Neurogenic Bladder This dysfunction is the result of lesions involving the sacral segments of the cauda equina. Meningomyelocele or occult spina bifida are the most frequent lesions. The symptoms are overflow incontinence with high residual urine and infections. Surgical therapy is directed toward facilitating bladder emptying. When bladder rehabilitation is unsuccessful, clean intermittent catheterization may be used. Cholinergic drugs may enhance detrusor tone, whereas sympatholytic agents can decrease urethral resistance.

Sensory Paralytic Bladder This results from sensory loss of bladder innervation such as from tabes dorsalis or cord degeneration. The patient is unable to sense bladder filling, which results in overflow incontinence. Treatment is similar to that for the conditions described above.

Motor Paralytic Bladder Dysfunction may be seen with poliomyelitis or infectious polyneuritis. Loss of motor activity results in a large capacity bladder. This may be reversible depending on the disease process.

Bladder drainage is required in the immediate posttrauma stage. This can be done with either indwelling catheters or intermittent catheterization. Chronic indwelling bladder catheterization is almost always accompanied by bacterial colonization. The specific complications of catheter drainage include acute cystitis and pyelonephritis, acute epididymitis, urethral abscess and fistula formation, and bladder or kidney stones. A regimen of intermittent catheterization should be used as soon as possible in these patients.

Rehabilitation of the Bladder During the first months after trauma, attention is directed to prevention of infection. After stabilization of the spine, the patient can resume the upright position and

begin rehabilitation. The patient's bladder function is assessed with a thorough urodynamic evaluation, and every attempt is made to remove any indwelling catheters. Cholinergic agents can be tried at this time. Clean self-intermittent catheterization also may be instituted. It may be necessary to reinsert an indwelling catheter and to reevaluate at a later date. Certain patients may require antibacterial suppressive therapy.

ACUTE INFECTIONS

Pathogenesis The most common entry site for urinary tract infections (UTIs) is the urethra. When there is obstruction, inflammation, or ulceration in the urinary tract, the defense mechanism is inadequate. Most UTIs occur in females because of the short urethra. In older age groups, the incidence of UTIs increases in males. Recurrent UTIs in children are most likely associated with congenital malformations of the urinary tract. UTIs also can result from hematogenous spread.

Bacteriology The most common urinary pathogen is *Escherichia coli.* Other common pathogens include *Proteus, Klebsiella,* the enterococci, and *Pseudomonas.*

Treatment The kidneys enhance the efficacy of certain antibacterial agents by increasing their concentration in the urine. Drug selection is facilitated by culture and sensitivities. Drugs that are rapidly excreted by the kidneys are preferred in the treatment of uncomplicated lower UTIs. Patients with acute pyelonephritis or urinary sepsis are treated with drugs that yield high blood and tissue concentrations. These patients usually require parenteral combination therapy for an extended period of time.

UTI is sometimes a result of anatomic abnormality. Upper UTIs may need additional evaluation after treatment of the infection. These patients also are at risk for recurrence, and close follow-up is mandatory. Occasionally, long-term, low-dose suppressive therapy is required.

Gram-Negative Bacteremia This syndrome is considered a urologic disease because the source usually is from the urinary tract. Bacteremia can result from instrumentation. The patients show signs of sepsis with hemodynamic alterations. Bacteria can be resistant to common antibiotics.

Acute Staphylococcal Infections of the Kidney

Staphylococcal pyelonephritis or abscess is of hematogenous origin and usually results from metastatic infection. The patients usually are very ill, with fever, flank pain, frequency, and dysuria. Complications include renal carbuncle or perinephric abscess. Treatment consists of parenteral antibiotic therapy.

Perinephric Abscess

This usually occurs after perforation of renal infection or abscess into the perinephric space. The patient presents with high fever and rigid abdomen. Radiographs reveal an absent psoas shadow and concavity of the spine to the site of the lesion. Treatment requires drainage and long-term antibiotics.

Acute Papillary Necrosis

Necrosis of renal papillae occurs in patients with diabetes, sickle cell disease, tuberculosis, and excessive ingestion of phenacetin. Along with symptoms of infection, renal colic may be seen. Diagnosis is made on intravenous pyelogram by demonstrating sloughed renal papillae. Treatment is conservative unless there is obstruction.

Acute Urethritis

Acute urethritis usually is venereal in origin. Most common organisms include gonorrhea, *Ureaplasm urealyticum, Chlamydia,* and *Trichomonas vaginalis.* Diagnosis is established by Gram's stain of the discharge and appropriate cultures. Gonorrhea is a common venereal disease that presents with symptoms of acute urethritis. Diagnosis can be made with identification of intracellular gram-negative diplococci. Unless resistant, they are best treated with penicillin-type drugs. Nonspecific urethritis is the more common venereal disease in males. *C. trachomatis* and *U. urealyticum* are the usual organisms. These can be treated with tetracyclines, whereas *Trichomonas* infections are treated with metronidazol (Flagyl).

Acute Bacterial Prostatitis

This usually is caused by the same organism that produces urinary tract infections. Infection usually is ascending from the urethra and the prostatic ducts. Symptoms consist of perineal pain, dysuria, and

frequency attended by fever, chills, and malaise. Liquefaction necrosis may lead to abscess formation. Parenteral antibiotics should be instituted pending appropriate cultures. Rectal examination should be performed gently and reveals a warm, tender prostate. Persistence of the symptoms suggests an abscess that requires drainage.

Acute Epididymitis

This is characterized by rapid swelling of the epididymis and testis along with pain. UTI is usually present with associated symptoms. It may be difficult to identify the pathogen if UTI is not present. The differential diagnosis includes acute torsion of the spermatic cord. Radioisotope and scrotal ultrasound may aid in diagnosis. Treatment consists of symptomatic measures such as scrotal elevation and broad-spectrum antibiotics. Abscess formation may occur and may require surgical drainage. Traumatic epididymitis can be seen after strain in lifting or scrotal trauma. Antibiotics usually are administered because infection cannot be ruled out.

CHRONIC INFECTIONS

Chronic Bacterial Prostatitis

Chronic bacterial prostatitis is characterized by recurrent UTIs, low back and perineal discomfort, urinary frequency, and dysuria. The duration of the symptoms can be variable; recurrence is common. Expressed prostatic secretions reveal many white blood cells, although the prostate usually is nontender. Most of the drugs that are effective in UTI are unable to penetrate the prostate. Trimethoprim, tetracyclines, carbenicillin, and quinolones seem to be effective. In nonbacterial prostatitis, although symptoms and findings are the same, cultures usually are sterile. Therapy in these cases usually is empirical and often unsuccessful.

Chronic Cystitis

Chronic cystitis can be the end result of recurrent bacterial cystitis. Infiltration of the bladder with the inflammatory process can impair detrusor function. There are often predisposing factors such as tumors, stones, or indwelling catheters. Irritating voiding symptoms usually are present. Diagnostic workup is directed toward identifying the predisposing factors. Chronic antibacterial therapy often is required.

Interstitial cystitis is a form of abacterial cystitis usually seen in females in their later years. The cause is unknown, and the symptoms

are that of cystitis. This must be differentiated from tuberculous cystitis and carcinoma in situ of the bladder. Treatment is very difficult. Periodic instillations of dimethyl sulfoxide (DMSO) may relieve symptoms. Agents that repleate the glycosaminoglycan layer in the bladder such as Elmiron also can be effective.

Chronic Epididymitis

This is characterized by persistent induration of the epididymis. The epididymis is minimally tender, and there usually is a history of acute epididymitis. Ultrasound examination may aid in the differential diagnosis. Treatment consists of empirical antibacterial therapy.

Chronic Pyelonephritis

Histologically, this represents a nonspecific inflammation with fibrosis and scarring. Radiologic findings include loss of parenchyma, calyceal blunting, and cortical scars. Treatment usually is directed at correcting the predisposing factors and antibacterial therapy.

Urinary Tuberculosis

Renal tuberculosis is the result of hematogenous spread from other lesions. This infection usually is cortical and bilateral and becomes symptomatic when it ulcerates into the collecting system. Symptoms are similar to those of cystitis. There is abacterial pyuria on Gram stain. Special cultures reveal *Mycobacterium tuberculosis*. Radiographic findings include calcification of caseous abscess, ulceration, and stenosis of the collecting system. Therapy usually is medical with combinations of isoniazid (INH), ethambutol, rifampin, and pyridoxine.

Genital tuberculosis may accompany renal tuberculosis or may exist alone as a result of hematogenous spread. The epididymis is the most frequent site of infection.

URINARY CALCULI

The consequences of urinary calculi are responsible for many hospital admissions. Primary metabolic stones result from excessive excretion of insoluble substances such as uric acid or cystine. In hyperparathyroidism, increased calcium and phosphorus excretion may result in stone formation. Idiopathic hypercalciuria may be the result of increased intestinal absorption or a renal tubular defect

that can lead to stone formation. Excessive absorption of oxalate can produce hyperoxaluria and result in urinary calculi. Secondary stones arise as a result of foreign bodies, obstruction, reflux, or prolonged recumbency. Infections with urea-splitting organisms result in ammonium–magnesium phosphate calculi.

Composition The calcium oxalate stones make up approximately 75 percent of calculi. Ammonium–magnesium phosphate is found with infected urine and accounts for approximately 15 percent of calculi. Uric acid stones constitute approximately 8 percent of all calculi. Cystine stones represent only 1 percent of stones.

Diagnosis Calculi within the ureter usually present with typical colic. Some stones can be asymptomatic, and urinalysis may be negative. Approximately 90 percent of the urinary calculi are radiopaque. Intravenous pyelography generally will diagnose the stone and reveal additional information about obstruction. Retrograde pyelography, ultrasound, and computed tomography (CT) may aid in the differential diagnosis.

Management (Fig. 38-1) Analgesics usually are necessary to relieve severe renal colic. Radiologic evaluation will assist in selecting treatment. About 93 percent of all ureteral calculi less than 4 mm in diameter will pass spontaneously. Those patients who are treated expectantly should have serial renal function evaluations.

Indications and Methods for Removal The mere presence of a stone within the urinary tract does not warrant intervention. Extracorporeal shock-wave lithotripsy (ESWL) is currently the treatment of choice for most urinary stones. This procedure is noninvasive, and morbidity is low. A major disadvantage is the fate of the fragments after treatment. These may cause ureteral obstruction and colic. Stones within the urinary tract also can be approached by endoscopic techniques. A number of energy sources (holmium laser, electrohydraulic, and pneumatic) can be applied directly to the stones for their removal; with the combination of ureteroendoscopy, percutaneous nephrolithotripsy, and ESWL, the need for open surgical procedures has decreased significantly.

Open Surgery The techniques described above should be the initial approach to most urinary calculi. Surgical removal of staghorn calculi represents a clinical challenge. The open surgical approach is recommended by some authors. Occasionally, large bladder stones have to be removed by cystolithotomy. Certain urinary calculi can be dissolved by direct irrigation. Uric acid stones

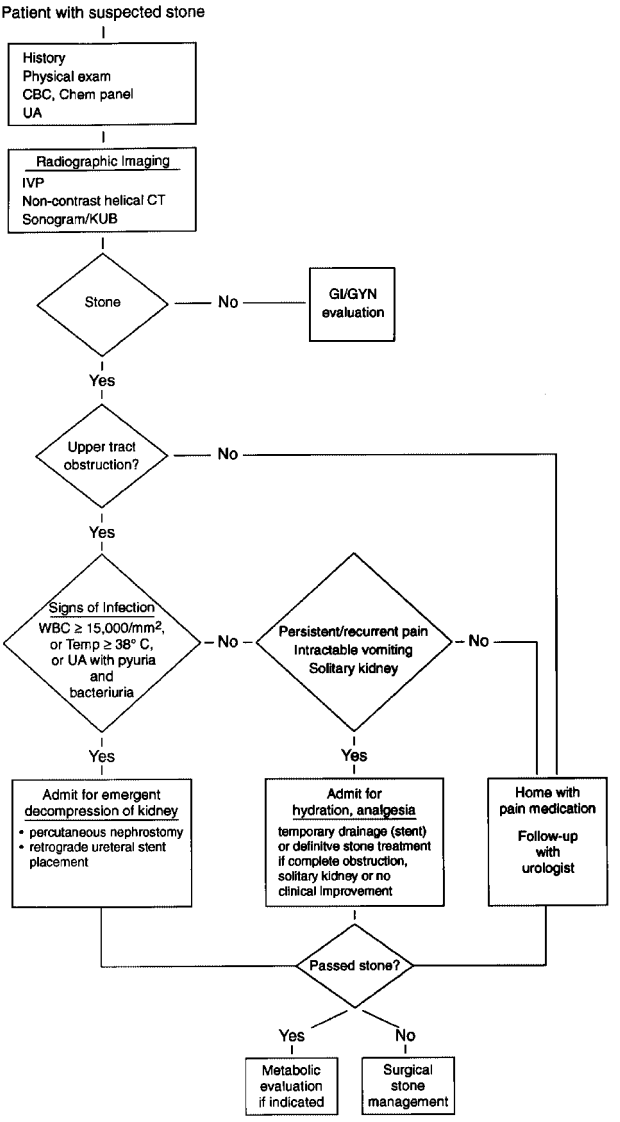

FIGURE 38-1 Algorithm for the management of an acute stone event.

dissolve with alkalinization. Infection stones can be dissolved with Renacidin.

Radiologic Procedures By placing percutaneous nephrostomy tubes, obstruction can be relieved and an emergency situation may become more elective.

Prevention of Recurrence Stones usually recur, and most patients have a previous history of stones. Hydration is the single most important factor in preventing stone formation. Because some stones rapidly form at certain pH levels, this could be adjusted easily. UTIs should be treated. Regulation of diet is particularly important in some situations. A low-protein diet is useful in lowering uric acid levels excreted in the urine. A low-oxalate diet may be effective in preventing calcium oxalate stones. A low-calcium diet may be beneficial in eliminating calcium-containing stones. Urinary calcium can be decreased by hydrochlorthiazides or cellulose phosphate binders. Allopurinol may reduce the uric acid stone formation.

Hyperparathyroidism Most patients with hyperparathyroidism present with urinary calculi. Patients with recurrent urinary calculi should be investigated for increased serum calcium and alkaline phosphatase and decreased phosphorus levels. Serum parathormone level should be assayed. Treatment consists of surgical removal of parathyroid adenoma.

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a common disorder of the prostate gland. It is more common after the fifth decade of life and is due to benign enlargement of the prostate.

Clinical Manifestations Under the influence of testosterone and aging, the prostate increases in size and can cause obstruction to the outflow of the urinary stream. The onset of symptoms of "prostatism," such as nocturia, urgency, and decreased force of urinary stream, is insidious. Acute urinary retention is the result of acute detrusor decompensation and usually is seen in patients with long-standing BPH. With digital rectal examination, an enlarged prostate with benign consistency usually can be palpated. A normal-sized gland does not exclude obstruction; cystoscopy is essential to inspect the urethra and the bladder. If radiographic techniques are used, increased bladder wall thickness, high bladder residual urine, and hydronephrosis may be noted. A serum creatinine determination should

be obtained to assess kidney function. A thorough urinalysis should be performed to rule out infection. The best noninvasive test to evaluate men with prostatism is to measure their urine flow velocity.

Treatment (Fig. 38-2) Those patients with mild symptoms or enlarged prostates not causing symptoms should be managed by watchful waiting. Men who develop urinary retention, recurrent infections, bladder stones, or renal insufficiency should be treated surgically. For those men with significant prostatism, watchful waiting, medical therapy, and surgery should be presented as treatment options. There are two medical approaches to the treatment of BPH. Alpha-adrenergic receptor blockers relax prostatic smooth muscle, partially relieving the active part of the obstruction. These drugs improve symptoms and flow rates in a significant number of patients. The 5α-reductase inhibitor finasteride reduces intraprostatic dihydrotestosterone levels without lowering plasma testosterone levels. With this drug, prostate size can be reduced significantly; however, only one-third of the men notice improvement in their symptoms.

Transurethral Prostatectomy This is performed by electroresection of the prostate through the urethra. Multiple pieces of the obstructing tissue are removed under direct vision. This procedure can be combined with endoscopic lithotripsy (crushing and removal of a bladder calculus). This technique also is applicable in carcinoma of the prostate that is not amenable to curative or palliative measures. Because of the excellent results obtained with transurethral resection of the prostate, open prostatectomy rarely is performed. The indications for open prostatectomy include large adenoma and associated bladder stone or tumor. Recently, minimally invasive techniques have been developed to relieve the obstruction. Transurethral microwave thermotherapy (TUMT), transurethral needle ablation of prostate (TUNA), and prostatic stents are being perfomed with increasing numbers.

Prognosis Over 90 percent of the patients have complete relief or improvement of their symptoms. Approximately 10–20 percent of the patients will have recurrent obstruction in 5 years.

NEOPLASMS

Renal Tumors

Incidence and Etiology Renal tumors account for 2 percent of all cancer deaths. Tumor probably arises from tubular cells. Etiology is unclear.

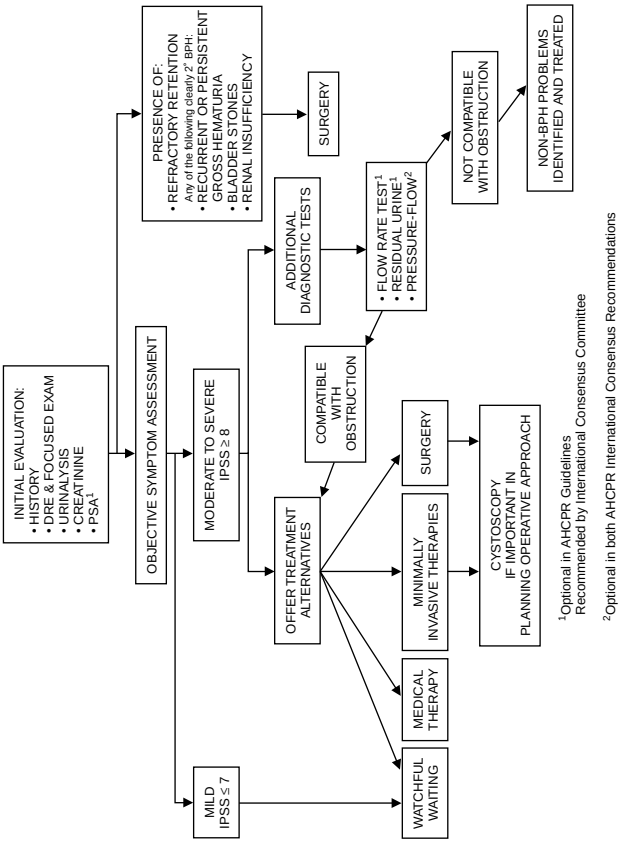

FIGURE 38-2 The decision diagram for the management of BPH recommended by the U.S. government's AHCPR BPH Guideline Panel.

Pathology There are three major types of malignant tumors of the renal parenchyma. Granular cell carcinoma and tubular adenocarcinoma account for 60 percent. Wilms' tumor (adenomyosarcoma), which is commonly seen in children, accounts for 14 percent. These are followed by sarcomas and tumors of the collecting system.

Clinical Manifestations The classic triad of pain, mass, and hematuria is seen in fewer than half the patients. Hematuria is a late manifestation. Passage of blood clots can mimic renal stone colic. A mass can be palpated if the lesion is in the lower pole. Fever may be seen, which can be because of necrosis. Hypertension may be the result of compromised renal perfusion from tumor compression. Renal tumors can secrete excessive erythropoietin, which will result in erythrocytemia. Metastases involve the lung, bone, lymph nodes, liver, and skin.

Diagnosis Excretory urography is frequently diagnostic. Nephrotomography is helpful in differentiating cysts from tumors. Calcified cysts are more suggestive of tumor. Ultrasound also is very helpful in differentiating cyst from tumor. Renal arteriography is occasionally needed, and inferior vena cavography may be necessary to rule out tumor extension into the venous system. CT not only is diagnostic but also gives valuable information regarding the extent of the tumor. Magnetic resonance imaging (MRI) also can be diagnostic and may be more sensitive for showing venous extension.

Treatment Removal of the kidney with perinephric fat and lymph nodes offers the best chance of cure. Radiation therapy or chemotherapy generally is not effective. There have been some promising results with adaptive immunotherapy.

Prognosis This depends on the grade and extension of the tumor. The overall survival rate for renal tumors is about 50 percent at 5 years.

Carcinoma of the Renal Pelvis and Ureter

Tumors of the pelvocalyceal system usually are transitional cell types. Squamous cell carcinoma is rare and generally associated with chronic infection or calculous disease. Gross hematuria and colic are a common mode of presentation. Intravenous pyelography is diagnostic, showing the filling defect in the pelvis or the ureter. Cytology also is helpful in establishing the diagnosis. Treatment is by removing the kidney and the ureter.

Tumors of the Urinary Bladder

Incidence and Etiology This tumor is seen more commonly after the fifth decade of life. The usual lesion is transitional cell car-

cinoma, and it is more common in males. Papillary bladder tumors have been linked to certain chemicals, cigarette smoking, schistosomiasis, and bladder calculi.

Clinical Manifestations Gross or microhematuria is the initial sign in most patients. When the tumor is confined to the bladder, physical findings are minimal. The tumor can be visualized on excretory urography; however, cystoscopy and biopsy are confirmatory. Local extension and metastasis can occur. Bimanual examination may reveal fixed bladder in the pelvis. Urine cytology and flow cystometry are also helpful in the diagnosis.

Treatment and Prognosis Endoscopic resection is suitable for superficial lesions. Most tumors recur with superficial lesions; very few patients eventually will have invasive lesions. For locally invasive tumors, the best treatment is total cystectomy with urinary diversion. Definitive radiation therapy and combination chemotherapy may provide satisfactory results. Intravesicle administration of certain chemotherapeutic agents or bacille Calmette-Guérin (BCG) may reduce the recurrence rate of superficial lesions.

Carcinoma of the Prostate

Incidence and Etiology The cause of prostate cancer is not known; it is rare before age 50 and not seen in eunuchs. It is the second most common cancer in males in the United States.

Early Carcinoma This is the stage in which the carcinoma is localized to the gland. Prostatic-specific antigen (PSA) is a sensitive but not specific blood test for detecting prostatic carcinoma. More than 50 percent of the nodules palpated on rectal examination are positive for cancer on biopsy. Patients with localized cancer are best treated with prostatoseminalvesiculectomy. Careful dissection will preserve continence and sexual function. Ultrasound-guided transrectal biopsy is the most accurate diagnostic technique. On rectal examination, carcinoma usually feels rock hard; however, this could be seen in prostatitis, BPH, calculus, and bladder or rectal cancer extension. Bony metastasis can be evaluated with a bone scan. Serum acid phosphatase may be elevated in metastatic cancer. Histologically, prostatic malignant tumors are adenocarcinomas. Prognosis depends on the degree of differentiation and the stage of the disease.

Alternative treatment of early carcinoma is radiation therapy. Some centers report similar survival rates with surgery and radiation therapy and brachytherapy. Cure can be achieved only by

total removal of the lesion. Patients who are not candidates for radiation therapy or surgery can be treated with antiandrogen therapy.

Advanced Carcinoma Patients can present with bladder outlet symptoms. Weight loss, extremity pain, gross hematuria, and lower extremity lymph edema can be seen. Rectal examination reveals a fixed, stony hard prostate. Acid and alkaline phosphatase and PSA are elevated. PSA also can be elevated in localized carcinoma. Treatment of symptomatic advanced carcinoma is with antiandrogen therapy. This could be done with bilateral orchiectomy, administration of estrogens, ketoconazole, flutamide, cyproterone acetate, amino glutethimide, and luteinizing hormone–releasing hormone (LHRH). Palliation is obtained in approximately 90 percent of the patients. Local radiation therapy for painful bone metastasis also is effective.

Testicular Tumors

Incidence and Etiology Testicular tumors account for 1 percent of cancers in the male. The average age at diagnosis is 30. They occur more frequently in undescended testes. Testicular cancer is infrequent in blacks.

Clinical Manifestations These patients usually present with a lump in their testis. The examination usually finds a firm, nontender, solid mass. These must be differentiated from hydroceles and epididymitis. Late symptoms of metastasis include weight loss, fatigue, lymph node enlargement, and ureteral obstruction.

Diagnosis and Treatment (Fig. 38-3) When a testicular tumor is suspected, an inguinal exploration is required. The testis, along with the spermatic chord, usually is removed, and a radical orchiectomy is performed. Before orchiectomy, human beta-chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) tumor marker levels should be obtained. Seminomas represent approximately 40 percent of malignant testis tumors, embryonal cell carcinomas and teratocarcinomas about 25 percent each, and teratomas 8 percent; choriocarcinoma is limited to approximately 1–2 percent. Benign tumors of the testis are very rare. Because seminomas usually are very radiosensitive, further operation usually is not indicated. Nonseminoma testicular tumors will require bilateral retroperitoneal lymph node resection for accurate staging of the disease. The use of combination chemotherapy has markedly increased the survival of these patients with advanced metastatic tumors. Survival depends on the cell type and the stage of the disease at the time of diagnosis.

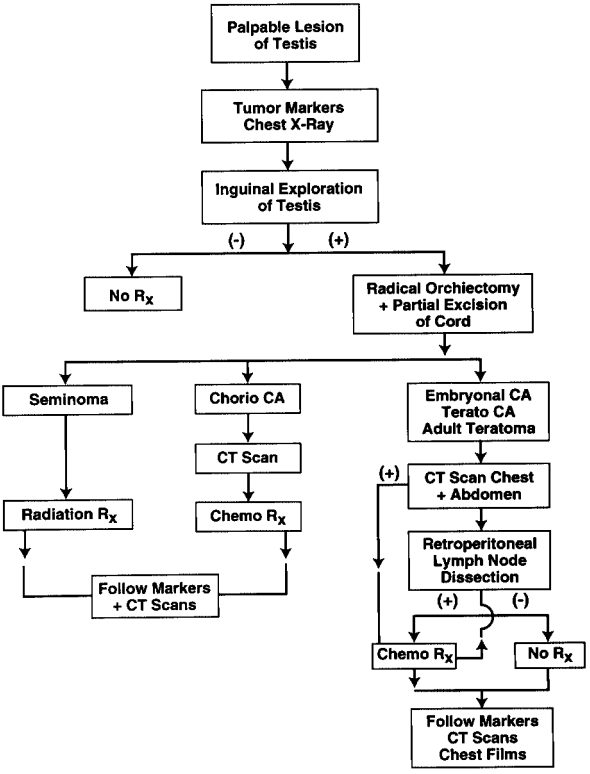

FIGURE 38-3 Algorithm for the evaluation and management of testicular cancers.

Carcinoma of the Penis

Carcinoma of the penis develops in the squamous epithelium of the glans and foreskin and is almost eliminated by circumcision at infancy. This lesion is uncommon in the United States, and the average age of onset is over 60 years. Patients usually present with an ulcerated lesion on the penis, and the diagnosis is obtained by biopsy. Local excision and radiation therapy are associated with a

90 percent 5-year cure rate when there is no distant metastasis. When there is lymph node involvement, the 5-year survival is reduced to 30 percent.

SEXUAL DISORDERS

Priapsm *Priapsm* is defined as prolonged erection without sexual excitement. It results from vascular disorders in which blood is trapped by venous occlusion and cannot escape. The most common cause is injection of erection-producing agents by the patient. The treatment is the slow injection of a few millimeters of 1:1000 epinephrine directly into the corpora. If this fails, heparinized saline may be effective. In some instances, incision and drainage are required.

Impotence *Impotence* is defined as the inability to generate or maintain an erection. Erection can be enhanced by alpha-adrenergic blockers, which are now available and effective. Erection also can be produced by a vacuum tube device or the implantation of solid or inflatable penile prosthesis.

Infertility In evaluating infertility, both partners must be investigated. The man is responsible in about 20 percent of cases and a contributing factor in about 30 percent. Semen analysis is best taken 3 days after sexual abstinance. Patients are classified as azoospermic, oligospermic (<20 million sperm/mL), or normospermic.

Failure to ejaculate can be caused by drugs, an incompetent bladder neck, advanced atherosclerosis, or diabetes mellitus.

GENITOURINARY TRACT INJURIES

Renal Injury (Fig. 38-4)

Blunt renal trauma is more common than penetrating kidney trauma. Rapid deceleration such as the impact after a fall may result in renal vessel injury. Patients who suffer renal injury usually will have gross hematuria or microhematuria. Diagnosis of renal injury is confirmed by excretory urography or CT scan. Abdominal CT may be the single most important diagnostic test. It will give not only adequate visualization of the renal structures but also an idea about other intraabdominal organs. Patients with renal contusions and lacerations without extravasation of urine may be treated conservatively. When there is failure to visualize a kidney on a CT scan

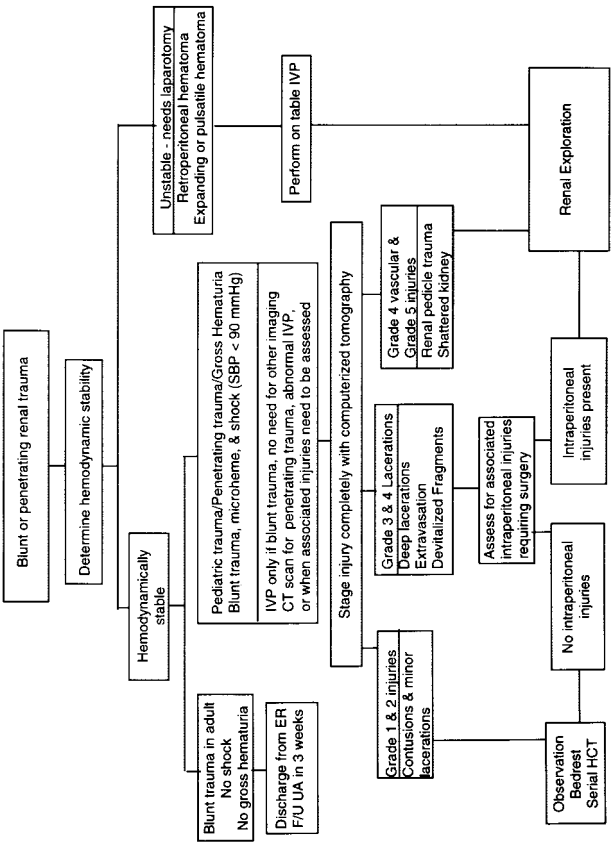

FIGURE 38-4 Algorithm for the management of renal trauma. (From: Wessels H, McAninch JW: Update on upper urinary tract trauma. *AUA Update Series*, vol 15, 1996, with permission.)

and arteriograph, or when there is significant extravasation, surgical treatment is considered. Every effort should be made to preserve renal parenchyma. In massive trauma to the kidney, nephrectomy may be a lifesaving procedure. Most cases of renal trauma can be treated conservatively.

Ureteral Trauma

Ureteral injuries occur mainly as a result of surgery. If the injury is recognized, direct repair over an indwelling stent can be performed. If it is not recognized, the patient may present with anuria, urinary fistula, or urinoma. The ureters also can be injured by penetrating objects such as bullets and knives. In this case, exploratory laparotomy and surgical repair usually are indicated.

Bladder and Urethral Injury

The full bladder is more vulnerable to trauma. Direct blows and penetrating injury by spicules of bone, stab wounds, and gunshot wounds may all result in rupture of the bladder. Direct blows usually cause intraperitoneal rupture; the penetrating injuries usually are extraperitoneal. Urine can be grossly bloody, and the patient may not be able to void. When there is suspicion of bladder trauma, a retrograde urethrogram and cystogram should be obtained. Blood at the meatus suggests urethral injury; retrograde urethrography should be done before any instrumentation of the urethra. Treatment of severe bladder trauma usually consists of surgical repair and cystostomy drainage. In most cases of bladder injury, conservative management without an operation may be satisfactory. This especially is true in extraperitoneal rupture of the bladder, in which catheter drainage may result in adequate healing. If the urethra is avulsed, this may be repaired at the time of repair of the bladder rupture. If the trauma is extensive and the patient's condition is poor, cystostomy under local anesthesia may be the procedure of choice, and this would allow second-stage repair.

External Genitalia

Penis Injury to the corpora cavernosa may result in extravasation of blood and urine within or outside of Buck's fascia. They may be caused by penetrating trauma or blunt trauma sustained during vigorous sexual intercourse. These injuries must be explored through a circumcising incision with degloving of the penis and repair of the corpora. Degloving injuries of the penis mandate surgical de-

bridement and skin grafting. Traumatic penile amputation can be salvaged with microsurgical repair of the dorsal penile arteries and vein and selective skin grafting.

Scrotum Scrotal skin is elastic and can be mobilized to cover extensive defects. If the scrotal tissue is insufficient, the testes can be temporarily placed in thigh pockets.

Testes Ruptured testes may occur from either blunt or penetrating trauma, and in some cases debridement can be performed and the tunica albuginea closed. A completely shattered testes will require orchiectomy.

PEDIATRIC UROLOGY

The genitourinary system should be evaluated in all instances of "failure to thrive" syndrome, undiagnosed febrile illnesses, externally apparent congenital anomalies, and abdominal masses. Wilms' tumor of the kidney and neuroblastoma of the adrenal gland are the most common solid tumors in children.

Congenital Anomalies

Phimosis (Redundant Prepuce) Poor hygiene predisposes this condition to infection and carcinoma of the glans penis. Circumcision usually is recommended.

Urethral Meatal Stenosis This condition can be congenital or acquired in the male. It is easily detected by inspection, and treatment consists of meatotomy.

Urethral Valves These usually are seen in boys and produce variable changes because of obstruction. Diagnosis is established by voiding cystourethrography and endoscopy. Along with dilatation of the posterior urethra, hydroureteronephrosis is common. Endoscopic incision or fulguration of the valves usually is done early. In some cases, excessive dilatation may require a supravesical diversion such as a cutaneous vesicostomy.

Neurogenic Bladder This usually is the result of autonomic dysfunction accompanying meningomyelocele. The patient presents with overflow incontinence, infection, and impaired voiding. Diagnosis is established by cystourethrography and cystometry.

Mild cases can be treated by bladder rehabilitation and preventing infections. Severe cases are treated by reducing residual urine with surgery or intermittent catheterization.

Ureterocele This is cystic dilatation of the intravesicle portion of the ureter. The ureteral orifice may or may not be stenotic. This may become large enough to obstruct the urethra. Diagnosis can be made with the cystogram phase of the intravenous pyelogram. The contrast-filled intravesicle mass is referred to as "cobra head" deformity. Treatment usually is surgical.

Vesicoureteral Reflux This may be associated with posterior urethral valves, "prune belly" syndrome, complete duplication of the collecting system, ectopic ureter, ectopic uretercele, neurogenic bladder, bladder neck obstruction, and bladder infections. In adults there are often no adverse effects of the reflux, and most cases can be managed without an operation by minimizing the amount of residual urine. Submucosal injection of polytetrafluoroethylene or collagen has been shown to eliminate vesicoureteral reflux. Reimplantation of the ureter into the bladder is required almost exclusively in young children.

Hydronephrosis This often is a result of a congenital obstruction at the ureteropelvic junction. This can result in significant dilatation and atrophy of the renal parenchyma. Children commonly present with a palpable abdominal mass. Intravenous pyelography and ultrasonography will establish the diagnosis. Pyeloplasty is the treatment of choice; however, nephrectomy may be required for poorly functioning kidneys.

Congenital Nonobstructive Renal Disease Congenital or neonatal glomerular disease usually is fatal. There are many forms of cystic disease of the kidney. In medullary cystic disease, collecting ducts are ectatic, whereas in polycystic disease, there is a failure of communication between tubules and glomeruli. Nonfunctioning multicystic disease may be a failure of development of the metanephric blastema. Detailed renal function studies and close follow-up are required.

Cryptorchidism About 30 percent of premature males have an undescended testicle. The incidence in full-term males is 4 percent. Spontaneous descent occurs in most patients by 1 year of age. Bilateral cryptorchidism after 1 year should be treated initially with gonadotropins, resorting to operation in refractory cases. Unilateral cryptorchidism can be treated with surgery, repairing the

associated indirect hernia at the time of orchiopexy. There is an association between cryptorchidism and testicular malignancy.

Hypospadias This is a fusion defect of the urethra. The anomaly consists of a dorsal hood (absent ventral foreskin), chordee (ventral curvature of the penis), and proximal location of the urethral opening. Hypospadias can be associated with abnormal urinary stream and infertility. Hypospadias with the urethral opening in the scrotum can be accompanied with bilateral undescended testicles; this must be differentiated from adrenogenital syndrome or pseudohermaphroditism. Treatment consists of surgical correction.

Epispadias This is associated with a dorsally cleft urethra, which is very rare.

Exstrophy of the Bladder In this anomaly, the bladder is part of the abdominal wall. Several procedures usually are required for total reconstruction.

Ectopic Ureteral Orifice This usually is associated with duplex ureters, and the ectopic orifice drains the upper collecting system. The condition is more common in females. When the opening is in the vagina, incontinence is the rule. Treatment is surgical.

Testicular Neoplasms

Embryonal carcinoma is the most common testicular tumor of children. Teratoma before puberty can be a benign tumor for which a high inguinal orchiectomy is curative. Conversely, teratoma after puberty should be managed as a teratocarcinoma. Gonadoblastoma usually occurs in patients with gonadal dysgenesis.

Torsion

Although torsion can occur at any age, it is more common before puberty. The isotope scan is helpful in making the diagnosis, but the scan should not delay surgical repair. At operation, the tunica vaginalis is opened, and the testicular necrosis is evaluated. A decision must be made as to whether to remove the testes. After detorting the cord, a bilateral orchiopexy should be performed.

Varicocele

This results from an incompetent valve or obstruction of the gonadal vein. There is an association between varicocele and

subfertility. The indications for repair include size, persistent scrotal pain, growth, and subfertility.

Hydrocele and Hematocele

Hydrocele is an accumulation of clear fluid within the tunica vaginalis. It is repaired as an indirect inguinal hernia. The collection of blood within the tunica vaginalis can result from trauma or rupture of the tunica or testes. This is known as a *hematocele* and should be treated by aspiration or open drainage.

OPERATIONS ON GENITOURINARY ORGANS

Nephrectomy

Nephrectomy can be performed by a retroperitoneal flank approach or by a transabdominal anterior approach. The flank approach usually is preferred in the treatment of inflammatory disease, calculi, perinephric abscess, hydronephrosis, and renal cystic disease. Nephrectomy for renal carcinoma is performed through the transperitoneal approach, in which the vascular ligation is carried out early.

Cutaneous Ureteroileostomy (Ileal Conduit)

This is the most popular method of supravesicle urinary diversion. The major indication for this procedure is urinary diversion after removal of the bladder. The patient has an ileal conduit that is continuously draining urine to the skin and requires carrying drainage bags. Recently, there have been modifications of the conduit in which the stoma has been made into a continent drainage system. These selected patients have to catheterize their conduits. There also is research developing continent neobladders using small or large bowel segments. An ileal loop usually is constructed through a midline abdominal incision. The stoma is created before the creation of the conduit on the appropriate area of the abdomen. A segment of ileum then is mobilized, and the bowel is reanastomosed end to end. The ureters are anastomosed to the conduit at one end, and the conduit at the other end is brought out through the skin as a stoma.

Cystostomy, Cystolithotomy

The bladder usually is approached with a lower abdominal incision, and the detrusor muscle can be incised longitudinally. If stones are present, these are removed. Drainage can be provided by a large

catheter. In the urinary tract it is important to use absorbable sutures such as chromic catgut. Introduction of any foreign bodies such as silk sutures will result in the formation of stones.

Prostatectomy

Transurethral Prostatectomy This is the most common operation to remove prostatic obstruction. This is done endoscopically using a resectoscope. Using electric current and a cutting loop, prostatic tissue is resected, and hemostasis is secured with electrocoagulation. A catheter is inserted and left in place for several days for hemostasis, after which it is removed and patient's voiding observed.

Suprapubic Prostatectomy This operation is performed through a cystotomy approach, as described previously. The adenoma is mobilized and enucleated using finger dissection. The surgical capsule of the prostate is left behind. Hemostasis is obtained, and a suprapubic tube as well as a urethral Foley catheter are left indwelling. The urethral catheter is removed in 5–7 days, and the patient is observed voiding.

This also is accomplished through an incision intraabdominally, but the bladder is not entered during this operation. An incision is made on the bladder neck, and the capsule of the prostate is incised. After this, the adenoma is exposed and dissected through the capsule of the prostate and removed. Hemostasis is established, and again, the capsule is closed with absorbable sutures. Adequate drainage of the urinary tract is established by a Foley catheter and a suprapubic tube.

Hydrocelectomy

A vertical scrotal incision is used; the hydrocele sac is approached and dissected. The sac is entered and fluid evacuated. The excess tunica is excised, and hemostasis is established. The layers are reapproximated with absorbable sutures. Hydrocelectomy in children is carried out through an inguinal incision. At this time, hernia repair usually is undertaken.

Inguinal Orchiectomy

This is performed when a testicular tumor is suspected. It provides access to the spermatic vessels before manipulation of the testis. The spermatic cord is identified and ligated. The spermatic cord and the testis are then removed and sent to pathology.

Orchiopexy

This is performed through an inguinal incision and permits mobilization of the spermatic cord and correction of the indirect hernia. The testis is then brought to the scrotum and placed in a Dartos pouch and fixed. No tension is placed on the spermatic cord.

Bilateral Vasectomy

This is a male sterilization procedure usually performed under local anesthesia in an outpatient setting. The vas deferens on each side of the scrotum are identified, and these are dissected, tied, and coagulated. A small portion of the vas is then sent to pathology for identification.

Vasovasostomy

This procedure is carried out on an in-hospital basis and can be done under local or general anesthesia. The incision is made in the scrotum on both sides of the vas. The granulomatous areas of the vas are excised until sperm is noted coming from the testicular portion of the vas. Using magnification with either surgical loops or a microscope, the anastomosis is performed in an end-to-end fashion.

Laparoscopic Surgery

Laparoscopic surgical techniques have been applied to urology. Pelvic lymphadenectomy, varicocelectomy, and nephrectomy have been performed. Living-donor nephrectomy has been performed with this approach. As the technology develops, it is believed that there will be more urologic applications.

For a more detailed discussion, see Pearle MS, McConnell JD, and Peters PC: Urology, chap. 38 in *Principles of Surgery,* 7th ed.

CHAPTER

39

GYNECOLOGY

ANATOMY

External Genitalia (Vulva) The vulva is bounded by the symphysis pubis anteriorly, the anal sphincter posteriorly, and the ischial tuberosities laterally. The labia majora form the cutaneous boundaries of the lateral vulva and represent the female homologue of the male scrotum. Adjacent and medial to the labia majora are the labia minora, smaller folds of connective tissue covered laterally by non-hair-bearing skin and medially by vaginal mucosa. The anterior fusion of the labia minora forms the prepuce of the clitoris; posteriorly, the labia minora fuse in the fossa navicularis, or posterior fourchette.

Musculature of the Pelvic Floor The levator ani muscles form the muscular floor of the pelvis. These muscles include, from anterior to posterior, bilaterally, the pubococcygeus, puborectalis, iliococcygeus, and coccygeus muscles. Distal or caudad to the levator ani muscles, or levator sling, are the superficial muscles that constitute the urogenital diaphragm. The lateral-most components are the ischiocavernosus muscles. The bulbocavernosus muscles arise in the inferoposterior border of the symphysis pubis and around the distal vagina before inserting into the perineal body. The transverse perinei muscles arise from the inferior rami of the symphysis just anterior to the pubic tuberosities and insert medially into the perineal body, lending muscle fibers to this structure as well.

Internal Genitalia The uterus and cervix are suspended by the cardinal, or Mackenrodt's, ligaments, which insert into the paracervical fascia and into the muscular sidewalls of the pelvis laterally. Posteriorly, the uterosacral ligaments support for the vagina and cervix and insert into the paracervical or endopelvic fascia. The fallopian tubes arise from the cornua of the uterus. Each widens in the distal third, or ampulla. The ovaries are attached to the cornu by the ovarian ligaments. These fibrous bands are analogous to the gubernaculum testis in the male and continue from the uterus as the round ligaments. These structures exit the pelvis through the

internal inguinal ring and course through the inguinal canal and external inguinal ring to the subcutaneous tissue of the mons veneris. The ovaries are suspended from the lateral pelvis by their vascular pedicles, the infundibulopelvic ligaments. The peritoneum enfolding the adnexa is referred to as the *broad ligament.*

The peritoneal recesses in the pelvis anterior and posterior to the uterus are referred to as the *anterior* and *posterior cul de sacs.* The latter is also called the *pouch* or *cul de sac of Douglas.*

Several avascular and therefore important surgical planes can be identified. These include the lateral paravesical and pararectal spaces and the prevesical space of Retzius and presacral spaces.

The muscles of the pelvic sidewall include the iliacus, the psoas, and the obturator internus. The blood supply arises from the internal iliac arteries, except for the middle sacral artery, which originates at the aortic bifucation. The hypogastric arteries divide into anterior and posterior branches. The latter supply lumbar and gluteal branches and give rise to the pudendal arteries. The nerve supply to the pelvis is composed of the sciatic, obturator, and femoral nerves. The ureters enter the pelvis as they cross the distal common iliac arteries laterally and then course inferior to the ovarian arteries and veins until they cross under the uterine arteries just lateral to the cervix.

DIAGNOSIS

Gynecologic History The gynecologic history should include the patient's age, date of her last menstrual period (LMP), the number of pregnancies, the number of deliveries, and the number of abortions. Gravidity, parity, and abortions are frequently indicated as G-P-A. The examiner should inquire as to when the patient's last cervical cytology was obtained and, in patients over age 35, the date of the patient's last mammogram.

Physical Examination The initial evaluation should include a general physical examination and a description of the patient's height, weight, nutritional status, blood pressure, head and neck, including thyroid, heart, lungs, and lymph nodes. The gynecologic portion of the examination should document an examination of the breasts, the abdomen, and the pelvis.

Diagnostic Procedures

Cervical Cytology Cervical cytology (Pap smear) should be performed beginning at 18 years of age or sooner if the patient is sex-

ually active. Most women should have a cervical cytologic evaluation yearly at the time of their annual pelvic examination. After total hysterectomy, the Pap smear should be obtained annually in patients treated for cervical neoplasia. After hysterectomy for conditions that did not include cervical neoplasia, the vaginal apex may be screened cytologically every 3–5 years. The practitioner should expect a report from the laboratory in the format of the Bethesda classification (Table 39-1) for cervical cytologic reporting. All cytologic reports must be studied carefully to determine whether further evaluation or treatment is indicated. Atypical smears or smears with severe inflammation should be repeated generally in 3 months. Persistent atypical smears should be evaluated with colposcopic examination. All smears that indicate dysplasia or neoplasia should be investigated with colposcopy. Colposcopy is a specialized technique that allows evaluation of the cervix under magnification to do directed biopsies. The colposcopic examination following abnormal cervical cytology will preempt cone biopsy and

TABLE 39-1
THE BETHESDA CLASSIFICATION FOR THE CLASSIFICATION OF PAP SMEAR ABNORMALITIES

Adequacy of the Specimen
Satisfactory for evaluation
Satisfactory for evaluation but limited by . . . (specify)
Unsatisfactory . . . (specify)

General Categorization
Within normal limits
Benign cellular changes: see Descriptive diagnosis
Epithelial cell abnormality: see Descriptive diagnosis
Descriptive Diagnosis
Benign cellular changes
  Trichomonas vaginalis
  Fungus organisms
  Predominence of coccobacilli
  Consistent with *Actinomyces* sp.
  Consistent with herpes simplex virus
Reactive changes
  Changes associated with inflammation
  Atrophy with inflammation
  Radiation
  Intrauterine contraceptive device

TABLE 39-1
THE BETHESDA CLASSIFICATION FOR THE CLASSIFICATION OF PAP SMEAR ABNORMALITIES (CONTINUED)

Epithelial Cell Abnormalities
Squamous cell
- Atypical squamous cells of undetermined significance
- Low-grade squamous intraepithelial lesion encompassing human papillomavirus
- High-grade squamous intraepithelial lesion encompassing moderate dysplasia, severe dysplasia, *carcinoma in situ*
- Squamous cell carcinoma

Glandular cell
- Endometrial cells, cytologically benign in postmenopause
- Atypical glandular cells of undetermined significance
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma
- Extrauterine adenocarcinoma

Adenocarcinoma, NOS
Other Malignant Neoplasms (specify)
Hormonal Evaluation (applied to vaginal smears only)
- Hormonal pattern compatible with age and history
- Hormonal pattern incompatible with age and history
- Hormonal evaluation not possible due to . . . (specify)

allow office treatment of cervical dysplasia in most patients. When an endocervical lesion is found, the biopsy indicates a lesser lesion than cytologic report, or the biopsy is indicative of microinvasion of the cervix, a cone biopsy is indicated (Fig. 39-1).

Office Tissue Biopsy Biopsy of suspicious lesions of the vulva, vagina, cervix, and uterus should be obtained in the office. Vulvar biopsy is obtained by infiltrating the biopsy site with a small amount of 1% lidocaine. Adequate biopsies can be obtained using a dermatologic skin punch. Biopsy of the ectocervix does not require anesthesia. Specialized cervical biopsy punches, such as the Kevorkian or Tischler type, are used. The endocervical canal should be sampled with an endocervical curette such as the Kevorkian. Biopsy of the endometrial cavity is an office procedure. It is essential to be assured that the patient is not pregnant before performing this procedure.

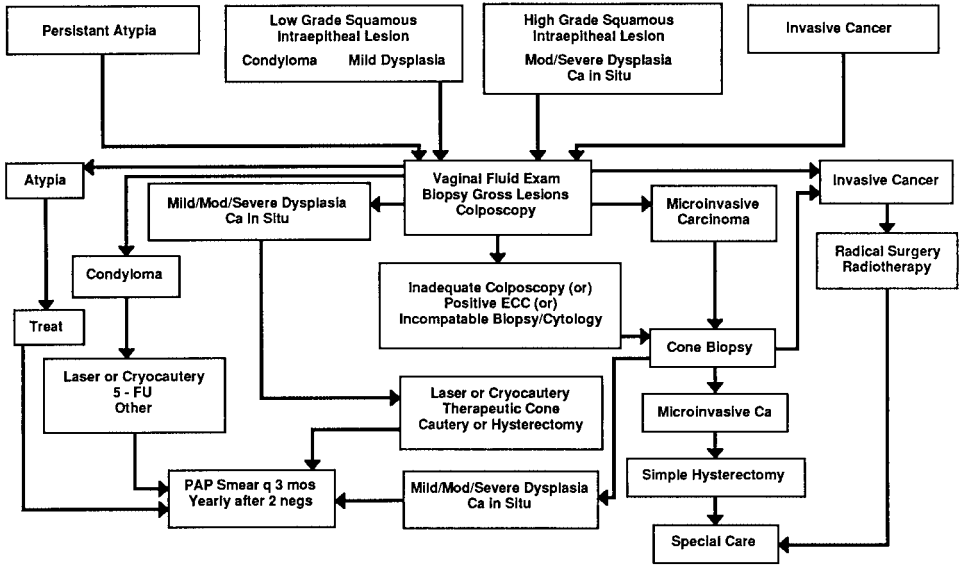

FIGURE 39-1 The management of abnormal cytologic findings.

Vaginal Discharge The patient's complaint of abnormal vaginal discharge should be investigated. The pH of the vagina, which is normally between 3.8 and 4.4, may be an aid to diagnosis. A vaginal pH of 4.9 or more indicates either a bacterial or protozoal infection. Vaginal fluid is collected for study. The "wet mount" is prepared by placing a small amount of the saline suspension on a microscopic slide with a cover slip and examining it under magnification. The examiner may note motile trichomonads, indicative of *Trichomonas vaginalis;* characteristic "clue cells," indicative of bacterial vaginosis; or pus cells, which may be indicative of a variety of vaginal, cervical, and uterine problems such as gonorrhea, chlamydia, or other bacterial infections. A drop of 10% potassium hydroxide is placed on the specimen, and the vaginal material is again evaluated. Potassium hydroxide has the ability to lyse cellular material to appreciate the presence of mycelia characteristic of *Candida* vaginitis.

Cultures Vaginal and cervical cultures are most useful for the detection of sexually transmitted disease. Gonorrhea is cultured on a chocolate agar plate. Cultures are most conveniently collected on a Thayer-Martin medium. Chlamydial infection is suggested by the finding of a characteristic thick yellow mucus (mucopus). Mucopus should be collected with a calcium alginate–tipped swab in transport medium specifically designated for *Chlamydia.*

Pregnancy Tests A number of pregnancy tests are available for use in the office. These tests measure increased amounts of the beta subunit of human chorionic gonadotropin (hCG) in urine. These urine tests are very sensitive and specific, measuring hCG as low as 50 mIU/mL. Serum tests are even more accurate and sensitive, and they have the advantage that they can be quantitated to give an hCG level.

Abnormal Bleeding

After the first menstrual period (menarche), cyclic bleeding is considered the norm. Menstrual interval varies from 21–45 days. Menstrual duration varies from 1–7 days. Abnormal genital bleeding falls into six categories.

Bleeding Associated with Pregnancy The availability of extremely sensitive pregnancy tests has made it possible to confirm pregnancy in the early days of gestation. Although bleeding can occur in up to 25 percent of all normally pregnant women, this symptom must be considered a threatened abortion until the bleeding is otherwise clarified. In the presence of threatened abortion, the pregnancy test is positive, the cervix is closed, and the uterus is gener-

ally consistent with the history of gestation. A threatened abortion is considered inevitable when the cervix is dilated and fetal tissue appears at the cervical os. Abortion is incomplete after a portion of the products of conception has been expelled; it is considered complete after all the products of conception have been expelled.

Ectopic pregnancy must be considered in any patient with a positive pregnancy test, pelvic pain, and abnormal uterine bleeding. Approximately 20 percent of patients with ectopic pregnancy have no bleeding. Gestational trophoblastic disease also causes abnormal bleeding associated with a positive pregnancy test. Molar pregnancy is suggested when the uterus is larger than would be expected from the history of gestation, vaginal bleeding, and the passage of grapelike tissue from the vagina. Gestational trophoblastic disease must be differentiated from normal pregnancy. Ultrasound examinations are helpful in diagnosis.

Dysfunctional Uterine Bleeding This type of bleeding abnormality is characterized by irregular menses with occasional extended intervals of amenorrhea. Evaluation of these patients should include a pregnancy test, which should be negative. Endometrial sampling reveals a nonsecretory or proliferative endometrium. In most instances the condition can be managed with cyclic estrogen/progesterone treatment.

Trauma The bleeding associated with genital trauma may be secondary to rape or genital injury. In the premenarchial female, the vaginal canal should be examined carefully for foreign bodies. Repair in the operating room under anesthesia may be necessary.

Bleeding Secondary to Neoplasm Tumors, both benign and malignant, involving the genital tract from the vulva to the ovary can produce abnormal bleeding. The most common cause of abnormal bleeding in the reproductive age group is leiomyomas (fibroids). Leiomyomas are almost always benign and are a common cause of menometrorrhagia.

Bleeding from Infection Bleeding is an uncommon symptom of pelvic inflammation.

Bleeding of Nongenital Etiology Genital bleeding can be associated with coagulopathy, systemic anticoagulants, clotting disorders, or blood dyscrasias.

Pain

Pelvic and abdominal pain is a common gynecologic complaint. Pain associated with menses is the most common office complaint.

Cyclic pain limited to that period is referred to as *dysmenorrhea.* Pain occurring without a demonstrable pathologic lesion is referred to as *primary dysmenorrhea. Secondary dysmenorrhea* is commonly associated with endometriosis, cervical stenosis, and pelvic inflammation. Acute pain may have its origin in abnormal pregnancy, benign or malignant neoplasia, or a variety of nongynecologic diseases. Pregnancy disorders include threatened abortion, inevitable abortion, incomplete abortion, and ectopic pregnancy.

Neoplasms cause acute pain through degeneration of a myoma or torsion of a myoma or ovarian neoplasm. The spontaneous rupture of an ovarian cyst can produce severe pelvic pain. Acute pain may be caused by salpingitis or endometriosis. Pain secondary to inflammatory conditions is associated with fever and other evidence of infection in most cases. Pelvic infection secondary to *Chlamydia trachomatis* is the exception to this rule. The possibility of a nongynecologic condition as the cause of pain always must be considered, e.g., appendicitis or urinary problems such as renal and ureteral stones. In women in the reproductive age group, a differential diagnosis commonly involves appendicitis, ectopic pregnancy, and salpingitis.

Bilateral low abdominal pain increased by movement of the cervix most often indicates acute pelvic inflammatory disease. Right abdominal pain with a history of gastrointestinal symptoms will indicate appendicitis. In many cases it may not be possible to make a definitive diagnosis. Direct visualization of the pelvis can be carried out with a laparoscope.

Pelvic Mass

The finding of a pelvic tumor is a common event in reproductive-age women. Pregnancy should be considered in all cases of uterine enlargement in reproductive-age women. In addition to a carefully performed pelvic examination, abdominal and vaginal ultrasonography is a useful tool. No imaging method will distinguish between benign and malignant disease, however.

INFECTIONS

Vulvar and Vaginal Infections

Vulvar, perineal, and perianal itching and burning are symptoms that may indicate an inflammatory condition.

Mycotic Infection The most common cause of vulvar pruritus is candidal vulvovaginitis. This is common in patients who are diabetic, pregnant, or on antibiotics. The majority of cases are caused

by *Candida albicans*. Diagnosis is confirmed by characteristic pseudomycelia. The condition is treated by topical application of any one of a number of imidazole preparations. Systemic treatment is possible through the oral use of fluconazole.

Parasitic Infections Pin worms (*Enterobius vermicularis*), which are common in young girls, cause vulvitis. Diagnosis is made by finding the adult worms or recognizing the ova. Mebendazole therapy is indicated. *Trichomonas vaginalis* causes primarily a vaginal infection. The patient complains of heavy, foul-smelling discharge. Diagnosis is made by microscopic examination. Treatment consists of metronidazole 250 mg given three times daily for 7 days. The vulvar skin is a frequent site for infestation by *Phthirus pubis* (crab lice) and *Sarcoptes scabiei* (scabies, itch mites). Treatment consists of lindane, available for medical use as Kwell.

Bacterial Infections Many bacteria attack the vulvovaginal region. The streptococci and staphylococci are the most common offenders. *Gardnerella vaginalis* is the most common bacterial pathogen. The patient complains of a foul, fishy, or "dead mouse" odor. Diagnosis is made by microscopic study to identify characteristic "clue cells." The condition is treated with metronidazole 500 mg orally every 12 h for 1 week.

Viral Infections A number of viral infections affect the vulva and vagina, the most common of these being condyloma acuminatum. The causative organism is the human papillomavirus. Treatment depends on the destruction of the lesions with caustic agents, cryocautery, laser ablation, or electrocautery.

Herpes simplex infection causes painful vesicles followed by ulceration of the vulva, vagina, or cervix. Culture is confirmatory for herpes infection. There is a tendency for the lesions to recur at various intervals for the life of the patient. The attacks may be aborted and the interval between attacks lengthened through the use of acyclovir 200 mg orally five times daily. Cesarean section is recommended in patients in labor with vulvar or vaginal ulceration as a result of herpes simplex infection.

Molluscum contagiosum causes groups of small pruritic nodules with an umbilicated center. The lesions are treated by ablation.

Pelvic Inflammatory Disease

While pelvic inflammatory disease is basically a medical problem, it has profound surgical implications. This condition could be responsible for over a hundred thousand surgical procedures

annually. The condition might produce infertility in 10 percent of the cases that occur; 3 percent or more of patients will have ectopic pregnancy, and chronic pain is a problem in many others. Pelvic inflammatory disease is largely limited to sexually active females. Pelvic inflammatory disease is classified as acute or chronic. The most common organisms that produce the condition are *Neisseria gonorrhoeae* and *Chlamydia*, but numerous other organisms have been incriminated. Diagnosis of pelvic inflammatory disease is based on clinical findings. The classic signs include fever, lower abdominal pain with pelvic tenderness, and purulent vaginal discharge. In patients requiring further study, laparoscopy, pelvic ultrasonography, and pelvic CT scanning may be helpful in confirming a diagnosis.

Treatment Patients with evidence of peritonitis, high fever, or suspected tuboovarian abscess should be admitted to the hospital for observation and intravenous antibiotics. Some specialists believe that all women with pelvic inflammatory disease should be admitted to the hospital for more intensive care, which might preserve their fertility. Recommendations include one of the following outpatient therapy combinations: cefoxitin 2.0 g intramuscularly with oral probenecid or ceftriaxone 250 mg intramuscularly or equivalent cephalosporin plus doxycycline 100 mg orally two times daily for 10–14 days.

Follow-up of patients treated on an ambulatory basis should be carried out within 48–72 h. If there is no improvement in the patient, she should be admitted for intravenous antibiotics. Recommendations from the Centers for Disease Control and Prevention for inpatient treatment include cefoxitin 2.0 g intravenously every 6 h plus a loading dose of gentamicin 2.0 mg/kg intravenously, followed by a maintenance dose of 1.5 mg/kg intravenously every 8 h. Doxycycline 100 mg orally twice daily is given after the patient is discharged from the hospital to complete a total of 10–14 days of therapy. An alternative regimen is clindamycin 900 mg intravenously every 8 h plus a loading dose of gentamicin 2.0 mg/kg intravenously, followed by a maintenance dose of 1.5 mg/kg intravenously every 8 h. Some patients may require surgery for persistent abscess or chronic pelvic pain.

Surgical Therapy Surgery becomes necessary under the following conditions: (1) the intraperitoneal rupture of a tuboovarian abscess, (2) the persistence of a pelvic abscess despite antibiotic therapy, and (3) chronic pelvic pain. At one time, total abdominal hysterectomy with bilateral salpingo-oophorectomy was considered the procedure of choice. Good antibiotics and a better understanding of

the pathophysiology of the disease allow less radical surgery. In the presence of unilateral disease, a unilateral salpingo-oophorectomy may be more appropriate. The rupture of a tuboovarian abscess is a true surgical emergency. A shocklike state commonly accompanies rupture. This problem was common, and mortality approached 100 percent. With prompt surgical intervention and intensive medical management, the mortality rate today is less than 5 percent. The patient with a ruptured abscess must be explored. Hysterectomy and oophorectomy are commonly indicated.

ENDOMETRIOSIS

Endometriosis is one of the most common conditions encountered; it is found in approximately 20 percent of all laparotomies in women in the reproductive age group. It is found most often in the third and fourth decades. Endometriosis persists into the postreproductive years. The cause of endometriosis is unknown, but the most common theory is retrograde menstruation. Endometriosis can be recognized as bluish or black lesions giving them a "gunpowder burn" appearance. It is found most commonly on the ovary. Other involved organs can include the uterosacral ligaments, the peritoneal surfaces of the deep pelvis, the fallopian tubes, the rectosigmoid, and a number of distant sites.

Many patients are asymptomatic even with widespread endometriosis; others have severe pain, particularly dysmenorrhea, and dyspareunia. Infertility and abnormal bleeding are common problems.

The finding of a pelvic mass and tender nodularity of the uterosacral ligament strongly suggests endometriosis. The mass usually represents an ovarian endometrioma, often referred to as a "chocolate cyst." Endometriomas are found in approximately a third of women with endometriosis and are often bilateral. Although endometriosis may be suspected on the basis of clinical findings, definitive diagnosis is made laparoscopically. Medical management of this condition should not be started without a confirmed diagnosis.

Treatment Choices of treatment include expectant management only, medical management, and surgery. Asymptomatic patients can be cared for through simple observation and management with cyclic oral contraceptives and simple analgesia. Pseudomenopause is currently the most common medical treatment for endometriosis. The most common medications used today for this purpose are the gonadotropin-releasing hormone agonists (GnRH-a). They can be

given by depot injection or daily nasal spray. Because bone loss is also a result of hypoestrogenism, it is recommended that the treatment not be continued for more than 6 months.

Conservative surgical therapy for endometriosis has become much more common with the advancement of laparoscopic surgery. Superficial endometrial implants can be ablated with electrocautery or laser, and ovarian endometriomas can be removed. Ovarian endometriomas deserve special consideration. These "chocolate cysts" cannot be treated effectively medically. Even large endometriomas can be drained and the cyst lining removed laparoscopically. Extirpative surgery is the only permanent treatment for symptomatic endometriosis. In younger patients, a normal ovary may be spared in some cases. If total hysterectomy with bilateral salpingo-oophorectomy is required, replacement hormone therapy is indicated, and recurrence is uncommon. To minimize the risk of recurrent endometriosis, it is recommended that replacement hormones include daily estrogen combined with a progestin such as medroxyprogesterone acetate 2.5 mg given orally.

ECTOPIC PREGNANCY

Women in the reproductive age group have an increased risk of ectopic pregnancy as they age. A history of salpingitis is common in women with ectopic pregnancy. Sterilization protects against ectopic pregnancy, but when sterilization methods fail, the risk of tubal implantation is increased.The most common complaint of patients with ectopic pregnancy is pain, frequently associated with irregular vaginal bleeding. Approximately 80 percent of affected women will recall a missed menstrual period. Physical findings include abdominal tenderness on cervical motion. An adnexal mass may be palpated in approximately 50 percent of patients.

The most helpful laboratory examination is measurement of the beta subunit of hCG (β-hCG). Pelvic ultrasonography, particularly when performed with a vaginal transducer, is proving important in differentiating uterine gestations from ectopic gestations. Vaginal probe enables the clinician to determine whether the developing pregnancy is in the uterus or in the tube at a time when the hCG levels are barely more than 1000 mIU/mL. Significant intraperitoneal hemorrhage also can be visualized. In those patients who do not desire to continue the pregnancy, curettage of the uterus with examination of the tissue can be diagnostic. A diagnostic laparoscopy is usually required in the symptomatic patient for definitive diagnosis. In the presence of hemodynamic instability, immediate laparotomy is indicated.

Treatment *Laparoscopic Procedures* The laparoscope has been an important diagnostic tool for the last several decades, but only recently has it become the standard approach for treatment. Linear salpingostomy is the treatment of choice for ectopic pregnancies less than 4 cm in diameter that occur in the distal third (ampullary) segment of the tube. Closing the tube is not necessary because the tube closes spontaneously. Partial or total salpingectomy is indicated when the pregnancy is located in the isthmic portion of the tube. Larger ectopic pregnancies are managed by total salpingectomy because adequate hemostasis is difficult to achieve without extensive tubal damage.

Medical Therapy A relatively new approach to ectopic pregnancy is the use of methotrexate. Conservative criteria for treatment of ectopic pregnancy with methotrexate include serum β-hCG levels less than 3500 IU/L and vaginal ultrasound that reveals the tubal pregnancy to be less that 3.5 cm in diameter with no visible fetal cardiac motion and no sign of hemoperitoneum. Intramuscular methotrexate will result in complete resolution of the ectopic pregnancy in 96 percent of patients.

PELVIC SUPPORT DEFECTS

Pelvic support defects include uterine prolapse, cystocele, rectocele, enterocele, urethral detachment, and posthysterectomy vaginal prolapse. Pelvic support defects may be produced by obstetric injury, conditions that increase abdominal pressure, obesity, decreased estrogen levels, and inherent tissue weakness secondary to genetic or nutritional factors.

Uterine Prolapse Uterine prolapse is abnormal descent of the uterus relative to the bony pelvis and vagina. If the entire uterus prolapses through the introitus, the condition is considered a total prolapse; otherwise, it is partial.

Cystocele and Rectocele These conditions are due to herniation of the bladder and the rectum into the vaginal canal, generally through a widened vaginal introitus.

Enterocele An enterocele, herniation of intraperitoneal organs generally at the vaginal apex, most often follows hysterectomy. The hernia sac is lined by peritoneum. Enteroceles are frequently misdiagnosed as rectoceles.

Urethral Detachment At one time, urethral detachment was called *urethrocele.* In most cases, the urethrocele coexists with a cystocele.

Stress Urinary Incontinence Urinary incontinence affects almost 40 percent of all women over 60 years of age and is a common problem for younger women. Before considering operation, the patient should be evaluated with a cystometrogram.

Therapeutic Considerations Minor asymptomatic support defects may be treated expectantly or by pubococcygeal exercises. Pubococcygeal exercises involve contracting and relaxing the levator muscle repetitively several times daily. Symptoms that may require surgery include urinary stress incontinence; symptomatic prolapse of the uterus, bladder, or rectum; urinary retention; vaginal ulceration due to prolapse; and constipation secondary to rectal sacculation.

BENIGN TUMORS

Ovarian Tumors

NONNEOPLASTIC CYSTS

By definition, a cystic enlargement of the ovary should be at least 2.5 cm in diameter to be termed a *cyst.*

Follicular Cysts These are unruptured, enlarged graafian follicles.

Corpus Luteum Cysts These cysts become as large as 10–11 cm. They can rupture and lead to severe hemorrhage and occasionally vascular collapse.

Endometriomas These account for most "chocolate cysts" and are cystic forms of endometriosis of the ovary.

Wolffian Duct Remnants These are not ovarian cysts. They are small, unilocular cysts. In most instances, they are incidental findings.

NONFUNCTIONING TUMORS

Cystadenomas Serous cystadenomas appear as cysts within translucent walls containing clear fluid and lined by simple ciliated epithelium. They are adequately treated by simple salpingo-oophorectomy. Some cystadenomas are classified as borderline tumors or adenocarcinomas of low malignant potential. These (grade 0)

carcinomas usually are associated with an excellent prognosis and, if they are unilateral, may be treated by unilateral adnexectomy for women in their reproductive years. Occasionally, a condition known as *pseudomyxoma peritoneii* is encountered; this is a locally infiltrating tumor composed of multiple cysts containing thick mucin. These tumors arise either from ovarian mucinous cystadenomas or from mucoceles of the appendix, both of which commonly coexist.

Mature Teratoma These germ cell tumors are thought to arise from the totipotential germ cells of the ovary. The tumors often contain calcified masses, and occasionally either teeth or pieces of bone can be seen on abdominal radiographs. If a teratoma (dermoid) is encountered in a young woman, it is preferable to shell it out from the ovarian stroma, preserving functioning tissue in the affected ovary. These cysts contain ectodermal, mesodermal, and endodermal tissues in addition to a thick, greasy, fatty material. If spilled during surgery, a chemical peritonitis may result; therefore, it is important to remove these tumors intact. In approximately 12 percent of patients, these tumors are bilateral.

Brenner Tumor These are rare epithelial tumors that usually do not secrete hormones. Histologically, the epithelial elements are similar to Walthard rests and are believed to arise from these. Simple oophorectomy is usually sufficient therapy.

Meig's Syndrome This pertains to ascites with hydrothorax, seen in association with benign ovarian tumors with fibrous elements, usually fibromas. Meig's syndrome can be cured by excising the fibroma.

FUNCTIONING TUMORS

Granulosa Cell–Theca Cell Tumor Pure theca cell tumors (thecomas) are benign, but those with granulosa cell elements may be malignant. Usually, granulosa cell tumors elaborate estrogen; these tumors have no hormone production. In young girls they are characteristically manifested by isosexual precocity, and in elderly women they are sometimes associated with endometrial carcinoma. If the tumor is discovered in the reproductive years and confined to one ovary without signs of surface spread or dissemination, a simple oophorectomy may be sufficient therapy. If it is discovered in later life, removal of both ovaries with the uterus is indicated.

Sertoli–Leydig Cell Tumors (Arrhenoblastomas) These rare but potentially malignant tumors are associated with androgen output and masculinization. They usually occur in the reproductive age

group and appear to contain tubular structures as well as Leydig-type cells. In young patients with a single involved ovary, unilateral oophorectomy is adequate therapy, provided there is no extension of the tumor. For older patients or for those with bilateral involvement, total hysterectomy and bilateral salpingo-oophorectomy are performed.

Struma Ovarii This refers to the presence of grossly detectable thyroid tissue in the ovary, usually as the predominant element in dermoid cysts. This tissue occasionally may produce the clinical picture of hyperthyroidism.

UTERINE TUMORS

Leiomyomas Uterine leiomyomas are the most common benign tumor in the female pelvis. It is estimated that up to 50 percent of all women at some time in their life have one or more of these uterine tumors. Many leiomyomas are asymptomatic; when they do produce symptoms, they cause pain, abnormal uterine bleeding, infertility, ureteral obstruction, bladder distortion, and pressure symptoms secondary to the enlarged uterus. Uterine leiomyomas are subject to a number of degenerative changes, including calcification, necrosis, and fatty degeneration. Malignant degeneration occurs in less than 1 percent of all tumors.

Treatment Most symptomatic tumors can be managed expectantly. When symptoms indicate surgical treatment, surgery should be fitted to the needs and desires of the patient. Therapeutic options might include myomectomy, total abdominal hysterectomy, or transvaginal hysterectomy.

Adenomyosis Adenomyosis is a growth of endometrial tissue in the myometrium of the uterus and is sometimes referred to as *endometriosis of the uterine corpus.* The condition occurs during reproductive years and leads to a thickening of the myometrial wall.

Polyps A polyp is a local hyperplastic growth of endometrial tissue that usually causes postmenstrual or postmenopausal bleeding or staining, which is cured by polyp removal or curettage. The polyps are usually benign, but cases of adenocarcinoma of the endometrium arising in a polyp have been reported.

Cervical Lesions Cervical polyps cause the same symptoms as endometrial polyps. They often can be removed as an outpatient procedure followed by cauterization of the base of the polyp. Nabothian cysts are mucous inclusion cysts of the cervix. They are

harmless, usually asymptomatic, and generally do not require surgery.

VULVAR LESIONS

The term *leukoplakia* is often used for any white patch of the vulva. These alterations may precede the development of malignant changes. Lichen sclerosus is a pruritic lesion that does not appear to be premalignant. Hyperplastic lesions termed *hypertrophic dystrophies* are found that may be benign (epithelial hyperplasia) or may show atypia, in which case dysplastic changes can be observed. The pruritic symptoms can be helped by topical application of corticosteroids or testosterone. Noninvasive malignant change of the surface squamous epithelium of the vulva occurs in the same way as that described for the cervix. Carcinoma in situ of the vulva both histologically and clinically behaves like carcinoma in situ of the cervix. Bowen's disease and usually Paget's disease are considered part of the carcinoma in situ complex of the vulva; they are adequately treated by wide local surgical excision (simple vulvectomy). The laser also is used to treat these lesions locally.

Malignant Tumors

OVARIAN TUMORS

Ovarian Carcinoma Ovarian carcinomas are divided histologically into epithelial, germ cell, and stromal malignancies. The majority of the 26,700 or more cases of ovarian cancer diagnosed annually in the United States are of the epithelial type. The median age at diagnosis for epithelial ovarian cancer is 61 years, and the overall 5-year survival rate for epithelial cancers is 37 percent.

Although the etiology of ovarian cancer is uncertain, approximately 5 percent of patients with epithelial tumors come from families where one or more first-degree relatives also have the disease. In such families, prophylactic oophorectomy may be considered at the completion of childbearing, especially if specific BRCA1 mutations are identified. Primary peritoneal carcinomatosis has been reported in women who have undergone prophylactic surgery, however.

The FIGO (International Federation of Gynecology and Obstetrics) staging system for ovarian cancer is outlined in Table 39-2. Efforts to establish other cost-effective screening programs using serum markers such as CA-125 and vaginal ultrasound examination are being developed. Vaginal ultrasound is a promising technology that is not presently cost-effective in screening programs. Currently, the majority of women with epithelial cancers have stage III tumors at the time of diagnosis.

TABLE 39-2
FIGO (1986) STAGING SYSTEM FOR OVARIAN CANCER

Stage	Characteristic
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites; no tumor on the external surfaces, capsule intact
IB	Growth limited to both ovaries; no ascites; no tumor on the external surfaces, capsule intact
IC	Tumor either stage IA or stage IB but with tumor on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells or with positive peritoneal washings
II	Growth involving one or both ovaries on pelvic extension
IIA	Extension or metastases to the uterus or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB with tumor on the surface of one or both ovaries, or with capsule(s) ruptured, or with ascites containing malignant cells or with positive peritoneal washings
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes; superficial liver metastases equals stage III; tumor is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor or one or both ovaries; histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative
IIIC	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastases equals stage IV

Treatment Therapy for epithelial ovarian cancer consists of surgical resection and appropriate staging followed by chemotherapy. Women with low-grade early-stage (IA or IB) cancers may be treated with surgery without adjuvant therapy. In all other patients (stage IA, grade 3, and stage IB and above), appropriate initial surgery includes bilateral salpingo-oophorectomy, abdominal hysterectomy if the uterus has not been removed on a prior occasion, appropriate staging, and tumor resection.

Staging Staging indicates surgical resection or biopsy of all potential areas of tumor spread. Among patients whose cancer is confined to one or both ovaries at the time of gross inspection, occult metastases can be identified by careful surgical staging in one-third. Epithelial ovarian cancers disseminate along peritoneal surfaces and by lymphatic channels. The omentum is a common site for metastases, as are both the paraaortic and pelvic lymph nodes.

The terms *debulking* and *cytoreduction* have been introduced to indicate aggressive surgical removal of ovarian cancer. When disease remaining after surgical resection consists of nodules or plaques less than 1–2 cm in diameter, the surgical effort is termed *optimal,* and when a larger volume of residual disease remains, the surgical removal is termed *suboptimal.* Because of the survival advantage, every effort should be made to resect as much disease at the time of diagnostic laparotomy as is possible.

"Second Look" Operations *"Second Look" Laparotomy* Ovarian cancer often defies diagnosis because it does not produce symptoms and is detectable neither radiographically nor serologically even in relatively advanced stages. CA-125 is more sensitive than radiographic or magnetic resonance scanning but is also associated with a number of false-positive results and may not be elevated in patients with mucinous tumors. In addition, approximately half of patients with advanced ovarian cancer whose CA-125 levels normalize during chemotherapy harbor viable and clinically undetectable disease.

"Second look" surgery is currently used primarily as a research tool. New treatment regimens can be evaluated quickly by performing a "second look" operation. "Second look" laparotomy is performed through a midline abdominal incision. Peritoneal washings are obtained from both abdominal gutters, the diaphragms, and the pelvis. Since persistent cancer is most likely to be identified in sites where there was tumor at the conclusion of the primary operation, these areas are explored first.

Other Secondary Operations Surgical resection of tumor after chemotherapy or at the time of relapse is termed *secondary*

cytoreduction. In the occasional patient who undergoes diagnostic biopsy only before the administration of chemotherapy, early reexploration may be termed *interval cytoreduction.* In patients with a massive tumor burden, this approach not only may be safer but also might result in a more successful tumor resection before the completion of chemotherapy.

Palliative Surgery In most cases of advanced ovarian cancer, death is associated with bowel dysfunction or frank obstruction. When bowel obstruction occurs early on in the clinical course of ovarian cancer, and particularly if it occurs before the administration of chemotherapy, surgical intervention is warranted and should be aggressive. When bowel obstruction occurs after chemotherapy, the prognosis is unfavorable. Surgery is often difficult to perform because of extensive tumor. Laparotomy may be complicated by enteric injury or fistula. Often the best approach in these patients is the use of a percutaneous or endoscopically positioned gastrostomy tube and intravenous fluids or conservative nutritional support.

Laparoscopy in Ovarian Cancer At present, our ability to resect large ovarian cancers successfully using laparoscopic equipment is limited. With the advent of new equipment and techniques, the role of laparoscopy in the staging and treatment of ovarian malignancies is expanding. Several investigators have developed successful methods of performing both pelvic and paraaortic lymphadenectomies using endoscopic equipment.

Tumors of Low Malignant Potential These are epithelial tumors of malignant potential intermediate between benign lesions and frank malignancies. Most are of the serous type. They are distinguished from invasive cancers microscopically by the lack of stromal invasion. The median age of diagnosis is approximately 10 years younger than that of patients with epithelial cancers. The vast majority occur in stage I. Surgery should include abdominal hysterectomy and bilateral salpingo-oophorectomy unless fertility is to be preserved in patients with unilateral lesions. These patients may undergo unilateral salpingo-oophorectomy. Patients with stage III and IV lesions have 5-year survival rates that approach 85 percent after complete surgical resection. There is little evidence that either chemotherapy or radiotherapy improves survival.

Germ Cell Tumors These tumors occur in women in the first three decades of life and typically grow rapidly. Most are unilateral, and all have a tendency to spread to the paraaortic lymph nodes. Dysgerminoma, the female equivalent of testicular semi-

noma, is composed of pure, undifferentiated germ cells. It is bilateral in 10 percent of patients and is occasionally associated with elevated levels of hCG or lactate dehydrogenase (LDH). It is the most common ovarian malignancy diagnosed during pregnancy. Patients should undergo appropriate staging at the time of the primary resection but need not undergo hysterectomy (if fertility is to be preserved) or removal of the opposite ovary if it is normal in appearance. Adjuvant therapy is unnecessary unless there is evidence of extraovarian spread. This tumor is exquisitely sensitive to chemotherapy or radiation.

The other germ cell tumors in order of frequency are immature teratoma, endodermal sinus or "yolk sac" tumor, mixed tumors, embryonal carcinomas, and choriocarcinomas. The first may be associated with elevated levels of alpha-fetoprotein (AFP). Elevated AFP levels are found in all patients with endodermal sinus tumors and mixed tumors that contain this component. Embryonal carcinomas are associated with abnormal levels of both AFP and hCG, and choriocarcinomas secrete hCG. These tumors are invariably unilateral. Except for those with completely resected stage I, grade 1 immature teratomas and those with stage I dysgerminoma, all patients with germ cell tumors require systemic chemotherapy. Three courses of a platinum and etoposide-containing combination suffice in those patients whose tumors are completely resected. Cure rates in these patients approach 90 percent.

CARCINOMA OF THE CERVIX

Carcinoma of the cervix accounts for about 16,000 cases and 5000 deaths annually in the United States. Risk factors include multiple sexual partners, early age at first intercourse, and early first pregnancy. DNA related to that found in the human papillomavirus has been identified in cervical dysplasia and carcinoma in situ, both precursor lesions, as well as in invasive cancers and lymph node metastases. In no cancer has widespread screening had as profound an impact on mortality as it has in carcinoma of the cervix. Georges Papanicolaou devised the cytologic smear that bears his name in 1943. Since that time, screening programs have dramatically reduced the rate of invasive cervical cancer. The Pap smear has shifted the frequency of cervical abnormalities toward the premalignant intraepithelial diseases, dysplasia, and carcinoma in situ. All intraepithelial lesions are noninvasive and can be treated successfully using conservative methods. Eighty percent of all cervical cancers are squamous cell in type and arise from the squamocolumnar junction of the cervix. The remainder of cervical malignancies arise in the endocervical canal and are either adenocarcinomas or adenosquamous carcinomas. Other rare histologic varieties associated with

poor prognosis are neuroendocrine small cell carcinomas and clear cell cancers. The latter are frequently associated with maternal exposure to diethylstilbestrol.

Staging Cervical cancers spread predominantly by lymphatic channels. The first lymph nodes involved are the paracervical or parametrial area. The supraclavicular lymph nodes are the most common site of distant nodal metastases. FIGO staging for cervical cancer is based on clinical examination, intravenous pyelography, and chest radiography. The FIGO staging system is illustrated in Table 39-3. All patients with stage IIB cancer and above are treated primarily with radiotherapy in the United States.

Treatment *Intraepithelial or Preinvasive Disease* Abnormal Pap smears must be evaluated by colposcopy and biopsy. Colposcopy is examination of the cervix with a low-power (10–50×) microscope after application of dilute acetic acid to the cervix. The acid solution is mucolytic and serves to desiccate the epithelium, a process that brings out subtle epithelial patterns referred to as *white epithelium, punctation, mosaicism,* and *abnormal vasculature.* Cervical intraepithelial neoplasia is treated in a number of ways. In general, the larger the lesion and the higher the grade of dysplasia, the greater is the failure rate. The most definitive treatment for cervical intraepithelial neoplasia is vaginal or abdominal hysterectomy. Cervical cone biopsy is curative in most cases of cervical intraepithelial neoplasia. In patients in whom the surgical margins of the cone specimen are uninvolved, the risk of recurrence is less than 5 percent. If the surgical margins are involved, half of such patients will develop recurrent disease.

More conservative methods of treating cervical intraepithelial neoplasia include wire loop excision, laser vaporization, and cryosurgery. Loop excision can be done under local anesthesia (paracervical block) in the outpatient setting.

Microinvasive Cervical Cancer Simple hysterectomy is adequate therapy. In some, cone biopsy and excision may be used, provided close surveillance is possible.

Early Invasive Cervical Cancer (Stage IB and IIA) Stage IB and IIA tumors are associated with a risk of pelvic lymph node metastases of 10–15 percent and a risk of spread to the paraaortic nodes of about 5 percent. Radical hysterectomy with pelvic lymphadenectomy or definitive radiotherapy is effective treatment in this stage cancer. Women with stage IB_2 cervical cancers (exceeding 4 cm in diameter), especially those endocervical primaries that distend the

TABLE 39-3
FIGO STAGING SYSTEM FOR CERVICAL CANCER

Stage	Characteristic
O	Carcinoma in situ
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
IA	Preclinical carcinomas of the cervix; that is, those diagnosed only by microscopy
IA_1	Minimal microscopically evident stromal invasion
IA_2	Lesions detected microscopically that can be measured. The upper limit of the measurement should not show a depth of invasion of more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates, and a second dimension, the horizontal spread, must not exceed 7 mm. Larger lesions should be staged as IB
IB	Lesions of greater dimensions than Stage IA^2 whether seen clinically or not. Preformed space involvement should not alter the staging but should be specifically recorded so as to determine whether it should affect future treatment decisions
IB^1	Tumor size no greater than 4 cm
IB_2	Tumor size greater than 4 cm
II	Involvement of the vagina but not the lower third, or infiltration of the parametria but not out to the sidewall
IIA	Involvement of the vagina but no evidence of parametrial involvement
IIB	Infiltration of the parametria but not out to the sidewall
III	Involvement of the lower third of the vagina or extension to the pelvic sidewall
IIIA	Involvement of the lower third of the vagina but not out to the pelvic sidewall if the parametria are involved
IIIB	Involvement of one or both parametria out to the sidewall
III (urinary)	Obstruction of one or both ureters on intravenous pyelogram (IVP) without the other criteria for stage III disease
IV	Extension outside the reproductive tract
IVA	Involvement of the mucosa of the bladder or rectum
IVB	Distant metastasis or disease outside the true pelvis

cervix circumferentially, may require a combination of radiotherapy and surgery. These large endocervical tumors are referred to as "barrel" lesions and are refractory to surgery or radiotherapy alone.

Stage IB_1 lesions and early stage IIA cancers may be treated successfully with radical hysterectomy and pelvic lymphadenectomy. Because early cervical cancer so rarely spreads to the ovaries, radical hysterectomy need not include oophorectomy. Ovarian preservation is one of the strongest arguments for the use of surgery over radiotherapy.

Locally Advanced Carcinoma of the Cervix (Stages IIB to IVA) These cancers are treated primarily with radiotherapy. Treatment consists of a combination of external therapy to the pelvis (teletherapy) from a high-energy source such as a linear accelerator and a local dose delivered to the cervix and parametrial tissue (brachytherapy) using a cesium applicator such as a Fletcher-Suite tandem and ovoids.

The finding of metastases in the common iliac or paraaortic chain indicates the need for extended-field radiotherapy encompassing these areas in addition to the pelvis. Even with such therapy, 5-year survival rates are low, seldom exceeding 20 percent.

Recurrent Cervical Cancer As a rule, patients who develop local recurrences after preliminary surgical therapy are treated most effectively with external- and internal-beam radiotherapy. Although those with lymph node failures may not be curable in this setting, those with vaginal recurrences often can be saved with such an approach. Women who develop recurrent cancer following primary radiotherapy are generally not candidates for curative therapy. If, however, the recurrent lesion is small, the interval to failure is a year or more, and the lesion is unaccompanied by symptoms such as back or leg pain or edema, surgical resection may be possible. Most gynecologic oncologists prefer to perform pelvic exenteration in such circumstances. Often, an anterior exenteration with en bloc removal of the bladder, cervix, uterus, and upper vagina is feasible. The preferred method of diversion in these patients is the creation of a sigmoid urostomy or transverse colon conduit. Other surgical options include a Koch pouch or the Indiana reservoir, both of which provide a means of urinary continence without an external applicance.

In general, about half the patients thought to be candidates for pelvic exenteration are found to have intraperitoneal spread or nodal metastases at the time of exploratory laparotomy and, in most centers, do not undergo resection. Of the remaining patients in whom surgery is possible, 30–50 percent will develop a second, nearly always fatal recurrence after surgery.

ENDOMETRIAL CANCER

Endometrial cancer is the most common female genital malignancy, accounting for 34,000 cases annually in the United States. It is a highly treatable cancer, and only 6000 deaths are reported each year.

Risk factors for endometrial cancer include obesity, diabetes mellitus, hypertension, low parity, early menarche, and late menopause. Excessive exposure to estrogens is implicated in the genesis of endometrial cancer and its precursor, endometrial hyperplasia. Women who take estrogens in the menopausal years are known to have a sixfold increase in the risk of endometrial cancer if progestational agents are not taken as well. There is also an increase in the incidence of endometrial lesions in women with a history of chronic anovulation (Stein-Leventhal syndrome) and in those with estrogen-producing ovarian stromal neoplasms such as granulosa cell tumors. Endometrial hyperplasia may be divided into simple and complex, depending on the microscopic architecture, and into those with or without atypia. Atypical complex hyperplasias are most likely to give rise to frank adenocarcinomas. Simple hysterectomy is the preferred method of treatment for the hyperplasias. In women with underlying health problems that preclude surgical therapy, therapy with progestational agents such as megestrol or medroxyprogesterone acetate may be used with success.

Treatment Endometrial cancer is staged according to the FIGO criteria detailed in Table 39-4. Pelvic lymph node metastases occur in about 12 percent of patients with endometrial cancer apparently confined to the uterus.

Risk factors associated with lymph node spread include high histologic grade (grade 2 or 3), low levels of progesterone receptor, deep myometrial or lymphatic channel invasion, spread to the adnexa, endocervical extension, and unusual histologic variants such as papillary serous or clear cell carcinomas.

Vaginal hysterectomy is occasionally useful in patients with early endometrial cancer when lymph node metastases are thought to be unlikely. This operation is particularly well suited for massively obese parous patients. It is critical to remove the ovaries in women undergoing surgery for endometrial cancer because 5 percent harbor occult metastases. Radiotherapy alone may be the treatment of choice in patients at excessive risk for operative intervention.

VULVAR CANCER

Vulvar cancer accounts for about 5 percent of all gynecologic cancers. Although uncommon histologic types such as malignant melanoma and adenocarcinoma of the Bartholin's gland occur, over

TABLE 39-4
FIGO (1988) STAGING SYSTEM FOR ENDOMETRIAL CANCER

Stages	Characteristics
IA G123	Tumor limited to endometrium
IB G123	Invasion to < 1/2 myometrium
IC G123	Invasion to > 1/2 myometrium
IIA G123	Endocervical glandular involvement only
IIB G123	Cervical stromal invasion
IIIA G123	Tumor invades serosa or adnexae or positive peritoneal cyotlogy
IIIB G123	Vaginal metastases
IIIC G123	Metastases to pelvic or para-aortic lymph nodes
IVA G123	Tumor invasion bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph node

Histopathology—Degree of Differentiation

Cases should be grouped by the degree of differentiation of the adenocarcinoma:

G1	5% or less of a nonsquamous or nonmorular solid growth pattern
G2	6%-50% of a nonsquamous or nonmorular solid growth pattern
G3	More than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on Pathologic Grading

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II tumor by 1.

In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rule Related to Staging

Because corpus cancer is now surgically staged, procedures previously used for determination of stages are no longer applicable, such as the finding of fractional D&C to differentiate between stage I and II. It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply but designation of that staging system would be noted.

Ideally, width of the myometrium should be measured along with the width of tumor invasion.

90 percent of vulvar malignancies are squamous carcinomas. Epidemiologic risk factors include older age, smoking, previous intraepithelial or invasive squamous cancer of the cervix or vagina, chronic vulvar dystrophy, and immunocompromise. Human papillomavirus-like DNA has been identified in both preinvasive and invasive squamous carcinomas of the vulva. It is likely that the human papillomavirus plays an important role. Spread of squamous carcinoma of the vulva is primarily via the lymphatics of the vulva.

The 1988 FIGO staging system for vulvar cancer (Table 39-5) is currently accepted. This system requires surgical evaluation of the inguinal lymph nodes and provides a schema in which prognosis and therapy are closely linked with stage.

Treatment Another area of progress in the surgical management of vulvar carcinoma has been the use of conservative surgery for early lesions of the vulva. Although specific criteria differ slightly, most investigators recognize that squamous cancers of the vulva less than 2 cm in diameter and no more than 1 mm thick, and that are of histologic grade 1 or 2, are associated with a very small risk of inguinal metastases. Such lesions are adequately treated with deep, wide excision, provided skin margins of 1 cm are obtained and the dissection is carried to the level of the superficial transverse perineal muscles. Inguinal lymphadenectomy can be omitted in such patients. A modified hemivulvectomy and ipsilateral inguinal lymphadenectomy have been used successfully. This approach should be considered if the primary lesion is less than 2 cm in diameter and 5 mm or less in thickness.

Another controversial area in the management of squamous carcinomas of the vulva is that of the patient with locally advanced disease. When extensive vulvar cancer involves more than the distal urethra, the vagina or rectovaginal septum, or the anal musculature, ultraradical surgery may be required. Anterior, posterior, or total pelvic exenteration may be necessary to resect such lesions successfully.

In recent years, such locally advanced lesions of the vulva also have been treated successfully with external-beam radiotherapy combined with radiosensitizing drugs such as cisplatin and 5-fluorouracil. At the completion of combination therapy, the areas of involvement are excised widely or biopsied.

Uncommon Vulvar Tumors *Melanoma* Lesions less than 1 mm thick or Clark level II lesions may be treated conservatively with wide local excision. The value of inguinofemoral lymphadenectomy is controversial in lesions of greater depth, although primary surgical cure is occasionally achieved in patients with microscopic nodal metastases.

TABLE 39-5
FIGO STAGING OF VULVAR CANCER

Stage 0	
Tis	Carcinoma in situ, intraepithelial carcinoma.
Stage 1	
T1 N0 M0	Tumor confined to the vulva and/or perineum—2 cm or less in greatest dimension. No nodal metastasis.
Stage II	
T2 N0 M0	Tumor confined to the vulva and/or perineum—more than 2 cm in greatest dimension. No nodal metastasis.
Stage III	
T3 N0 M0	Tumor of any size with
T3 N1 M0	(1) adjacent spread to the lower urethra and/or the vagina, or the anus
T1 N1 M0	(2) unilateral regional lymph node metastasis.
T2 N1 M0	
Stage IV A	
T1 N2 M0	Tumor invades any of the following:
T2 N2 M0	Upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastasis.
T3 N2 M0	
T4 Any N M0	
Stage IV B	
Any T, Any N, M1	Any distant metastasis, including pelvic lymph nodes.

Intraepithelial Disease Intraepithelial disease (Bowen's disease, bowenoid papulosis, vulvar intraepithelial neoplasia, carcinoma in situ) may be treated successfully by removing the involved epithelium. Also effective in the treatment of intraepithelial disease is the carbon dioxide laser.

Gynecologic Operations

DILATATION AND CURETTAGE (D&C)

At one time dilatation of the cervix and curettage of the endometrial cavity were among the most common surgical procedures performed in this country. Office biopsy and medical means of dealing with abnormal bleeding have largely replaced the need for diagnostic dilatation and curettage. The are indicated for removal of endometrial polyps or therapeutic termination of pregnancy and for retained placental tissue following abortion or obstetric delivery.

The major complication of D&C is perforation of the uterus. Perforation is diagnosed when the operator finds no resistance to a dilator or curette at a point where he or she normally would expect it. Perforation generally is treated in an expectant manner. Falling hematocrit and other signs of intraperitoneal bleeding indicate the need for laparotomy and control of the bleeding site. Any infection following D&C should be treated with antibiotics.

In recent years, suction curettage for incomplete abortion, hydatid mole, and therapeutic abortion has become popular. Suction machines fitted with cannulas that vary from 4–12 mm in diameter evacuate the uterus in less time and save blood loss.

ENDOSCOPIC SURGERY

Endoscopic surgery, including both laparoscopy and hysteroscopy, has assumed a major role in gynecology.

For a more detailed discussion, see Sutton GP, Rogers BE, and Hurd WW: Gynecology, chap. 39 in *Principles of Surgery,* 7th ed.

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CHAPTER

40

NEUROSURGERY

GENERAL CONSIDERATIONS

A detailed history and physical examination are the foundation of neurosurgical diagnosis. For patients with nervous system disorders, an accurate history needs to be taken once, but the neurologic examination must be repeated and recorded often to gauge the course of the illness and to judge the urgency of subsequent diagnostic and surgical interventions.

Diagnostic Studies Plain films of the spine are useful in the evaluation of traumatic and degenerative spine disorders. Myelography and postmyelogram computed tomographic (CT) scanning remain valuable imaging tools in the assessment of spinal nerve root and spinal cord integrity in trauma and neoplastic and degenerative spine disease. CT is the initial study of choice in the evaluation of head injury, subarachnoid hemorrhage, and hydrocephalus. Magnetic resonance imaging (MRI) is an unparalleled modality for imaging the cranial spinal junction and provides exquisite anatomic detail throughout the neuraxis, exclusive of the assessment of bony involvement, which might require CT. MR angiography is used increasingly in assessments of the extracranial (i.e., carotid) and intracranial (i.e., circle of Willis) circulatory system. For the present, however, cerebral angiography is the "gold standard" in the diagnosis of aneurysms and arteriovenous malformations (AVMs) and provides a vehicle for the application of sophisticated interventional techniques. These therapeutic angiographic techniques include transfemoral microballoon dilation of vasospastic intracranial arteries, occlusion of carotid-cavernous fistulas, and embolization of tumors, aneurysms, and AVMs. Ultrasound is useful in the assessment of neonatal hydrocephalus and in real-time intraoperative localization procedures. Neurophysiologic tests including visual, auditory, and somatosensory evoked potentials provide evidence of nervous system integrity during cranial and spinal operative procedures. The electroencephalogram (EEG) provides an important tool in perioperative diagnosis and as an indicator of physiologic

integrity during cerebrovascular surgery. Electromyography and nerve conduction velocity testing (EMG/NCV) are often used in the diagnosis of peripheral nerve and nerve root lesions both to localize lesions and to assess recovery from injury.

SPECIAL SITUATIONS

Seizures Seizures are presenting signs of cerebral neoplasms in 40–90 percent of patients harboring these lesions and also occur in the setting of cerebral trauma and infection. Repetitive seizures or status epilepticus must be treated vigorously. A benzodiazepine such as lorazepam (0.02–0.12 mg/kg I.V. slowly over 2 min) or diazepam (10 mg) should be administered as initial doses and may be repeated if ineffective. Simultaneously, the patient should be loaded with phenytoin (18 mg/kg, $<$50 mg/min), watching for hypotension during infusion. If this fails, phenobarbital infusion ($<$ 100 mg/min until seizures stop or 20 mg/kg total dose) is recommended, with attention at all times to airway maintenance.

Raised Intracranial Pressure Space-occupying lesions, trauma, and hypoxia/ischemia are all associated with increased intracranial pressure (ICP). Symptoms of elevated ICP include headache, stupor, diplopia, nausea and vomiting, and neck stiffness. Hypertension, bradycardia, and respiratory irregularity (Cushing's triad) are late signs. The upper limits of normal ICP are 10–15 mmHg, with ICPs greater than 20 mmHg considered clearly pathologic.

The treatment of elevated ICP may include head of bed elevation, hyperventilation (PCO_2 25–30 mmHg), and osmotic diuresis (mannitol 1.5 g/kg/24 h) to a maximum serum osmolality of 300–310 mOsm/L. Steroids (dexamethasone, 4–6 mg, q4h) are effective in the setting of brain tumors associated with ICP elevations but are generally not employed following head injury. High fever may exacerbate brain swelling and should be controlled with alcohol sponging, antipyretics, and hypothermia blankets.

Infections Among the common central nervous system (CNS) infections, meningitis may be treated with antibiotics alone, whereas subdural empyema, brain abscess, and epidural abscess are generally treated with a combination of surgical debridement and prolonged antibiotic therapy. Variable antibiotic penetration of the normal blood-brain barrier and specific targeting of antibiotics to specific infections are important considerations. Pending definitive culture results, broad-spectrum antibiotics are recommended for life-threatening infections. These include nafcillin (2.0 g I.V. q4h)

or vancomycin (1.0 g I.V. bid) and gentamicin (75 mg I.V. q8h). Prophylactic antibiotic therapy in the setting of persistent cerebrospinal fluid (CSF) leak is not recommended.

Fluid Balance Mild fluid restriction (2000 mL/24 h, D_5, 0.5% NS) and avoidance of free water in intravenous solutions are recommended in neurosurgical patients. Fluid balance should be monitored carefully (I/O, daily weight) and enteral feedings initiated, if possible, 3 days after injury or after surgery.

Disturbances of fluid balance include the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and diabetes insipidus. In SIADH, inappropriately high antidiuretic hormone (ADH) levels are associated with retention of free water, hyponatremia, high urinary sodium, low serum osmolarity, and high urinary specific gravity and is best treated with fluid restriction. In diabetes insipidus, inappropriately low levels of ADH cause serum hypernatremia and hyperosmolarity along with high urine volumes and low urinary specific gravity. Careful rehydration and administration of antidiuretic hormone are essential.

State of Altered Consciousness *Coma* is an alteration in the level of consciousness from which the patient cannot be aroused by any stimulus. In *stupor*, the patient can be partially aroused by loud command or painful stimulus but promptly lapses into unconsciousness with withdrawal of stimulation. Common causes of coma and stupor include acute alcoholic intoxication with blood alcohol levels greater than 400 g/10 dL, narcotic poisoning, diabetic coma, and hypoglycemia precipitated by insulin overdose, starvation, or vigorous exercise.

Emergency management measures include intubation if the respiratory rate is less than 10 breaths per minute, the PO_2 is less than 70 mmHg, or the PCO_2 is greater than 50 mmHg with the patient breathing oxygen through a mask. Arterial blood-gas (ABG) monitoring, blood glucose determination, and toxicologic analysis are recommended. For possible hypoglycemia, narcotic overdose, and Wernicke's encephalopathy, 50 mL of 50% dextrose in water, 0.4 mg naloxone, and 100 mg thiamine are administered intravenously, respectively.

TRAUMA

Severe head injury (Glasgow coma scale score > 7) is associated with injury to other organ systems in 60 percent of patients. In neurosurgical evaluation, it is important to remember that loss of

consciousness may have preceded the traumatic event and may have a separate etiology (aneurysmal subarachnoid hemorrhage, seizure, hypoglycemia, etc.). Primary consideration must be given to respiratory exchange, control of hemorrhage, and maintenance of peripheral vascular circulation. As vital functions are stabilized, a preliminary evaluation of the nervous system is essential, followed by careful repetitive neurologic examinations to detect improvement or deterioration.

Scalp Injury Scalp lacerations may cause hemorrhage and shock and should be treated promptly with pressure dressings or by clamps applied to the galea, which pull it back over the dermis. If lacerations are found to overlay a depressed skull fracture or penetrating wound, neurosurgical consultation and debridement/closure in the operating room are essential. In the absence of such injury, simple scalp lacerations should be debrided and irrigated to prevent infection and should be closed primarily, with particular attention paid to galeal closure to provide hemostasis. Scalp avulsions may require split-thickness skin grafts or free myocutaneous flaps attached by microsurgical vascular anastomosis.

Skull Fractures Skull fractures are classified on the basis of intactness of overlying skin or mucous membrane (*closed* or *open/compound*), degree of inward displacement (*depressed* or *nondepressed*), involvement of the skull base (*basilar*), and geometric pattern (*linear, stellate, comminuted*). Simple fractures (linear, stellate, or comminuted nondepressed) do not usually require treatment but may lead to hemorrhage if they cross vascular channels in the skull or to infection if assessory nasal sinuses are involved. Linear or stellate nondepressed open fractures may be treated with simple debridement and closure of the scalp wound. Severely comminuted open fractures and depressed open fractures require debridement and closure in the operating room with inspection of the dura to identify lacerations not visualized on the CT scan. Basilar skull fractures involve the floor of the calvarium and may be associated with ecchymosis in the periorbital region (*raccoon sign*) or behind the ear (*Battle's sign*), suggesting the location of the basilar skull fracture. Basilar skull fractures may be associated with facial nerve paralysis, usually with spontaneous resolution of most facial nerve deficits and rarely requiring operative decompression. CSF rhinorrhea or otorrhea are important concomitants of basilar skull fractures and usually resolve spontaneously within 7–10 days. Persistence of CSF leak is treated with lumbar CSF drainage, followed by surgical exploration if this is in-

effective. Prophylactic antibiotics are not usually recommended in the setting of CSF leak following trauma.

Brain Injury Mechanisms of brain injury include direct disruption of the brain by a penetrating object, focal injury to the brain from rapid deceleration/rotation of the brain within the confines of the rigid skull, or *diffuse axonal injury* caused by rotational/shear stresses. The initial impact producing neuronal and axonal disruption constitutes the *primary injury*. Subsequent events including the development of intracranial hematoma, cerebral edema, hypoxia, hypotension, hydrocephalus, and endocrine disturbance may lead to *secondary injury* that compounds the initial insult to the nervous system.

Mild head injury or concussion is not usually associated with significant primary brain injury or neurologic deficits. Moderate–severe head injury is more likely to be associated with neurologic deficits of variable reversibility. Accompanying secondary injury is often present.

Elevated ICP may contribute to secondary brain injury by reducing cerebral perfusion pressure (CPP), which is defined by the difference between mean arterial blood pressure (MABP) and cerebral venous pressure or ICP (CPP = MABP − ICP). Elevation of ICP in the setting of a stable MABP results in the decline in CPP. When CPP falls below 50 mmHg, cerebral ischemia and secondary injury may occur. Intracranial hypertension associated with cerebral ischemia constitutes a potentially reversible mechanism of secondary insult; thus aggressive management is indicated.

Evaluation Rapid clinical assessment is essential following head injury, and the Glasgow Coma Scale (GCS) is used to follow the neurologic status and to predict the ultimate outcome in individual patients. A GCS score of more than 7 constitutes "severe closed head injury" (Table 40-1).

The initial evaluation includes a detailed history of the etiology and mechanism of injury, the level of neurologic and autonomic function at the scene of the accident and during transport, as well as a careful neurologic assessment on arrival in the emergency room. CT scan is generally not indicated in patients without headache, lethargy, or a focal neurologic deficit, in whom observation and discharge in the care of responsible family members often will suffice. Patients who are symptomatic, with or without a focal deficit, require CT scanning of the head. If the CT is unremarkable and a high index of clinical suspicion exists, additional observation, angiography, and/or spinal imaging may be necessary.

TABLE 40-1
GLASGOW COMA SCALE

Best motor response	Obeys	M6
	Localizes	5
	Withdraws	4
	Abnormal flexion	3
	Extensor response	2
	Nil	1
Verbal response	Oriented	V5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	Nil	1
Eye opening	Spontaneous	E4
	To speech	3
	To pain	2
	Nil	1

NOTE: The coma scale score is the sum of the sectional scores.

In the unconscious patient, the examiner must rely on serial evaluations of brainstem reflexes to determine the level of brain compromise. These serial evaluations may reveal subtle changes in status that may herald impending problems, warranting further investigation and/or surgical intervention.

Treatment The global objectives of treatment include maintenance of adequate oxygenation and brain circulation, removal or amelioration of mass effect, control of ICP, prevention of infection, and ultimately, rehabilitation. Frequent monitoring of vital signs, arterial blood gases, and fluid intake and output is a reactive necessity. Any focal mass from hemorrhage, devitalized brain, or swelling that alters level of consciousness usually should be removed. The subsequent goals of management are normalization of CPP and prevention of secondary injury to the damaged brain. ICP monitoring is usually indicated in patients with a GCS score of more than 7 or in comatose patients requiring emergency extracranial (abdominal, thoracic, orthopaedic, etc.) surgery.

Ventriculostomy allows continuous assessment of ICP and therapeutic intervention via drainage of CSF to lower ICP. Other methods of ICP management include head elevation in the neutral position, pharmacologic sedation if posturing and combative activity

are present, hyperventilation (PCO_2 25–28 mmHg), anticonvulsant prophylaxis, mild fluid restriction, prompt treatment of SIADH, prevention of hypotension, aggressive treatment of hypertensive episodes, and management of hyperthermia. If the ICP remains elevated, mannitol (0.5–1.0 g/kg) and furosemide (0.1 mg/kg) are useful. Deep sedation with narcotics and the use of paralytic agents may provide additional benefit. Barbiturate coma in refractory ICP elevation is seldom used. Corticosteroids have no proven benefit in patients with brain injury. Attention must be paid from the outset to pulmonary hygiene, venous stasis, and skin care to prevent pneumonia, pulmonary embolism, and skin breakdown that may complicate recuperation from head injury.

SPECIFIC INJURIES

Diffuse Axonal Injury

Diffuse white matter injury from rotational/shear forces is associated with high mortality and substantial neurologic morbidity. Despite massive anatomic disruption, both the CT scan and the ICP may be relatively normal.

Epidural Hematoma

The most common cause of epidural hematoma is a fracture of the temporal bone leading to disruption of the middle meningeal artery and the accumulation of arterial blood between the cranium and the dura mater. Little or no brain injury occurs at the time of the skull fracture; thus, if properly recognized and treated, these lesions can be evacuated and neurologic morbidity completely prevented. Classically, a blow to the head fractures the skull and causes a brief period of unconsciousness. The patient may then regain consciousness, entering a "lucid interval," where there are minimal neurologic symptoms or signs. With enlargement of the hematoma over several hours, hemispheric distortion ensues, leading to compression of the temporal lobe and "herniation" of the medial temporal lobe over the tentorial edge. Uncal herniation causes compression of the ipsilateral cerebral peduncle and adjacent oculomotor nerve (*transtentorial herniation*). The neurologic concomitants are ipsilateral pupillary dilatation and contralateral decerebrate posturing. Coma, fixed and dilated pupil(s), and decerebration are the classic triad indicating transtentorial herniation.

Although epidural hematomas resulting from arterial or venous bleeding in the epidural space are curable lesions, the mortality rate remains unacceptably high due to a lack of recognition of this

entity. A patient may be seen during the "lucid interval" and discharged; thus, if a high index of suspicion for epidural hematoma exists, a CT scan or careful period of observation (6–8 h) is recommended.

Subdural Hematoma

Acute subdural hematomas are associated with severe head injury and arise from a combination of torn bridging veins, disrupted cortical vessels, and cortical lacerations. Surgical evacuation of clot may lead to improvement of symptoms attributable to mass effect. Persistent deficits, however, often remain attendant to the widespread parenchymal injuries often seen in these patients. *Subacute subdural hematomas* are associated with progressive lethargy, confusion, and focal neurologic deficits that appear over several days and which may reverse following hematoma removal. *Chronic subdural hematomas* usually arise from tears in bridging veins resulting from a minor and often unrecognized head injury. These hematomas are seen most common in elderly individuals with brain atrophy or in infants. Slowly progressive mental status changes with or without focal signs are noted. Hematoma drainage often results in complete recovery.

Spinal Cord Injury

Mechanism of Injury Traumatic injury of the spinal cord may result from vertebral fracture, fracture/subluxation, hyperextension of the cervical spine in a patient with a narrow spinal canal, acute herniation of intervertebral disc material into the canal, and penetrating injuries including gun-shots and stabbings. In recognition of the common association of head injury with spinal cord trauma, head-injured patients should be immobilized on a backboard with a hard cervical collar and cervical immobilization maintained until a thorough examination and radiographic assessment are completed.

Clinical Findings Spinal tenderness to palpation, extremity weakness, numbness or paresthesias, respiratory embarrassment, and hypotension suggest spine or spinal cord injury. When spinal nerve roots are involved, *radiculopathy,* characterized by motor and sensory impairments in corresponding myotomes and dermatomes, may be seen (Fig. 40-1). When the spinal cord itself is involved, *myelopathy* ensues with variable manifestations.

Complete lesions of the spinal cord result in the loss of all motor and sensory function below the level of injury. Areflexia, lucid-

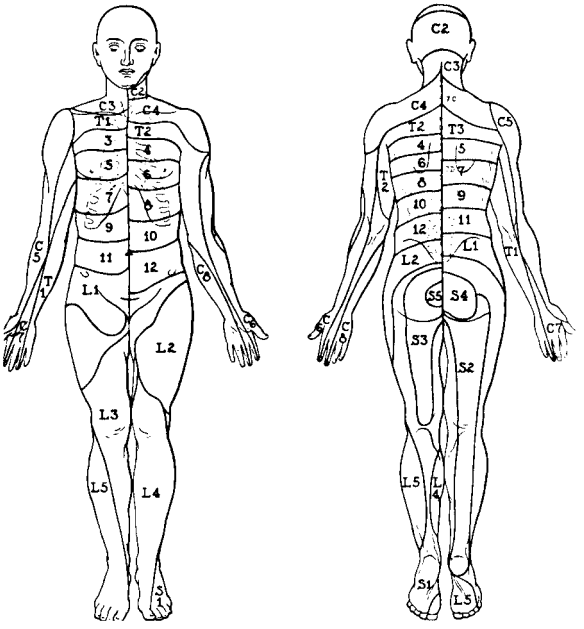

FIGURE 40-1 Diagram of sensory nerve root distribution.

ity, anesthesia, and autonomic paralysis below the level of the lesion are seen. Arterial hypotension may occur with lesions above T5 (Fig. 40-2).

Incomplete spinal cord lesions have variable presentations. The *Brown-Séquard syndrome* is produced by a cord hemisection resulting in ipsilateral motor paralysis and loss of position/vibratory sensation (dorsal columns and corticospinal tract injury) and contralateral loss of pain and temperature sensation (spinothalamic tract injury) below the level of injury. The *central cord syndrome* often follows a flexion/extension injury of the cervical spine in the setting of a narrow spinal canal and is characterized by bilateral weakness and loss of pain/temperature sensation in the upper extremities, with relative preservation of these modalities in the lower extremities. The *anterior spinal artery syndrome* constitutes an ischemic deficit in the irrigation territory of this artery, with a

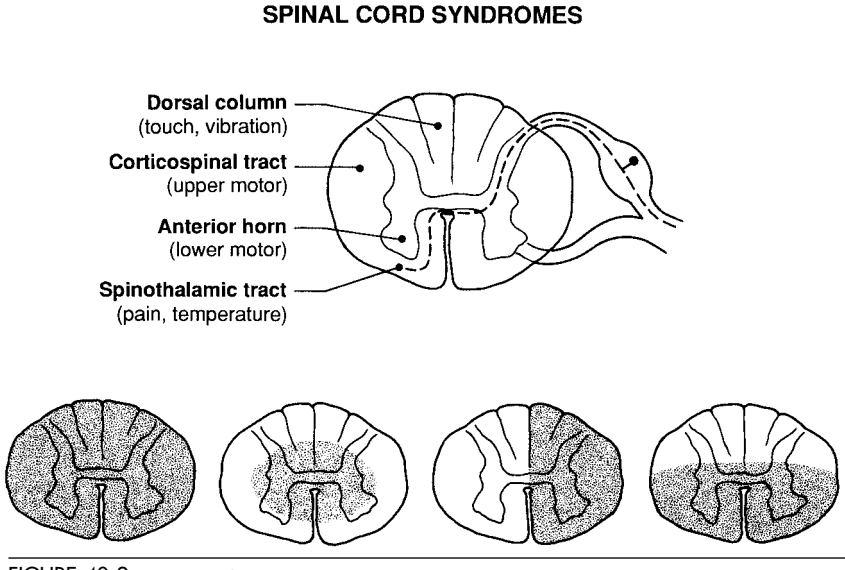

FIGURE 40-2 Diagram of spinal cord anatomy and common clinical syndromes that accompany spinal cord lesions.

lesion of the anterior two-thirds of the spinal cord and preservation principally of the dorsal columns. Bilateral loss of motor function and pain/temperature sensation with sparing of position, vibratory, and light touch sensations constitute the classic picture. The *cauda equina syndrome* may result from lumbar spine trauma below the conus (L1–L2) and has a variable presentation. Lower extremity motor, sensory, and reflex functions may be affected, along with compromise of bowel and bladder performance.

Myriad autonomic concomitants of spinal cord injury bear recognition. With cord injury above C3, respiratory effort is lost completely. In C4–C6 injuries, insufficient tidal volumes may lead to progressive hypoxia and CO_2 retention. Spinal cord injury may lead to ileus and gastric distention, necessitating nasogastric drainage, and bladder distention, requiring catheterization. Injuries above T5 compromise sympathetic tone, with a resulting hypotension requiring the administration of intravenous fluids. Postural changes (i.e., upper body elevation) may lead to precipitous declines in blood pressure because reflex tachycardia and peripheral vasoconstriction that often compensate hypotensive episodes are compromised.

Evaluation Once hemodynamic stability is ensured, spinal radiographs with the patient still immobilized on a backboard with a hard cervical collar are obtained. Comatose or severely injured patients require plain-film imaging of the complete spine. Flexion/extension views should not be performed in the setting of neurologic deficit or in patients with compromised mental status. Adjunctive imaging studies include CT scans, myelograms and post-myelogram CT scans, and MRI.

Treatment The objectives of treatment include correction of spinal alignment, protection of undamaged neural tissue, restoration of function to reversibly damaged neural tissue, and achievement of permanent spinal stability. Closed reduction of cervical dislocation involves progressive axial traction using a halo or skull tongs under x-ray control to a maximum of approximately 50 lb. *Open reduction* combined with fusion is reserved for patients in whom attempts at closed reduction are unsuccessful (i.e., locked facets). Thoracic and lumbar injuries are treated by immobilization on a firm surface without traction. Early operation is indicated when closed reduction of malalignment is unsuccessful, when neurologic deterioration is identified in a patient with an incomplete cord lesion initially, when severe spinal cord compression via an intraspinal mass is revealed by imaging studies in a patient with some preservation of cord function, or when a penetrating injury

with or without a CSF leak is identified. Emergent decompression does not improve neurologic recovery in patients with complete transverse deficits, and reports of worsening of existing deficits in patients with incomplete lesions undergoing emergent operations have lead to a more conservative approach to these individuals.

External immobilization for a period of approximately 3 months is usually recommended following either closed or open (surgical) reduction. A Philadelphia collar may suffice when anterior and posterior metal plating procedures are used.

Peripheral Nerve Injury

Acute peripheral nerve injuries encompass three pathophysiologic processes: (1) *neurapraxia* is a temporary loss of function in the absence of axonal disruption, usually following a compression injury; (2) *axonotmesis* is disruption of the axon with preservation of the myelin sheath due to prolonged compression or stretch injuries, leading to a complete sensory/motor deficit and a variable proximal to distal recovery (1–2 mm/day) depending on axonal regrowth; and (3) *neurotmesis* is a disruption of both the axon and axon sheath resulting from nerve transection, which requires surgical repair to facilitate nerve regeneration (1 in/month).

Evaluation of peripheral nerve injury requires a detailed history and precise neurologic examination through which the site of injury can be localized with great accuracy. Radiographs of the injury site may identify any occult fracture or foreign body. EMG constitutes an effective aid to the evaluation of the degeneration/regeneration process but is not useful within the first 3 weeks following injury.

Treatment Surgical repair of nerve lacerations may incorporate end-to-end anastomosis or interpositional grafts. Immediate repair is indicated when the wound is clean and uncomplicated (e.g., stab wounds, glass lacerations, and surgical incisions). Secondary or delayed repair (i.e., 6 weeks) is performed when wounds are dirty or complicated (e.g., gunshots, avulsions with tissue disruption, and wounds older than 5–6 h). Significant motor return cannot be expected in any muscle more than 15 in from a nerve suture.

Nerve injuries in continuity (contusion/compression) are often explored if they do not improve within 6 weeks of injury and may respond to neurolysis or removal of scar tissue that inhibits axonal regrowth. Stretch injuries are common in the brachial plexus and are usually treated conservatively with careful recording of motor/sensory loss via serial examinations and MRI to identify root avulsions.

Prompt institution of physical therapy to improve muscle function and maintain joint motion minimizes the complications of denervation. Orthopedic reconstruction and long-term rehabilitation are often appropriate.

NEOPLASMS

Nervous system tumors represent almost 10 percent of all neoplasia. Of these, 15–20 percent occur in children. Most adult tumors are found above the tentorium (supratentorial), whereas most childhood tumors are found below (infratentorial). CNS tumors are the most common solid tumors in children and of all pediatric cancers are second only to leukemia in frequency.

Intracranial Tumors

Clinical Manifestations Intracranial tumors may exert local effects due to focal irritation or destruction of neural tissue. Focal seizures are a common presenting sign of intracranial tumors, whereas focal neurologic deficits may occur as a result of invasion, compression, or destruction of essential cerebral centers. Tumors also may exert more generalized effects resulting from raised ICP due to the presence of the tumor mass, which may be compounded by obstructive hydrocephalus and cerebral edema. These generalized effects may lead to headache, nausea and vomiting, depressed consciousness, and/or impaired cognition. If tumor enlargement is gradual, substantial volumes may be attained with only subtle alterations in personality, behavior, recent memory, or attention and concentration. A patient's family may notice gradual changes over months or years. However, as intracranial compensatory mechanisms are exhausted, a precipitous clinical demise may occur at the time of presentation. Evaluation requires a careful history of progressive and often subtle neurologic deficits and behavioral/cognitive symptoms followed by imaging with CT or MRI.

Treatment Histologically benign tumors (i.e., meningiomas or schwannomas) are curable if totally removed; however, proximity to vital brain structures may preclude resection. Solitary, symptomatic metastases from extracranial sites are removed if accessible and if the patient's systemic cancer is under control or treatable. Primary malignant brain tumors are not usually curable, but significant palliation may be obtained with a combination of surgery, radiation, and chemotherapy. The recent introduction of external stereotactic radiosurgical methods (gamma-knife and Linnac) offer

great promise for the treatment of both benign and malignant neoplasms. In addition, stereotactic biopsy methods have been useful in the safe identification of deep-seated neoplasms. Finally, stereotactic surgical methods are rapidly evolving and promise to facilitate resection of intraaxial tumors.

Classification of Intracranial Tumors Intrinsic brain neoplasms (Table 40-2) are classified on the basis of their cells of origin. Glial neoplasms (e.g., astrocytoma, oligodendroglioma, ependymoma, microglioma, and choroid plexus papilloma) are classified as *low-*

TABLE 40-2
BRAIN TUMORS

	Percent
Gliomas	40–50
Astrocytoma, grade 1	5–10
Astrocytoma, grade 2	2–5
Astrocytoma, grades 3 and 4 (glioblastoma multiforme)	20–30
Medulloblastoma	3–5
Oligodendroglioma	1–4
Ependymoma, grades 1–4	1–3
Meningioma	12–20
Pituitary tumors	5–15
Neurilemomas (mainly VIIIth nerve)	3–10
Metastic tumors	5–10
Blood vessel tumors	
Arteriovenous malformations	
Hemangioblastomas	
Endotheliomas	0.5–1
Tumors of developmental defects	2–3
Dermoids, epidermoids, teratomas	
Chordomas, paraphyseal cysts	
Craniopharyngiomas	3–8
Pinealomas	0.5–0.8
Miscellaneous	
Sarcomas, papillomas of the choroid plexus, lipomas, lymphoma, unclassified, etc.	1–3

grade (astrocytoma), *intermediate-grade* (anaplastic astrocytoma), and *high-grade* (glioblastoma) tumors. Low-grade astrocytomas in children have an 80 percent 10-year survival rate. In adults, low-grade astrocytomas are accompanied by a 5-year survival rate of 35–50 percent, whereas high-grade tumors are extremely malignant and carry a life expectancy of 1–2 years. Neuronal tumors (ganglioglioma) are associated with a possibility of surgical cure. Leptomeningeal cells give rise to meningiomas, which arise from the dura mater, in an extraaxial location, and which are completely curable if surgically removed.

The most common adult primary tumor is malignant astrocytoma, followed by meningioma, pituitary tumor, and neurilemoma (see Table 40-2). In childhood, the most common primary tumor is the astrocytoma of the posterior fossa, followed by medulloblastoma, appendemoma, and cranial pharyngioma. Pituitary tumors are generally benign adenomas of anterior pituitary lobe origin and may cause symptoms by hormonal overproduction including amenorrhea/galactorrhea from hyperprolactinemia, acromegaly/gigantism from hypersecretion of growth hormone, and Cushing's disease from hypersecretion of adrenocorticotropic hormone (ACTH). Alternatively, mass effect may result in compromised anterior pituitary function or neurologic symptoms through compression of adjacent structures (e.g., optic nerve, carotid arteries, cavernous sinus). Finally, hemorrhagic infarction of the pituitary or pituitary apoplexy may present with subarachnoid hemorrhage, acute headache, oculomotor paresis, visual loss, and a decline in the level of consciousness.

Spinal Cord Tumors

Classification Spinal tumors constitute 20 percent of all CNS tumors and are classified according to the compartment in which they appear. *Intramedullary tumors* constitute 16 percent of spinal cord tumors and include ependymomas, astrocytomas, hemangioblastomas, and epidermoid/dermoid tumors. *Intradural, extramedullary tumors* are almost always primary CNS tumors, including neurofibroma, schwannoma, meningioma, metastasis of a primary brain tumor, ependymoma, and lipoma. Most intradural spinal neoplasms are benign and amenable to surgical excision. Intramedullary lesions may produce weakness, spasticity, and sensory loss. Extramedullary lesions may present with radicular pain from nerve root involvement as well as long tract signs from compression of corticospinal tract pathways. With conus involvement, early loss of bowel and bladder function may predominate.

Extradural Tumors Extradural tumors include metastatic lesions, myeloma, lymphoma, chordoma, sarcoma, and neuroblastoma, and 90 percent of these tumors are malignant. About 75 percent of extradural tumors are metastatic (e.g., lung, breast, lymphoid, prostatic, kidney, and thyroid), whereas 98 percent of intradural tumors are primary CNS neoplasms. Extradural tumors produce neurologic manifestations either by direct cord compression or by bony involvement with vertebral collapse, leading to progressive paraparesis and sensory loss. Malignant extradural tumors are treated with an emphasis on decompression of the spinal cord, stabilization of the vertebral column, and reduction of tumor volume.

The identification of spinal cord tumors requires the careful assessment of any evidence of bilateral progressive neurologic loss below any transverse level of the body. MRI and CT scans following the injection of intrathecal contrast material constitute the definitive imaging studies.

Peripheral Nerve Tumors

Tumors can arise from peripheral and cranial nerves, spinal roots, and the autonomic nervous system. The more common tumors are schwannoma, neurofibroma, and malignant nerve sheath tumor. Malignant transformation of schwannoma is rare and more common for neurofibromas.

CEREBROVASCULAR DISEASE

Cerebrovascular disease represents a leading cause of death and disability. Approximately 140 per 100,000 persons suffer an ischemic cerebral event each year, and over 30 percent of these individuals die or have significant retained neurologic deficit. Another 20 per 100,000 persons sustain a hemorrhagic cerebral event (hypertensive hemorrhage, subarachnoid hemorrhage) each year, and in excess of 50 percent of such patients suffer a fatal outcome. The human suffering is incalculable; the economic cost is estimated at over $2 billion per year.

Cerebral Ischemia

The brain normally receives approximately 60–80 mL of blood per 100 g of brain tissue per minute. If cerebral blood flow (CBF) falls below 20 mL/min, symptoms of ischemia and frank infarction occur. A normal cerebrovasculature has significant “reserve” owed to

autoregulation, which allows cerebral vessels to dilate in the face of falling flow. Systolic blood pressures as low as 50 mmHg will maintain adequate flow in a healthy individual. Patients with atherosclerotic changes, altered autoregulation due to trauma, or subarachnoid hemorrhage are less able to adapt to decreasing flows.

Cerebral ischemia is divided into those events caused by (1) emboli and (2) primary occlusive disease of the vasculature. The former causes ischemia as the emboli pass through the cerebral circulation and lodge at various locations (usually in the middle cerebral artery territory), whereas the latter is owed to a direct loss of flow due to stenosis of extracranial or intracranial vessels.

Embolic Ischemia

Recent data strongly support the concept that approximately 70 percent of all ischemic strokes are due to emboli. The emboli can originate at any location from the heart to the cerebral vessels themselves. The ischemia caused by embolic occlusion may present as a wide variety of neurologic deficits. The flow pattern in the cerebral vessels favors passage of the embolus into the middle cerebral artery; most commonly presenting as a weakness in the contralateral face and arm. Ischemia in the dominant hemisphere middle cerebral region also causes loss of expressive and/or receptive speech. Ischemia in the anterior cerebral territory may cause weakness in the contralateral leg. Vertebrobasilar ischemia, clinically much less common than carotid circulation ischemia, may cause diplopia, difficulty swallowing, multiple cranial nerve palsies with or without weakness, and frank syncope.

The duration and severity of the neurologic deficit vary according to the degree of ischemia. Deficits that resolve within 24 h are termed a *transient ischemic attack* (TIA). Deficits that resolve between 1 and 7 days are termed a *reversible ischemic neurologic deficit* (RIND). Those deficits which persist are cerebral *infarctions.* The definitions are somewhat arbitrary but serve a useful purpose for clinical classification.

The evaluation of a patient with an ischemic neurologic deficit requires a search for the source of potential emboli. This endeavor should begin at the heart. Electrocardiogram (ECG) and enzyme studies will screen for myocardial infarction, a potential cause of mural thrombi and therefore emboli, which may find their way to the brain. Atrial fibrillation also may cause embolization into the cerebral vasculature. An echocardiogram is also indicated in the setting of cerebral ischemia. The clinical evaluation simply proceeds through the vascular tree from the heart to the brain. If no clear source is identified in the heart, the thoracic arch and carotid

arteries should be evaluated with noninvasive (e.g., ultrasound, MR angiography) or invasive (e.g., angiogram) techniques. The patient who sustains a TIA or RIND has been found to have a significant risk for recurrent ischemia and potential infarction. Identification of the source of the emboli allows treatment options to be selected. Cardiac origin may require formal anticoagulation with Coumadin; carotid plaques without significant stenosis may be treated with antiplatelet therapies; those with significant stenosis may warrant carotid endarterectomy.

Occlusive Ischemia

Narrowing of extracranial or intracranial vessels may cause "low flow" states in the absence of any embolic phenomena. Once felt to be the leading cause of cerebral ischemia, it is now felt to be less common than embolic ischemia. The vasculature may be stenosed by a variety of mechanisms: atherosclerosis at the thoracic arch or carotid or vertebral arteries, fibromuscular dysplasia or other vasculopathies such as Moya Moya disease.

The clinical presentation of occlusive (low-flow) ischemia is very similar to that with ischemic phenomena. The neurologic deficit depends on the zone of ischemia and its severity. As is the case in evaluation of embolic events, a search for occlusive ischemia must include a thorough investigation of the major vessels supplying the brain. MR angiography is improving rapidly and in the future may replace formal angiography, but at the time of this writing, four-vessel cerebral angiography remains the study of choice.

Both embolic and occlusive ischemia cause a zone of nonfunctional or suboptimally functional neural tissue. The size of this area and the time it remains in a suboptimal state depend on the degree and duration of ischemia. If the tissue is hypoperfused for a sufficient period (the exact time frame depends on location, metabolic rate, and many as yet undetermined factors), an infarction occurs. Urgent revascularization procedures and endovascular "salvage" procedures to acutely open vessels are being investigated, but thus far definitive data are not available. A fixed area of infarct can become a hematoma if excessive reflow is established, and complications have been recorded with successful revascularization in such a setting. Prevention of future episodes remains a cornerstone of treatment, using medical therapies such as antiplatelet agents, anticoagulation coupled with carotid end-arterectomy, and other vascular procedures. Extracranial-to-intracranial bypass procedures, such as the superficial temporal artery to middle cerebral artery bypass, have occasional indications but were not found to be widely applicable in a large multi-center study.

Intracranial Aneurysm

An intracranial aneurysm is a saccular distention of the cerebral blood vessels generally found at the bifurcation points in the circle of Willis. Cerebral vasculature has a high elastin content and decreased muscularis, making the vessels less stress resistant. The blood vessels of the brain also lack a firm parenchyma immediately surrounding the vessel wall, therefore making them susceptible to internal stress due to lack of wall support (cerebral vessels at the circle of Willis are essentially "free floating" within the subarachnoid space). These factors, associated with the constant stress on the bifurcation of the vessel due to the flow of blood, can lead to aneurysm formation. There may be congenital weakening and other as yet undetermined factors that potentiate the risk of aneurysm development. They are seen only rarely in children but are noted in 1–2 percent of cerebral angiograms done for various reasons in adults. Approximately 28,000 people per year sustain a subarachnoid hemorrhage in North America, the incidence being fairly constant throughout the world at approximately 12 per 100,000 population.

Subarachnoid hemorrhage from an aneurysmal bleed is heralded by a *sudden, "thunderclap" headache.* This symptom alone, severe sudden headache, is the most reliable diagnostic tool. Because the blood is in the subarachnoid space, as opposed to the brain itself, the patient may have a normal or near-normal neurologic examination. In fact, the patients with the best chance of a good outcome have only the headache and other subjective symptoms. The mortality and morbidity of aneurysmal subarachnoid hemorrhage are devastating. Fully 25 percent of the patients die within 24 h, and another 25 percent die over the first week. Nearly 50 percent of the survivors will have a retained neurologic deficit. Prompt diagnosis, particularly in a good-risk patient based on the history of sudden severe headache, can allow a cure for this morbid disease.

Once the history suggests subarachnoid hemorrhage, a CT scan of the head with and without contrast should be performed. Over 85 percent of subarachnoid bleeds can now be seen on CT scan. The CT scan also will exclude other important processes such as tumor or cerebellar hemorrhage. If the CT scan is negative, a lumbar puncture should be performed. Lumbar puncture has a nearly uniform diagnostic capability for detecting fresh blood (RBCs in the thousands) as well as xanthochromic staining on a spun specimen, which can detect blood in the CSF for 10–14 days after a bleed. If either the CT scan or the lumbar puncture suggest a hemorrhage, cerebral angiography is mandatory to search for an aneurysmal lesion.

Patients with a ruptured aneurysm are at risk for two major morbidities after the initial bleed. Approximately 20 percent of patients will have a rebleed in the 14-day period after the first bleed. This carries a nearly 75 percent death rate if unchecked. Another 10–15 percent will sustain vasospasm (a tight, spasmodic stenosing of the vessels) that can lead to cerebral infarction. Rebleeding can be prevented by prompt craniotomy and clip placement on the aneurysm neck, thereby occluding the aneurysm from the circulation. Vasospasm is treated by maintenance of adequate vascular volume and occasionally by induced hypertension, both factors aimed at optimizing flow through the stenosed vessels. Calcium channel blockers are now used extensively in the treatment of subarachnoid hemorrhage to reduce the risk of ischemic injury from vasospasm. Although they appear to reduce the risk of infarction, the mechanism by which this is accomplished is not established.

The outcome in patients with aneurysmal subarachnoid hemorrhage is directly related to the neurologic status on arrival. Those patients who are arousable, verbal, and following commands (Grades I and II) have a death rate of approximately 10–20 percent. Patients who are comatose or near comatose (Grades III and IV) have a death rate in excess of 65 percent. Once the diagnosis is suspected, a rapid CT scan and lumbar puncture, if needed, may lead to prompt clipping of the aneurysm and effectively eliminate the risk of a rebleed. Intravenous fluids at 100 mL/h of D_5 NS plus 20 mEq KCl and Nimodipine (60 mg PO/NG q4h) should be started on admission. Patients stuporous and who might have difficulty protecting their airway are best intubated "prophylactically" rather than waiting for a hypoxic arterial blood gas, by which time the neurologic damage has already begun. Steroids (Decadron, etc.) have not been conclusively shown to benefit the subarachnoid patient although Decadron, 4 mg, q6h, is currently the drug of choice. Because of the risk of seizures with cortical irritation, Dilantin, 100 mg, tid, is started on admission.

Arteriovenous Malformation of the Brain

Arteriovenous malformations (AVMs) are congenitally abnormal connections between arteries and veins without the proper intervening capillaries and small-caliber vessels. Such an abnormal connection allows high-flow, high-pressure arterial blood to pass into relatively weak-walled veins without a steady cascade of small vessels to dampen the flow. The physiologic stress involved in such a system can lead to rupture of the AVM. The AVMs are located in the brain itself (unlike aneurysms, which are in the subarachnoid

space) and therefore generally cause intracerebral hematomas as opposed to subarachnoid hemorrhage. Any hemorrhage into the brain parenchyma should raise the suspicion of an AVM. AVM bleeds can occur at any age but tend to occur in the first two to three decades of life. Each bleed carries an approximately 10 percent mortality and 20 percent morbidity. The neurologic presentation depends on the location of the AVM. Intracerebral hematomas in the dominant hemisphere may cause aphasia associated with hemiplegia of the contralateral arm and/or leg. Those in the occipital region may cause visual field cuts.

Hematomas large enough to cause elevated ICP and possible herniation need to be surgically evacuated. Those of smaller dimensions, found on angiography to be the result of an AVM, may be carefully observed in hospital in the acute phase. The early rebleed rate with AVMs is low, and definitive surgical removal of the AVM by craniotomy is often intentionally delayed 3–4 weeks to allow the brain edema to recede. Although complete surgical removal remains the goal of therapy, radiosurgical techniques are showing promise in the treatment of AVMs, particularly those smaller than 3 cm in difficult surgical locations.

Hypertensive Brain Hemorrhage

Chronically elevated blood pressure (generally well in excess of 150/90 mmHg) may lead to changes in the cerebral vasculature. Most of the significant changes are at the branching points of small blood vessels such as the lenticulostriate arteries that originate from the middle cerebral arterial trunk. Small aneurysms and weak spots occur, eventually leading to intracerebral hemorrhage. Most intracerebral bleeds are at the basal ganglia, pons, or cerebellum. Those in the basal ganglia lead to a contralateral hemiplegia. Pontine bleeds are often acutely catastrophic, the patient being rendered comatose with pinpoint pupils, quadriplegia, and labored breathing. Cerebellar bleeds have a subtle clinical presentation if small in size, often with only minor cerebellar signs. Large cerebellar bleeds present with a decreased level of consciousness and cranial nerve loss.

The patient often has a relatively “silent” onset of sudden neurologic deficit. The key point, as with all the vascular syndromes, is the sudden onset. Although headache often is present, it is usually moderate, the deficit being the predominant complaint. The death rate with large hematomas is high, in excess of 40 percent. Surgery is generally deferred in basal ganglia bleeds unless life-threatening hematoma exists. Surgical removal has not been found to improve functional outcome in small to moderate-sized hematomas. Cerebellar bleeds are a surgical emergency because the

posterior fossa tolerates raised pressure very poorly, and sudden death may occur. The cerebellum also is a "forgiving" neurologic structure, and even fairly poor-grade cerebellar bleeds may have a good functional outcome with surgery. Pontine bleeds are not surgical candidates and have a death rate in excess of 75 percent. The best treatment of hypertensive hemorrhage is prophylactic treatment—aggressive treatment of hypertension before a bleed occurs. Hemorrhage of this type has decreased over the last 30 years, probably owing in large part to improved treatment of hypertension.

DEGENERATIVE SPINE DISEASE

Degenerative changes in the spine are a normal part of the aging process, as they are in other bodily subsystems. Only a subset of individuals eventually has clinical problems from this degenerative change. The cervical and lumbar regions are at greatest risk because of the constant motion (and therefore stress) seen in those regions of the spine. The rib cage "struts" the thoracic spine, and degenerative problems of a clinical magnitude are much less common in this region.

Intervertebral Disc Disease

Lumbar Lumbar discs are subjected to tremendous physiologic stress in humans because of our biped nature. The discs are greater than 60 percent water in infancy but rapidly desiccate after age 30. This process of desiccation and degenerative changes in the joints and ligaments of the spine predispose the disc to shearing forces. The disc may "fail," forcing a fragmented piece of nucleus pulposus through the annulus, which surrounds the disc. The posterior longitudinal ligament (lining the back of the vertebral body) generally keeps the disc fragment from going directly posterior into the spinal canal. Instead, the fragment forces its way into the neural foramen. The cartilaginous disc material may cause a compressive force on the nerve at the level of the foramen, the clinical picture of this process being termed *lumbar radiculopathy.* Lumbar radiculopathy may occur at any level (L1–S1 nerve roots), and the clinical picture varies accordingly. The most common compressive lumbar radiculopathy occurs at the L4–5 and L5–S1 interspaces. Nearly all radiculopathies present as a painful extremity. Most of the pain will be in the buttock, posterior thigh, and calf. Generally, paresthesias are present in the foot. A disc fragment at the L4–5 level causes an L5 nerve root compression (because the L4 root exits the spinal canal above the disc space). Radiculopathy at the L5 root

causes intense pain in the extremity, as noted above, and may be associated with a weak dorsiflexion of the foot (the extreme case being a foot drop). Numbness will be present on the dorsum of the great toe. A disc fragment at the L5–S1 level will entrap the S1 nerve root (the L5 nerve exits above the L5–S1 disc; the S1 nerve crosses it) and may cause a decreased ankle reflex and a weak plantar flexion of the foot.

The hallmark of true lumbar nerve entrapment is significant lower extremity pain in the aforementioned location, with a lesser degree of low back pain per se. Patients with intense low back pain without lower extremity symptoms generally have musculoskeletal insults and/or lumbar joint disease, spondylolisthesis, etc. rather than nerve compression. The first, and most important, clinical decision to make in evaluation of the "back pain" patient is whether it represents a mechanical lumbar spine process (with predominant low back pain) or a neural compressive (lumbar radicular) process. The symptoms often are aggravated by activity, as well as by coughing and sneezing. Coughing and sneezing cause an increase in spinal fluid pressure, which is transmitted to the irritated nerve root.

Other subsystem diseases can mimic lumbar radiculopathy (sciatica) very closely. The patient with lumbar pain and lumbar pain with true radiculopathy should always have a thorough review of subsystems. Nephritis, invasive colonic or gynecologic neoplasia, metastatic spine tumors, diabetic neuropathy, ectopic pregnancy, abdominal aortic aneurysm, and hip arthritis can all present with low back pain and/or symptoms consistent with radiculopathy. Careful attention to the history and other subsystem symptoms will avoid this serious pitfall.

Physical examination often will find an increase in the pain when the leg is raised, thereby flexing the patient at the hip and stretching the involved root (straight leg raising test). Although not essential for the diagnosis, it is often present. The reflexes should be normal to decreased. An L3 or L4 nerve root may cause a decreased knee reflex, L5 often causes no change, and S1 radiculopathy may decrease the ankle reflex. Motor loss in the quadriceps would be noted in the L3 nerve root presentations; the L5 and S1 nerve losses are as noted above.

The natural history of lumbar radiculopathy is often one of natural resolution. Greater than 80 percent of patients with true lumbar root entrapment improve dramatically over 2–4 weeks with no specific intervention. Although many "conservative" measures have been used (e.g., bed rest, chiropractic, traction, physical therapy, etc.), most studies suggest that the simple passage of time allows many such radiculopathies to clear. Patients seen acutely should

have a thorough subsystem clearance as noted above (a complete blood count and urinalysis will aid in this regard), possible plain films of the lumbar spine to rule out occult compression, fracture from metastatic disease, spondylolisthesis, etc., and then patient observation for 2–3 weeks. Analgesics such as the modest use of codeine (30 mg PO q3–4h) and an anti-inflammatory agent usually will suffice to tide the patient over the acute phase. Only if there is no improvement after 3 weeks should intervention be contemplated. Final diagnosis can be made with MRI of the lumbar spine or lumbar myelography and a postmyelogram CT scan. If a disc fragment is found as the cause of the problem, surgical decompression and disc fragment removal are effective. The results in properly selected patients (i.e., those with primarily neural compressive presentations as opposed to pure low back pain) are good.

Cervical As noted in the lumbar spine, degenerative changes may cause compression of neural structures in the cervical spine. This may present as nerve root entrapment (*cervical radiculopathy*) or as spinal cord compression (*cervical myelopathy*).

Cervical radiculopathy most commonly affects the C5, C6, or C7 roots. Neck pain is present in most patients, but the predominant pain courses into the muscle masses of the arm and terminates as numbness in the appropriate dermatome in the hand. Weakness in the deltoid (C5), biceps (C6), or triceps (C7) may be present. A review of subsystems must be made to exclude high lung tumors (Pancoast) as a cause of nerve involvement. Many patients improve with conservative care (from collar and analgesics, occasionally traction) over 3–4 weeks. Those who fail become candidates for MRI or myelogram to define the diagnosis. Both posterior surgical approaches (posterolateral foraminotomy) and anterior cervical discectomy are effective means of alleviating the problem. In properly selected patients, over 90 percent are improved after surgery.

Cervical myelopathy is a more serious disorder that presents as progressive spinal cord dysfunction owing to a decrease in the dimension of the spinal canal with advancing degenerative changes. Some or all of five clinical examination hallmarks will be present with myelopathy: (1) clonus, (2) hyperreflexia, (3) decreased position sense, (4) abnormal heel to toe walk, and (5) an extensor Babinski sign. A combination of these findings should lead to MRI or myelogram. Decompressive laminectomy, multiple-level anterior decompression, and decompression with instrumentation with fusion have all been effective in relieving the compression in the spinal cord. Results vary with the severity of the spinal cord dysfunction at the time of admission.

INFECTIONS

Infections may enter the central nervous system by (1) hematogenous spread (e.g., a cardiac anomaly such as atrial septal defect or ventricular septal defect), (2) contiguous spread (e.g., middle ear, sinus infections), or (3) contamination by penetrating trauma. The infection may accumulate in the brain itself (*cerebral abscess*) or in the subdural or epidural spaces (*empyemas*). The mortality rate is very high (>35–40 percent) if left untreated. The patient generally complains of severe headache and may have focal deficits such as hemiparesis, speech loss, etc. Emesis may accompany the headache due to an elevation in ICP. The empyema patient often is "toxic" on presentation with febrile episodes, chills, and leukocytosis. The cerebral abscess patient may have a normal white blood count and only a modest temperature. The erythrocyte sedimentation rate (ESR) is usually elevated in both cases. Diagnosis is established with CT scanning. Emergent craniectomy or craniotomy is needed for drainage and culture. Multiweek intravenous antibiotics (i.e., ceftriaxone, metronidazole, and nafcillin combined) are used postoperatively.

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES

Approximately 2 percent of newborns possess some type of congenital abnormality. Sixty percent of these involve the central nervous system, and over half of these are related to defective development or closure dorsal midline structure (Table 40-3).

TABLE 40-3
CONGENITAL NEUROLOGIC MALFORMATIONS

Arnold-Chiari malformation
Dandy-Walker malformation
Spinal dysraphism
Meningocele
Myelomeningocele
Lipomyelomeningocele
Diastematomyelia
Dermal sinus
Myeloschisis

Spinal Dysraphism

This is a failure of the neural groove to close posteriorly in the midline to form a neural tube. Dysraphism implies an abnormal fusion of normally united parts. Spina bifida occulta is the failure of bony structures to close. Patients with this anomaly have a normal spinal cord and normal cord function. This is usually a radiographic finding. If the meninges fail to close, a meningocele develops, producing a cutaneous abnormality without compromise of neurologic function.

Failure of the neural tissue to fuse is called *spina bifida aperta.* Myelomeningocele is the more common form and usually occurs in the lumbar region. It may be partially or totally covered with epithelium, and the accompanying neurologic deficit usually consists of complete absence of motor and sensory function below the level of cord involvement. The most severe form of spinal dysraphism is myeloschisis, which occurs in the thoracolumbar region and usually is associated with paraplegia.

Both myelomeningocele and myeloschisis are associated with hydrocephalus, which is caused by a developmental abnormality of the hindbrain. The treatment of spinal dysraphism is surgical. Meningoceles are excised; myelomeningoceles and myeloschisis are closed as early as possible to reduce the risk of meningitis.

Cranial Dysraphism

This is about one-tenth as common as spinal dysraphism and consists of a midline skull defect through which small portions of the brain protrude, creating an encephalocele. It should be treated by surgical repair, and only 35 percent of the patients attain normal intelligence.

Hydrocephalus

Hydrocephalus implies an increase in the amount of CSF within the ventricular system. It is almost always due to a decrease in the absorption of fluid and is classified as communicating and noncommunicating, related to the presence or absence of communication with the subarachnoid spaces outside the brain through the fourth ventricular foramina.

Infantile Hydrocephalus This usually occurs before the second year of age and frequently is due to a congenital abnormality but occasionally is the result of meningitis or ICP. The patients often have a bulging anterior fontanelle and distended scalp veins.

Childhood Hydrocephalus Causes include tumors, meningitis, and intracranial hemorrhage. The patients present with headache, nausea, vomiting, lethargy, and coma.

Adult Hydrocephalus This results from obstructive tumors, meningitis, and hemorrhage. It may be idiopathic.

The treatment of all types of hydrocephalus is by ventricular fluid shunting. The most commonly used procedure is a lateral ventricle to peritoneal cavity shunt with a one-way pressure-regulating valve in the system.

Craniosynostosis

This is the premature closure of one or more of the cranial sutures. It usually manifests within the first 6 months of life. This may compromise brain growth, and treatment is surgical, with opening of the affected suture(s) along its entire length. The operation should be carried as soon as the diagnosis is made to accommodate brain growth.

NEUROSURGICAL MANAGEMENT OF PAIN

Cranial Nerves Trigeminal neuralgia is one of the more commonly occurring neuropathic painful conditions. It presents as pain in one of the divisions of the trigeminal nerve and may be extremely severe. The evaluation should include a CT scan or MRI. The surgical treatment is the production of preganglionic lesions in the involved branch(es). Retrogasserian rhinotomy may be performed. A nonablative approach involves microvascular decompression of the trigeminal nerve in the posterior fascia.

Spinal Cord Surgical procedures on the spinal cord for ablation of pain include cordotomy to obliterate the spinothalamic tract. This rarely is effective for chronic pain conditions. Ablative lesions can be made in the dorsal route entry zones of the spinal cord, and about 50 percent of patients obtain relief. Intrathecal morphine can be given temporarily or permanently by infusion of small doses. In chronic painful states of nonmalignant spinal origin, transcutaneous excitatory nerve stimulation (TENS), which blocks nerve conduction of pain impulses, may be effective.

Peripheral Nerve Pain from a partial or complete nerve injury follows the sensory distribution of that nerve. Chronic pain may be altered by interruption of the sympathic nerve supply to the

affected extremity. Major causalgia is most commonly related to partial injury of the sciatic or median nerve and may be treated by sympathetic denervation.

EPILEPSY AND MOVEMENT DISORDERS

Epilepsy

The removal of specific areas of the brain can cure epilepsy. Epilepsy has many causes. Congenital anomalies of the brain are common in the pediatric age group. Birth injury also has been implicated. EEG and MRI are monitoring tools to select the patients who will benefit from an operation and to define the region to be ablated. Seizure surgery is performed with the patient under local anesthesia, and electrocorticography is carried out to identify the focus of the seizures.

Movement Disorders

The most commonly recognized of these is Parkinson's disease. The symptoms of tremor and cogwheel rigidity have been controlled with dopamine supplements. Surgical approaches have been used, and currently, stereotactic methods to accomplish pallidotomy have become popular.

RADIOSURGERY

Radiosurgery is a highly focused ionizing radiation used to treat lesions in the depths of the brain. The technique using the so-called gamma-knife allows delivery of radiation to a specific target without adverse affects on the surrounding tissue. Other systems use different techniques to achieve focused-radiation ablation of tumors. Radiation surgery is particularly adaptable to deep intracerebral lesions. It causes sclerosis of vascular structures and necrosis of tumors. It is used to treat neoplasms such as intracranial schwannomas and meningiomas.

PEDIATRIC NEUROSURGERY

Myelomeningocele is expressed as a failure of closure of the neural tube, generally in the lumbar region. The patient often has a significant neurologic deficit below the lesion. Chiari II malformation (caudal descent of cerebellar tonsils with brainstem compression

and microgyria) and hydrocephalus are present in over 80 percent of patients. The myelomeningocele is closed within 24–48 h to reduce the risk of meningitis. The hydrocephalus and Chiari malformation are treated if clinically appropriate as the child progresses. The incidence of this anomaly has decreased markedly with the advent of perinatal ultrasound, alpha-fetoprotein protein testing, etc.

Hydrocephalus in children may result from a multitude of causes: aqueductal stenosis, after meningitis, after intraventricular hemorrhage, and less commonly owing to tumors blocking CSF drainage pathways. The patient often presents with progressive enlargement of the skull, a full fontanelle (if patent), headache, emesis, and blunting of developmental milestones. Therapy is primarily surgical; placement of a ventriculoperitoneal shunt system is preferred. Intellectual capabilities in later years depend on the cause and severity of the hydrocephalus.

For a more detailed discussion, see Hoff JT, Boland MF: Neurosurgery, chap. 40 in *Principles of Surgery,* 7th ed.

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CHAPTER

41

ORTHOPAEDICS

MANIFESTATIONS OF MUSCULOSKELETAL DISORDERS

Pain

Pain is the most common symptom of musculoskeletal disorders. Stimulation of peripheral receptors by noxious agents produces a spatiotemporal pattern of nervous impulses that is interpreted as pain within the higher cerebral centers. Neural pain activity is modulated by analgesics, as well as by neurohormones called *endorphins*, which function as endogenous pain-inhibiting substances.

Pain may be described as localized, diffuse, radicular, or referred. *Local pain* occurs at the site of the pathologic process, whereas *diffuse pain* appears to be more characteristic of deep tissues. *Radicular pain* involves the anatomic distribution of a peripheral nerve and is generally due to pathology involving the nerve or nerve root, as in sciatica. Pain is *referred* when manifested at a location remote from the site of pathology. Examples of referred pain include knee pain as a manifestation of hip joint pathology or pain in the flank or gluteal area secondary to a spinal problem. Muscle pain may result from direct injury or from muscle spasm, a sustained reflexive contraction of muscle. Peripheral nerve pain can be caused from external pressure (neuralgia) or internal compression of a nerve between anatomic structures (compression neuropathies), ischemia, infection (e.g., herpes zoster), metabolic disturbances, or toxins such as lead or arsenic.

Bone lesions in the vertebrae such as metastatic carcinoma, multiple myeloma, infections, or osteoporotic compression fractures can also cause persistent local and occasionally radicular pain.

UPPER EXTREMITY PAIN

Shoulder pain can result from cervical disc protrusions or tumors, rotator cuff tears or impingement syndrome, or arthritis of the

shoulder joint or can be referred to the shoulder from the heart, lungs, or pleura. The rotator cuff consists of the common tendinous insertions of the supraspinatus, infraspinatus, teres minor, and subscapularis. Tendinitis and bursitis are common and usually result from an impingement of the rotator cuff on the coracromial ligament (impingement syndrome). Rotator cuff tears present with acute pain and difficulty with active shoulder abduction. Diagnosis can be made with arthrography, magnetic resonance imaging (MRI), or ultrasound. Elbow pain can result from epicondylitis (such as tennis elbow), ulnar nerve compression at the elbow, arthritis of the elbow, or radicular pain from a compressed nerve root. Pain in the hand or wrist can result from tendinitis (such as trigger finger or deQuervain's disease), arthritis, or median nerve compression (carpal tunnel syndrome).

Cervical Disc Disease Cervical disc herniation can cause neck or radicular pain, neurologic symptoms, and compression of either the spinal cord or nerve roots. Thus motor weakness or sensory abnormalities can occur either in a nerve root distribution or diffusely below the level of the lesion. Myelography or MRI can demonstrate the lesion. The C4–C6 levels are most commonly involved, and patients usually present with relatively acute pain, with neurologic findings depending on the level and extent of the herniation. Cord compression will cause motor weakness and hyperreflexia in the lower extremities and occasionally incontinence. Treatment consists of cervical traction, followed by anti-inflammatory medication and a cervical collar. If neurologic deficit does not respond promptly to traction, surgical discectomy and fusion of the involved level may be necessary.

LOWER EXTREMITY PAIN

The most common causes of foot pain are metatarsalgia and plantar fasciitis, which result from repetitive loading of the metatarsal heads or of the attachment of the plantar ligament to the calcaneus. Additional causes of foot and ankle pain include arthritis, peroneal tendon subluxation, stress fractures, and tarsal tunnel syndrome. Repetitive loading of the tibia can lead to "shin splints," or activity-related pain and tenderness over the tibia, as well as to stress fracture. Muscle cramps, deep venous thrombosis, ischemia, and lumbar nerve root impingement from disc herniation or spinal stenosis are other causes of leg pain. Knee pain can result from internal derangements such as meniscal tears, arthritis, chondromalacia of the patella, and patellar tendinitis or can be referred from hip pathology. Hip pain generally manifests in the inguinal area and can be due to arthritis, osteonecrosis, synovitis, tumors, or infec-

tions. Lateral hip pain commonly results from trochanteric bursitis. Posterior hip pain must be differentiated from sciatica due to lumbar spine pathology.

LOW BACK PAIN

Low back syndrome refers to a disease or injury of the lumbosacral spine that may be acute or chronic in nature. Table 41-1 lists causes of low back pain. Clinically, low back pain may be activity-related, aggravated by sneezing or coughing, or associated with muscle spasm. Referred pain may occur in the buttocks or leg, and nerve root compression can cause radicular pain and/or sensory and motor symptoms in a given nerve root distribution.

Examination of the patient should include assessment of spinal range of motion, the straight-leg-raising test (for sciatic irritability; produces radicular pain if positive), and a complete neurologic examination. Most often low back syndrome is due to traumatic or

TABLE 41-1
CAUSES OF BACK PAIN

1. Structural (anomalous or transitional vertebrae, spina bifida, spondylolysis, spondylolisthesis, facet anomalies)
2. Functional (scoliosis, leg length discrepancy, work or postural attitudes, pregnancy, hip or knee flexion contractures)
3. Infections (pyogenic osteomyelitis, tuberculosis, etc.)
4. Inflammatory (arthritis, ankylosing spondylitis, myositis, fibrositis, etc.)
5. Degenerative (osteoarthritis, senile kyphosis, degenerative disc disease, spinal stenosis)
6. Neoplastic (multiple myeloma, giant cell tumor, eosinophilic granuloma, or metastic bone disease from breast, prostate, lung, kidney, or thyroid carcinoma)
7. Traumatic (compression fracture, transverse process or posterior element fracture, ligament sprain or muscle strain, disc herniation)
8. Metabolic (osteoporosis, osteomalacia, hyperparathyroidism, Paget's disease, renal osteodystrophy, pulmonary osteoarthropathy, osteogenesis imperfecta, etc.)

mechanical causes, and usually it will respond to conservative treatment of bed rest, anti-inflammatories, local heat, and occasionally antispasmodics for muscle spasm. With subsequent mobilization, isometric back and abdominal exercises, and occasionally a corset or back brace, are helpful.

Spondylolisthesis Spondylolisthesis is a forward subluxation of one vertebral body on another and can be caused by (1) spondylolysis (a defect in the pars interarticularis), (2) fracture of posterior elements, (3) facet deficiency (congenital), (4) facet deficiency due to degenerative disc disease, or (5) elongation of the pars (isthmic). Clinically, spondylolisthesis may be asymptomatic, although back pain may be present along with variable degrees of hamstring tightness, sciatica, and rarely, neurologic symptoms. Lateral radiographs will best demonstrate the displacement, and oblique views will show any defect in the pars (spondylolysis). Treatment is conservative, with rest and abdominal exercises, unless progression of the subluxation or of symptoms occurs, in which case a posterolateral fusion usually is done. There has been recent interest in reduction of severely displaced spondylolisthesis and in direct repair of pars defects.

Sciatica Sciatica is a symptom and not a disease, and the term is used to describe radicular-type pain. Sciatica can be caused by nerve root compression by a herniated disc, tumor, abscess, or foraminal narrowing due to degenerative arthritis with facet hypertrophy. Occasionally, an intrapelvic or gluteal tumor or abscess can cause sciatica, as can inflammatory or toxic processes. Disc herniations and degenerative arthritis are by far the most common causes. Disc herniations occur most commonly at the L5–S1 and L4–L5 levels, when a tear in the annulus fibrosus allows herniation of the soft, gelatinous interior nucleus pulposus posteriorly into the spinal canal. The herniated disc then impinges on nerve roots, causing back and radicular pain (sciatica) and sometimes neurologic symptoms. Disc herniations are uncommon in children and older adults and occur most often in middle-aged individuals. Pain is usually aggravated by sitting, coughing, and sneezing, and forward flexion. Symptoms also will be elicited by straight-leg raising, particularly with additional dorsiflexion of the foot (Lasegue's sign). The lesion can be demonstrated by computed tomographic (CT) scan, although generally visualization is better with myelography or MRI. Treatment is generally conservative initially, with 80–90 percent of patients improving spontaneously and not requiring surgery. Surgical excision of the extruded portion of the disc or digestion by percutaneous injection of chymopapain or collagenase into the disc

can be effective invasive treatments. Recent approaches of microdiscectomy and percutaneous suction discectomy remain controversial.

Spinal Stenosis Spinal stenosis is a narrowing of the spinal canal or neuroforamina and can be either acquired, as with degenerative disc disease, or congenital, as in achondroplasia. Currently, the disorder is most readily diagnosed with MRI or CT scans. Patients present with back or leg pain, generally exacerbated by standing and walking and relieved by sitting, in contradistinction to discogenic back pain. Neurologic signs and symptoms may be present, including hyporeflexia. Treatment is conservative, with flexion exercises and bracing, anti-inflammatories, or epidural steroids. Refractory cases are treated by wide posterior surgical decompression, with or without fusion.

Pyogenic Osteomyelitis of the Spine The most common organism responsible for this condition is *Staphylococcus aureus*, which spreads hematogenously from other sites of infection. Patients have back pain, radiographic destruction of the disc space, and sometimes neurologic deficit. They may or may not have fever or other systemic symptoms of infection. Usually leukocytosis and an elevated erythrocyte sedimentation rate (ESR) are present. Treatment usually involves intravenous antibiotics, immobilization, and frequently surgical debridement, often with anterior bone grafting.

DISORDERS OF MUSCLE

Muscle Paralysis and Spasticity

Motor paralysis is loss of voluntary control of muscular contraction. Normally, muscle has some resting tone, which is absent with lower motor neuron lesions, causing flaccid paralysis. Tendon reflexes are also abolished with interruption of the lower motor neuron pathway. *Spasticity* refers to abnormal increases in muscle tone with passive stretch and is seen with upper motor neuron lesions. Loss of inhibitory control of tendon reflexes with upper motor neuron lesions also causes hyperreflexia. Electrical diagnosis of disorders of nerve and muscle is assisted by electromyography (fine needles inserted into muscles record intrinsic electrical activity of the muscles) and by nerve conduction velocity studies (electrical stimulation of a peripheral nerve with recording of the distally induced muscle action potentials). The clinical grading of muscle strength is shown in Table 41-2.

TABLE 41-2
CLINICAL GRADING OF MUSCLE STRENGTH

Grade	Muscle Power
0	Paralysis—no muscle contraction
1	Flicker of contraction without joint excursion
2	Some joint motion, but not against gravity
3	Full joint motion against gravity with no resistance
4	Less than normal strength, but full motion against resistance
5	Normal muscle strength

Intrinsic Diseases of Muscle

Muscular Dystrophies These are hereditary disorders of muscle with progressive degeneration. Types: Duchenne (fatal), fascioscapulohumeral (benign), and limb girdle.

Myotonias These are hereditary progressive disorders, including myotonic dystrophy and myotonia congenita (Thomsen's disease).

Myositis This is an inflammation of muscles that may be caused by a virus, parasite, or spirochete, as well as occurring in association with the various collagen vascular diseases such as dermatomyositis, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis.

Poliomyelitis This is an acute viral disease that invades the central nervous system, causing destruction of the anterior horn cells in the spinal cord, which results in flaccid paralysis. In the acute phase, patients have a febrile illness with malaise and headache, and they may recover or go on to a paralytic phase within a few days. The convalescent phase follows, and some motor improvement may occur for up to 2 years. Treatment is with physical therapy to maintain joint range of motion and prevent contractures. In the final residual stage, surgical procedures may be needed to stabilize flaccid joints by arthrodesis, correct leg-length inequalities, and transfer tendons to restore lost functions. In tendon transfers, a loss of one grade of muscle strength will occur, so only muscles of

grade 4 or 5 are suitable. Foot deformities are common and can be corrected by bracing initially and by combinations of tendon transfers and, near skeletal maturity, arthrodesis.

Cerebral Palsy Cerebral palsy occurs in about 3 births per 100,000. It can be caused by head injury or birth trauma, anoxia, or viral diseases (such as measles or cytomegalovirus). Fifty percent of patients are spastic, 25 percent are athetoid, 5 percent are ataxic, 5 percent are rigid, and 15 percent have a mixed clinical picture. Sixty percent of spastic patients have hemiplegia (ipsilateral upper and lower extremity involvement). The next most common form is diplegia (lower extremities), with quadriplegia (all extremities involved) the final form. Treatment is directed toward prevention of contractures, gait training, and surgical correction of deformities that develop from muscle imbalance. Bracing may help prevent equinus deformities of the ankle, adduction and flexion contractures of the hip, and flexion contractures of the knees. Adductor spasticity of the hip can cause painful hip subluxation or dislocation and may require treatment with adductor tenotomies, obturator neurectomies, or varus/derotation osteotomies of the proximal femur. Recently, transfer of the rectus femoris to the hamstring has been used to improve the swing phase of gait. Hamstring releases and Achilles tendon lengthening may be necessary to correct contractures; occasionally, spinal fusion is needed to control progressive neuromuscular scoliosis.

Myelodysplasia (Spinal Dysraphism) *Myelodysplasia* describes a developmental defect in the vertebral column associated with a neurologic lesion. Failure of midline fusion of vertebral elements may occur without cord involvement (spina bifida occulta) or with a myelomeningocele, a neural tube defect at the level of the lesion. Antenatal screening for alpha-fetoprotein can aid in the diagnosis. New evidence suggests that folate supplementation during the first trimester of pregnancy may markedly decrease the incidence of meningomyelocoele. Eighty percent of patients have associated hydrocephalus. Patients with myelomeningocele generally have paralysis below the level of the defect and are treated shortly after birth by surgical closure of the cystic defect and shunting for hydrocephalus. Functional prognosis varies with the level; with lesions below the L4 level, patients usually will be ambulatory, although lower extremity deformities such as talipes equinovarus and hip subluxation may occur, requiring surgical correction. Additionally, lack of sensory function makes pressure sores a common recurring problem.

Degenerative Diseases of the Nervous System with Skeletal Deformity *Peroneal muscle atrophy* (Charcot-Marie-Tooth

disease) is an inherited progressive process usually beginning in the first or second decade and involving initially the peroneal nerve, with foot drop, cavovarus foot deformities, claw toes, and later intrinsic atrophy in the hands. Treatment involves surgical correction of deformities. *Friedreich's cerebellar ataxia* is a familial disease that begins in childhood; it involves the spinocerebellar tracts, corticospinal tracts, and posterior columns. Patients have progressive gait disturbance, speech disturbance, and also scoliosis and foot deformities, with a steady downhill course. Finally, *syringomyelia* is a degenerative condition of the spinal cord with neuronal destruction centrally resulting in a cavity or syrinx, usually in the cervical area. Onset is usually in the second or third decade and involves intrinsic muscles of the hand initially, followed by progressive loss of both motor and sensory function in the upper and lower extremities. Orthopaedic treatment is directed at bracing for prevention of contractures and deformities or arthrodesis of neuropathic joints.

REQUIREMENTS FOR EFFICIENT LOCOMOTION

1. Stability of joints, normal bone length, normal skeletal relationships
2. Normal joint range of movement and normal muscle power
3. Cortical control of voluntary muscle action
4. Normal muscle tone, including coordination as well as postural tone
5. Normal sensory modalities
6. Cerebellar control of muscle action and intact ocular and auditory balance mechanism

Gait disturbances can result from neurologic disorders such as ataxia (from cerebellar lesion, posterior column lesion, Guillain-Barré syndrome, or Friedreich's ataxia) or from spastic paraplegia (upper motor neuron lesion, stroke, or cerebral palsy). Mechanical causes include limb-length discrepancy, hip joint pathology (congenital dysplasia or dislocation, slipped femoral capital epiphysis, Legg-Calvé-Perthes disease, arthritis), or knee joint problems (arthritis, osteochondritis dissecans, genu valgum or varus, etc.). A new method of correcting limb-length discrepancies is called *distraction osteogenesis* (Ilizarov technique), in which a cortical osteotomy is performed after gradual lengthening of the bone in an external fixation apparatus.

SPINAL DEFORMITIES

Kyphosis refers to an increase in the normal posterior convexity of the thoracic spine involving a number of vertebral bodies. A *gibbus deformity* is an acute kyphotic angular deformity and can be congenital, traumatic, or due to infection such as tuberculosis. In adolescence, kyphosis can be the muscular or postural type (benign, and treated with exercise) or discogenic (Scheuermann's disease). Scheuermann's disease tends to be progressive and is associated with abnormalities of the vertebral end plates with disc herniations into the vertebrae (Schmorl's nodes). It is treated with exercises and occasionally with bracing or spinal fusion in refractory cases with severe deformities. Senile kyphosis occurs most commonly with osteoporosis, where multiple compression fractures cause wedging of the vertebrae.

Scoliosis

Scoliosis refers to any lateral deviation of the spine from its usually straight form. Congenital scoliosis is associated with vertebral anomalies such as hemivertebrae or complete or partial fusions of vertebral bodies. Progression of these types of scoliosis is treated by early limited fusion. Paralytic or neuromuscular scoliosis usually is associated with a long C-shaped thoracolumbar curve and often requires instrumentation and fusion if bracing does not prevent progression. Idiopathic scoliosis progresses during adolescence, and important factors are the age of onset and site of the curve. Thoracic curves starting before age 10 have a poorer prognosis. After skeletal maturity, progression is minimal. The most common curve is the right thoracic curve, usually seen in girls. Generally, rotation of the vertebral bodies occurs in addition to lateral curvature. The rotational component is accentuated with forward flexion, causing an obvious asymmetry or prominence of the ribs or transverse processes on the convex side of the curve. Lateral bending radiographs help to determine the flexibility of the curve. Treatment consists of regular follow-up to determine progression radiographically and postural exercises. With progression, bracing is used, such as a Milwaukee brace or plastic thoracolumbar sacral orthosis (TLSO). Alternatively, electrical muscle stimulators on the convex side of the curve also have been used but remain controversial. For progressing curves greater than 40 degrees, surgical correction with Harrington rods or Luque instrumentation (sublaminar wiring) and posterior fusion is generally indicated. Use of segmental fixation may obviate the need for postoperative cast

immobilization. Also, the recent use of more rigid Cotrel-Dubosset fixation allows better correction of both sagittal and lateral curvatures. For rigid thoracolumbar curves or adult degenerative scoliosis, anterior fusion with Zielke instrumentation may be used.

FOOT AND ANKLE DEFORMITIES

Pes planus (flatfoot) can be flexible or rigid. Congenital flexible flatfoot is the most common type and is usually painless and benign. Rigid flatfoot (peroneal spastic flatfoot) is usually due to a tarsal coalition or congenital fusion between the calcaneus and the navicular, talus, or cuboid and is frequently painful and treated by insoles or often resection of the coalition bar. Acquired flatfoot may result from trauma with rupture of midfoot ligaments, posterior tibialis tendon rupture, or muscle imbalance from a neurologic disorder such as poliomyelitis.

Contracture

Contracture refers to a permanent shortening and rigidity of muscles, joints, and fascial structures and may be congenital or acquired. Congenital examples include clubfoot and arthrogryposis multiplex congenita. Acquired contractures of joints can result from periarticular trauma, muscle imbalance (as previously discussed with cerebral palsy), burns, or idiopathic conditions such as Dupuytren's contracture of the palmar fascia. Volkmann's ischemic contracture results from a compartment syndrome of the forearm muscles following trauma. Swelling within muscle compartments bounded by fascia leads to ischemia with permanent muscle necrosis and later fibrosis. A similar problem can occur in the lower extremities. Clinical signs include diminished perfusion or pulses, pain with passive stretch of involved muscles, paresthesias, and motor weakness. Diagnosis is made by measurements of muscle compartment pressures using a special catheter and monitor, and treatment consists of prompt surgical decompression of involved compartments.

EPIPHYSEAL DISORDERS (OSTEOCHONDRITIS OR OSTEOCHONDROSIS)

The term *osteochondritis* refers to an abnormality of the secondary ossification centers of the long bones. Generally, the pathologic changes are most consistent with avascular necrosis of the epiph-

ysis. The most common locations of osteochondritis are the lunate (Kienböck), scaphoid (Preoser), tarsal navicular (Köhler), vertebral epiphyses (Scheuermann), capitellum (Panner), femoral head (Legg-Calvé-Perthes), patella (Sinding-Larsen), tibial tubercle (Osgood-Schlatter), calcaneus (Sever), and metatarsal heads (Freiberg). Patients usually present with pain and radiographic abnormalities in the associated epiphysis.

Legg-Calvé-Perthes disease of the hip usually occurs in males between 5 and 9 years of age and is bilateral in 10 percent of patients. Patients present with hip or knee pain and limping in the initial or prodromal stage. This becomes associated with loss of motion in the hip and flattening of the femoral head (coxa plana). Later, with revascularization of the epiphysis, symptoms and signs diminish, although limitation of motion and deformity of the femoral head may be permanent. The key to treatment is containment of the femoral head within the acetabulum, usually with ambulatory abduction bracing, until the restoration or revascularization stage is completed (about 1–2 years). In some patients with severe involvement, varus osteotomy for containment is necessary.

Osgood-Schlatter disease of the tibial tubercle presents in patients in the 13–15-year age range, sometimes with a history of antecedent injury. Pain, tenderness, and enlargement of the tibial tubercle occur, with a fragmented appearance radiographically. Treatment is symptomatic, with restriction of activities, and for more severe cases a plaster cylinder cast or knee immobilizer for 6 weeks. The disease is self-limited, although prominence of the tibial tubercle is permanent.

Köhler's disease involves the tarsal navicular in young children between the ages of 3 and 6 years. Symptoms consist of pain and swelling, and diagnosis is made by radiographs demonstrating sclerosis of the navicular. Treatment consists of a plaster cast for a few weeks and a molded arch support subsequently.

CONGENITAL ORTHOPAEDIC DEFORMITIES

Deformities Present at Birth Metatarsus adductus, valgus hindfoot, unilateral externally rotated leg, internal tibial torsion, and an adducted thigh with external rotation of the leg are thought to result from in utero position, and this also may be a contributing factor to talipes equinovarus (clubfoot) deformity. These conditions generally respond to passive stretching exercises, with corrective casts occasionally being used in refractory cases.

Congenital dislocation of the hip (CDH) consists of partial or complete displacement of the femoral head from the acetabulum,

with an incidence of 0.67 per 1000 births. Treatment is most successful if undertaken early, and all babies must be examined carefully for CDH. On examination, a hip click (Ortolani's sign) can be elicited as the hip reduces in abduction and flexion. Also, limitation of abduction to 75 degrees or less, apparent shortening of one thigh (Galeazzi's sign), and asymmetric gluteal creases may be present. If undetected in infancy, the child will have a noticeable limp or waddle when beginning to walk. Radiographically, delay in ossification of the epiphysis will occur, and the acetabular index (angle of the acetabulum from horizontal) will be greater than normal (22 degrees). Arthrography of the hip, MRI, or ultrasonography also will demonstrate the dislocation. Treatment of subluxation in the neonate usually can be accomplished with a Pavlik harness worn for 3–6 months. If the hip does not reduce in abduction or in older infants, a period of skin traction followed by closed reduction in an abduction spica cast may be needed. Open reduction is generally unnecessary in children under 1 year of age but may be needed in cases of late diagnosis. In the older child, femoral shortening and innominate osteotomies may be necessary to ensure a stable concentric reduction with containment of the femoral head by the acetabulum.

Congenital talipes equinovarus (clubfoot) is a deformity involving flexion of the ankle, inversion of the foot, adduction of the forefoot, and medial rotation of the tibia. Incidence is about 4 per 1000 births. Without treatment, the deformity is permanent and ambulation difficult. Treatment begins immediately after birth, with passive stretching exercises followed by application of serial corrective plaster casts. The forefoot adduction is corrected first, then the hindfoot varus, and only then the equinus. If the deformity recurs or correction is incomplete, surgical release of the hindfoot must be done with open reduction of the deformity and subsequent casting. In the older child, mild degrees of recurrence can be treated by lateral transfer of the tibialis anterior and/or Achilles tendon lengthening.

Congenital convex pes valgus (vertical talus) involves a dislocation of the talonavicular joint, with the talus in a vertical position and the navicular articulating with the dorsum of the talus. The sole of the foot has a rocker-bottom flatfoot deformity and is rigid. Early manipulation with plaster casting may be successful, but most patients will require operative reduction and pinning with Achilles tendon lengthening. Triple arthrodesis may be indicated in the older child.

Arthrogryposis multiplex congenita, or amyoplasia, is associated with fibrous tissue replacement of muscles at birth causing loss of joint mobility and associated deformities such as CDH,

clubfoot, and knee dislocation, which are treated as previously described.

Sprengel's deformity (congenital high scapula) is caused by embryonic failure of the scapula to migrate to its normal position. Occasionally, the scapula is attached to the vertebral column by an abnormal band of fibrous tissue or cartilage called the *omovertebral mass.* Mild cases need no treatment, but in more severe cases, surgical correction may be undertaken, although it is generally delayed until age 3–6 years.

Klippel-Feil syndrome, or congenital short neck, is caused by multiple fusions of cervical vertebrae and generally is not treatable. Congenital wryneck (torticollis) is caused by unilateral contracture of the sternocleidomastoid muscle causing a lateral inclination of the head and is thought to be posttraumatic, with a tender swelling in the muscle preceding the deformity. Treatment consists of stretching exercises and, in refractory or late-diagnosed patients, surgical release of the muscle.

Other congenital deformities include radioulnar synostosis (fusion of the proximal radius and ulna), Madelung's deformity (bowing of the distal radius with subluxation of the radioulnar joint), and congenital aplasia or dysplasia of long bones (most commonly, absence of the radius with radial "clubhand," fibula, or proximal femoral focal deficiency).

GENERALIZED BONE DISORDERS

Bone Composition *Organic components:* 90 percent type I collagen; the remaining constituents include phosphoproteins, bone-specific proteoglycan, sialoprotein, osteonectin, osteocalcin, and growth factors such as transforming growth factor-beta, fibroblast growth factor, and bone morphogenetic proteins.

Inorganic components: calcium phosphate in the crystalline form of hydroxyapatite and 8–9 percent water. *Bone cell enzymes:* Osteoclasts contain acid hydrolases, collagenase, and acid phosphatase, whereas osteoblasts contain alkaline phosphatase and collagenase activity.

There are two primary forms of ossification or mineral deposition within skeletal tissues. The long bones form developmentally by mineralization of cartilage initially, with subsequent conversion of this mineralized tissue to bone. This process is called *endochondral ossification,* and in addition to embryonic bone formation, it gives rise to the growth plates of long bones, secondary ossification centers of the epiphyses, and callus formation in fracture healing. The other form of ossification is called *intramembranous*

ossification and involves mineralization of osteoid by osteoblasts directly without a cartilage phase. Bone remodeling occurs when osteoclasts resorb bone, which is followed by a tightly coupled formation of bone by osteoblasts and occurs constantly throughout the skeleton.

Because of the content of growth factors in the matrix of bone, it can be readily transplanted, and as it is resorbed, it stimulates local bone formation (osteoinduction). In addition, osteoblasts deposit new bone directly on graft surfaces (osteoconduction), which act as a scaffold supporting bone replacement. Bone grafts are used in nonunion of fractures, to stimulate arthrodeses, and to replace segmental loss of bone resulting from trauma, infections, or tumors. Bone allografts are almost as effective as autografts, given the negligible amount of antigenic cellular material. Recent advances also include the use of vascularized bone grafts, where microvascular anastomosis of the bone blood supply allows rapid incorporation of a living segment of bone, and use of synthetic bone graft substitutes such as hydroxyapatite, demineralized bone matrix, or growth factors such as the bone morphogenetic proteins (BMPs).

Developmental Disorders of Bone

Achondroplasia This is the most common form of dwarfism, and it is associated with relatively normal trunk height but shortened extremities; it is autosomal dominant in inheritance.

Ollier's Disease (Dyschondroplasia) Multiple abnormal rests of cartilage in the metaphyses lead to deformities of the long bones. Malignant degeneration into chondrosarcoma occurs in 15–25 percent of patients.

Multiple Exostoses This autosomal dominant hereditary disorder is characterized by numerous cartilaginous outgrowths from the metaphyses of the pelvis and long bones. These require surgical excision only when symptomatic or occasionally when malignant degeneration into a chondrosarcoma occurs.

Polyostotic Fibrous Dysplasia This disease usually appears in childhood and results in dysplastic bone formation by fibroblastic-like cells in the metaphyses and diaphyses of long bones. Pathologic fractures or bowing of the bones can occur and may require surgical treatment.

Osteogenesis Imperfecta This is a familial disorder of the type I collagen gene with several subtypes. Patients may have blue sclera

and deafness, and all have fragile bones that fracture easily. The fetal form is severe and lethal. The infantile form is less severe, and the adolescent form, called *osteogenesis imperfecta tarda,* is the least severe. In children, intramedullary rodding and osteotomies are often used to prevent long bone fractures.

Osteopetrosis (Albers-Schönberg Disease, Marble Bones, Congenital Osteosclerosis) This is a rare hereditary disease with defective osteoclasts incapable of bone remodeling, characterized by dense bones radiographically, anemia, and frequent fractures and infections. Several reported cases have been cured by bone marrow transplantation.

Melorheostosis This disease involves regional asymmetric osteosclerosis of cortical bone with the radiographic appearance of candle drippings, local pain, and adjacent joint fibrosis.

Metabolic Diseases

Scurvy Vitamin C deficiency results in defective cross-linking of collagen and therefore weakness of vascular endothelium. Subperiosteal hemorrhages occur, as well as increased density of the calcification zone of the growth plate due to defective remodeling and bone formation. Treatment with vitamin C is rapidly curative.

Rickets Vitamin D deficiency can be caused by a number of diseases and results in inadequate absorption of calcium in the intestine. Nutritional deficiency and intestinal malabsorption syndromes cause inadequate vitamin D absorption, whereas renal or hepatic diseases result in inadequate hydroxylation of vitamin D to the active form. In children, the long bones are soft and bowed, with widening of the growth plate and enlarged and tender epiphyses. Treatment is with vitamin D repletion. Vitamin D–resistant rickets is a hereditary disease that requires massive doses of vitamin D plus phosphate to treat the bone disease.

Hypophosphatasia This rare hereditary disorder is characterized by low levels of alkaline phosphatase and urinary excretion of phosphoethanolamine.

Osteomalacia This disease is the adult equivalent of rickets and is caused by any derangement of vitamin D metabolism, as noted earlier. Pathologic fractures can occur, and treatment is with vitamin D.

Osteitis Fibrosa (Parathyroid Osteodystrophy) Multiple bony lesions and areas of bone resorption are caused by excessive secretion of parathyroid hormone. Hypercalcemia may be present in the case of primary hyperparathyroidism, and pathologic fractures or bowing of long bones can occur. Parathyroidectomy is generally the treatment of choice.

Osteoporosis This condition results from an inadequate amount of bone that is otherwise biochemically normal. It is seen in association with Cushing syndrome, thyrotoxicosis, chronic steroid therapy, and most commonly in postmenopausal women as a consequence of estrogen loss. Treatment is with calcium and physiologic doses of vitamin D (to offset any component of superimposed osteomalacia), exercise, estrogen supplementation when appropriate, and occasionally, antiresorptive agents such as calcitonin or bisphosphonates.

Pituitary Disturbances Hypopituitarism in childhood can cause dwarfism, whereas hyperpituitarism in childhood leads to gigantism. In adulthood, onset of hyperpituitarism (usually due to a pituitary adenoma) causes acromegaly, with enlargement of the skull, thorax, and digits.

Hypothyroidism (Cretinism) Delayed ossification results in short stature, and the bones are short with a thick cortex. Epiphyseal ossification is delayed and irregular, resembling osteochondroses such as Legg-Calvé-Perthes disease. Thyroid replacement is curative if begun in infancy.

Mucopolysaccharidoses A series of 12 hereditary disorders of mucopolysaccharide (glycosaminoglycan) metabolism have been identified, including Hurler, Hunter, Scheie, Sanfilippo, and Morquio syndromes. These vary in severity and are variably associated with spinal deformities, mental retardation, osseous abnormalities, corneal opacities, and joint stiffness.

Paget's Disease (Osteitis Deformans) This disorder of bone turnover is thought to be caused by a slow viral infection of osteoclasts. Early in the disease there is excessive osteoclastic resorption and vascularity, followed by abnormal bone formation and sclerosis, with trabecular and cortical thickening. In the late phase, dense sclerotic woven bone and inactive fibrous marrow replacement predominate. The disease begins between the ages of 35 and 50 years and is painful in about 30 percent of patients. Pathologic fractures

occur, and bowing of long bones also occurs. Serum alkaline phosphatase and urinary hydroxyproline levels are elevated and correlate with activity of the disease. Diphosphonates or calcitonin are useful in controlling the disease by inhibiting bone resorption.

Reticuloendothelial Disorders

Lipoid Granulomatosis This results from any disturbance of lipid metabolism. In Gaucher's disease, a cerebroside lipoprotein accumulates; in Niemann-Pick disease, a phosphatide lipoid; in Hand-Schüller-Christian disease, cholesterol; in Tay-Sachs disease, a cerebroside protein. Radiographs show lytic skeletal lesions.

Eosinophilic Granulomatosis This may present as a solitary skeletal lesion in childhood or multiple lesions that are then referred to as Hand-Schüller-Christian disease. Hand-Schüller-Christian disease is also associated with hepatosplenomegaly, exophthalmos, and diabetes insipidus. Solitary eosinophilic granulomatosis may cause vertebrae plana or pathologic fracture in long bones and generally responds to conservative treatment, being a self-limited disorder. The most severe form of disease is Letterer-Siwe, which presents in infancy and is generally fatal. The systemic forms of eosinophilic granulomatosis respond to treatment with vinblastine and prednisone.

Hodgkin's Disease This is a form of malignant lymphoma that may present with lytic lesions in bone secondary to bone marrow involvement. Symptomatic lesions respond to radiation therapy, and the systemic disease is responsive to chemotherapy.

Leukemia Leukemia may produce bone lesions, most commonly in lymphoblastic leukemia, which can demonstrate lucencies adjacent to the growth plate in the metaphyses.

Multiple Myeloma This is a proliferation of malignant plasma cells that produces sharply demarcated, "punched-out" lesions in bone. The skull, ribs, and long bones are all affected, and diagnosis can be made on bone marrow biopsy or by demonstration of an abnormal monoclonal immunoglobulin on serum immunoelectrophoresis.

Hemolytic Anemia This can cause bone marrow changes in the vertebrae and skull, with a "hair on end" or "sun ray" appearance, particularly in the skull.

FRACTURES (SEE TABLES 41-3, 41-4, AND 41-5)

A *fracture* is, by definition, a deformation or discontinuity of bone produced by forces exceeding the strength of the bone. Fractures are classified according to pattern (transverse, spiral, oblique, segmental, comminuted), location (diaphyseal, metaphyseal, epiphyseal), and integrity of the surrounding skin and soft tissue (open or compound versus closed). A *pathologic fracture* is one through bone that is abnormally weakened by a pathologic process such as metabolic bone disease or a tumor. Clinical manifestations include pain, swelling, deformity, ecchymosis, instability, and crepitus. Diagnosis requires two orthogonal radiographs as a minimum, including views of the joint above and below the fracture site. Evaluation should include assessment for other injuries, as well as assessment of the neurologic and vascular function in the injured extremity. Open fractures represent orthopaedic emergencies, requiring immediate debridement in the operating room setting to prevent occurrence of osteomyelitis. Debridement should be carried out within 6–8 h, and wounds generally are not closed primarily. Any devitalized tissue is removed, and the fracture is stabilized in either an external fixator or a plaster cast.

Associated vascular injuries require early recognition and treatment, since irreversible muscle ischemia will occur within 6–8 h. Also in the presence of ischemia, prophylactic fascial compartment releases are necessary to prevent compartment syndrome on reperfusion of the limb. Fat embolism syndrome, a form of adult respiratory distress syndrome (ARDS), occurs in some patients, particularly those with multiple long bone fractures. This syndrome occurs 2–3 days postinjury and is attended by hypoxemia, confusion, fever, and transient petechiae. Treatment is with respiratory support and corticosteroids.

Nerve injuries may be associated with fractures and range from neurapraxia (a transient, reversible impairment of nerve function), to axonotmesis (axons transected but nerve sheath intact; can regenerate), to the most severe, irreversible form of neurotmesis in which the entire nerve is transected. Transected nerves should be repaired primarily when possible at the time of fracture fixation or debridement.

Joint injuries are assessed radiographically to rule out intraarticular fractures, which often require surgical treatment. Physical examination is important to evaluate ligamentous instability, which may be treated by immobilization or repair depending on the particular injury. Arthroscopic examination is a useful tool in evalua-

tion and treatment of joint injuries and is used most commonly in the knee and shoulder. Surgical arthroscopy can be used to treat meniscal tears, osteochondral fractures, cartilage degeneration, synovitis, shoulder instability due to glenoid labral tears or intraarticular loose bodies, and anterior cruciate ligament tears. Morbidity and rehabilitation time are diminished when compared with comparable open surgical procedures.

Fracture Healing The stages of fracture healing include

1. *Stage of impact:* energy absorbed to failure
2. *Inflammatory stage:* hematoma, necrosis of fracture edges, cytokines released, granulation tissue in gap—lasts about 2 weeks
3. *Reparative stage:* cartilage and bone differentiate from periosteal and mesenchymal cells; cartilage undergoes endochondral calcification, and membranous bone formed by osteoblasts at the periphery of the callus gradually replaces the calcified cartilage with bone—lasts from one to several months
4. *Remodeling stage:* woven bone converted to lamellar bone through coupled resorption and formation; bone tends to resume its original shape by remodeling under influence of mechanical stresses—lasts months to years.

Cartilage Healing Articular cartilage has a very limited repair capacity. Injury results in loss of proteoglycans with increased mechanical stress, chondrocyte death, fibrillation, and progressive degeneration. Surgical penetration of the subchondral bone can allow repair of a defect by fibrocartilage formation.

Delayed Union and Nonunion *Delayed union* refers to a fracture that takes longer than average to heal and is somewhat poorly defined. *Nonunion* refers to a fracture that fails to progress toward healing. Causes of nonunion include excessive motion at a fracture site, excessive distraction, infection, and severe soft tissue disruption. Nonunions may be treated by bone grafting or stimulation with pulsed electromagnetic fields.

Stress Fractures Stress or fatigue fractures are a result of repeated stress to a bone that would not be injured by isolated forces of the same magnitude. They can occur on long marches, after jogging, or during other activities. Radiographic findings may be subtle but eventually show periosteal reaction. Treatment is with immobilization.

Epiphyseal Plate Injuries Longitudinal growth occurs from the growth plate adjacent to the epiphyses of the long bones. The zone

TABLE 41-3
FRACTURES AND JOINT INJURIES IN THE UPPER EXTREMITY

Injury	Type	Diagnostic aids	Treatment	Complications
Sternoclavicular dislocation	1. Anterior 2. Posterior	P. exam; AP x-ray	Closed reduction; figure-of-8 strap	Airway or nuerovasc. compromise (posterior only)
Clavicle fracture	Usually middle 1/3	AP x-ray	Figure-of-8 strap	Nonunion rare
Acromioclavicular dislocation	1. Grade 1 or II sprain 2. Grade III (tear of conoid/trapezoid lig.)	AP x-ray ± weights	Sling Sling or ORIF*	AC arthiritis or prominence of distal clavicle with sling Rx
Scapula fracture		Routine x-rays	Sling/swathe	
Shoulder dislocation	1. Anterior 2. Posterior	AP and axillary or transcapular x-rays	1. CR*, sling/swathe 2. Or abduction pillow (posterior)	Neurologic injury, esp. axillary nerve; recurrent dislocation
Proximal humerus	1. Surgical neck 2. Comminuted	Routine x-rays	Sling Surgical repair	Shoulder stiffness, esp. in elderly
Humeral shaft		Routine x-rays	CR with cast or splint	Radial neurapraxis
Supracondylar	Children	Comparison views of normal elbow	CR; percutaneous pinning	Neurovasc. injury; compartment synd.
Radial head/neck	1. Minimally displaced 2. Comminuted	Routine x-rays; fat pad sign on lateral	1. Sling/splint 2. Excision of r. head	1. Elbow stiffness; 2. Late instability
Lateral condyle	Children	Comparison views	ORIF usually needed	Growth disturbance

Olecranon fracture		Routine x-rays	ORIF usually needed	Elbow stiffness
Elbow dislocation	Usually posterior	P. exam; x-rays	CR; splint/sling	Elbow stiffness
Monteggia fracture	Ulna fracture with radial head dislocation	Routine x-rays	ORIF or ulna often necessary	
Radius/ulna fractures	1. Incomplete (child) 2. Adult	Routine x-rays	1. Complete fracture; CR/cast 2. ORIF	Loss of pronation and supination if not anatomic
Distal radius (Colles)	1. Extraarticular 2. Intraarticular	AP, lateral and oblique views	1. CR; cast or splint 2. CR; pins or ext. fix.	Residual deformity common
Scaphoid		AP, lat., navicular view	CR; cast	Nonunion common
Metacarpal		Routine x-rays	CR; cast — occ. pinning	
Bennett's fracture (CMC* joint thumb)	Usually intraarticular and unstable		CR; percutaneous pinning	
Phalanges	Intraarticular or extra-articular		Splinting with IPs* in extension, MCPs* in flexion	IP* or MCP* joint stiffness
Mallet finger	Avulsion fracture of extensor		Splint DIP in hyperextension	

*ORIF = open reduction and internal fixation; CR = closed reduction; CMC = carpometacarpal; IP = interphalangeal; DIP = distal interphalangeal; MCP = metacarpophalangeal.

TABLE 41-4
FRACTURES AND JOINT INJURIES IN THE LOWER EXTREMITY

Injury	Type	Diagnostic aids	Treatment	Complications
Femoral neck fracture	1. Minimally displaced 2. Displaced	AP* and tube; lateral x-rays needed	1. Pinning 2. Pinning; prosthesis in older patients	Nonunion and avascular necrosis; esp. in displaced
Intertrochanteric fracture	May be comminuted	"	ORIF*, screw & plate	Loss of fixation
Subtrochanteric fracture	"	Routine x-rays	ORIF	Nonunion common
Femoral shaft	"	"	Skeletal fraction or IM* rodding	Malunion, limb-length discrepancy
Knee injuries	ACL* tear MCL* tear LCL* tear PCL* tear	+ Lachman; drawer + Valgus stress test + Varus stress test + Posterior drawer	Isolated tears may be treated by brace or cast; ACL & multiple may require repair	Symptomatic instability, stiffness
Meniscal tears	Medial or lateral; can be peripheral or in body of meniscus	MRI; arthrogram; diagnostic arthroscopy	Peripheral tears repaired; otherwise fragment removed arthroscopically	Recurrent tears; late degenerative arthritis
Patella fracture	Transverse or comminuted	Routine x-rays	ORIF; or excision of smaller fragments	Knee stiffness; patellofemoral DJD*

Tibial plateau fracture	1. Min. depressed 2. Displaced and/or comminuted	Varus/valgus stress views; tomograms	1. Cast, crutches 2. ORIF, occ. bone grafting	Late DJD*; knee stiffness
Tibial shaft fracture	1. Closed 2. Open and/or comminuted	Routine x-rays	1. CR; long leg cast 2. Debridement, external fixator	Delayed or nonunion common; infection in open fractures
Ankle sprain	Inversion most common	Stress mortise views may be helpful	Ace wap, splint, or cast, depending on severity	Recurrent instability
Ankle fracture	Medial, lateral, and/or posterior malleoli	AP, lat., and mortise views needed	CR, cast; if not anatomic, ORIF	DJD if nonanatomic result
Talus fracture	± Subtalar dislocation	Routine x-rays	CR if nondisplaced; ORIF if displaced	Avascular necrosis of talus
Calcaneus fracture	± Subtalar joint involv.	″	CR, cast; occ. ORIF	Poor prognosis if subtalar joint involved
Metatarsal fractures		AP, lat., oblique views	usually short leg cast	Nonunion in Jones type (5th MT* shaft)
Phalangeal fractures			Buddy taping	

*ACL = anterior cruciate ligament; MCL = medial cruciate ligament; LCL = lateral cruciate ligament; PCL = posterior cruciate ligament; AP = anterioposterior; ORIF = open reduction and internal fixation; IM = intermedullary; DJD = degenerative joint disease; MT = metatarsal.

TABLE 41-5
FRACTURES AND JOINT INJURIES OF THE PELVIS AND SPINE

Injury	Type	Diagnostic aids	Treatment	Complications
Hip dislocation	1. Anterior (rare) 2. Posterior	1. Leg abducted 2. Leg adducted	CR; light traction	Sciatic nerve injury; avascular necrosis
Acetabular fracture	Displaced or nondisplaced	45° obliques; CT scan	Displaced — ORIF*; nondispl., traction	DJD* common
Pubic ramus fracture	Isolated		Bed rest, crutches	
Pelvic ring disruption		CT scan; pelvic inlet and outlet views	Bed rest, ext. fixator, or ORIF, depending on severity	SI joint disruption may lead to DJD
Cervical spine	Facet dislocation compression fracture	Important to see all 7 vertebrae on x-ray; CT scan helpful	CR; halo traction and/or fusion if unstable	Neurologic deficits, including quadriplegia
Thoracolumbar spine	1. Compression 2. Burst fractures 3. Fracture/dislocation	AP* and lat x-rays; CT scan	1. Brace 2. Cast or ORIF 3. ORIF/fusion	Neurologic deficits

*AP = anterioposterior; ORIF = open reduction and internal fixation; DJD = degenerative joint disease.

of provisional calcification of the plate is a mechanically weaker area of the bone, and it is through this zone that fractures about the epiphysis usually occur. The Salter-Harris classification of growth plate injuries is in wide use:

Type I–II: Transverse fracture through metaphyseal side of growth plate; excellent prognosis after closed reduction.
Type II: Fracture through growth plate partially, exiting through the metaphyseal bone; also excellent prognosis with closed reduction.
Type III: Fracture longitudinally through the articular surface and epiphysis and then transversely through the metaphyseal side of the growth plate; prognosis good with anatomic reduction only.
Type IV: Longitudinal fracture through epiphysis and growth plate and exiting through metaphyseal bone; open reduction generally necessary and has higher risk of late growth disturbance.
Type V: Crush injury to the growth plate; high incidence of late growth disturbance.

Fractures in children generally heal more rapidly than those in adults, with nonunions being extremely rare. Greater capacity for remodeling also allows acceptance of greater angular deformities. However, limb-length discrepancies can occur with growth after fractures, as can progressive angular deformities, unlike the adult.

Closed treatment of fractures generally involves application of plaster casts. Complications of cast treatment include swelling, which can impair circulation and cause ischemic limb damage; pressure sores; and neurapraxias. Neurovascular compromise in a cast initially is treated by splitting the cast and underlying padding to relieve pressure. If prompt resolution does not occur, measurements of compartment pressure must be made to rule out compartment syndrome, which would necessitate emergent surgical fasciotomies. Casts should include the joint proximal and distal to the fractured bone. Body casts can be used for spinal fractures.

External fixation is used in open fractures associated with soft tissue injury or loss. Pins inserted into the bone above and below the fracture are connected to an outrigger and stabilize the fracture while allowing access to wounds. Another method of stabilizing a fracture is with traction. In children, skin traction with adhesive tapes can be used, although with older children and adults skeletal traction through a transverse percutaneous pin is necessary.

Electrical stimulation can be used through either percutaneous pins or externally applied coils to stimulate a high percentage of nonunions or delayed unions to heal without surgery.

DISEASES OF JOINTS

Joints consist of hyaline articular cartilage bounded by a fibrous capsule that has a lining of synovial cells, which secrete the synovial fluid that provides nourishment and lubrication of the articular surface. Articular cartilage matrix is composed of 40 percent type II collagen, 40 percent proteoglycan, and 20 percent glycoproteins as the organic components. Minor collagens (type IX and XI) are also found in the matrix, as well as growth factors such as transforming growth factor-beta and fibroblast growth factor. Normal synovial fluid contains hyaluronate and up to 200 nucleated cells, as well as glucose and electrolytes.

Clinical examination of a joint includes measurement of range of motion, presence of effusion, synovial thickening, warmth, erythema, and tenderness. Radiographic examination includes standard biplanar radiography and, occasionally, arthrography if meniscal or capsular pathology is suspected. Synovial fluid analysis is helpful. Normal synovial fluid is clear and straw-colored. When the cell count is increased or crystals are present, turbidity results. Viscosity is decreased as a result of the breakdown of hyaluronate when inflammation is present. A poor mucin clot is another indication of inflammation. Normal synovial fluid contains 10 mg/dL less glucose than serum, and this gradient is increased in the presence of large numbers of inflammatory cells.

Pyogenic arthritis refers to a bacterial infection, or septic arthritis, and can result in rapid and irreversible destruction of the articular cartilage. *S. aureus* and hemolytic streptococci are the most common organisms, but many organisms are possible agents. Patients may have fever, effusion, pain with motion of the joint, and an elevated white blood cell count and ESR. The white blood cell count in the synovial fluid is generally greater than 50,000/mm^3, with 90 percent polymorphonuclear leukocytes. Organisms may be identified by Gram stain or culture of the fluid aspirated. Treatment is generally by surgical drainage of the joint in conjunction with appropriate intravenous antibiotics. Some infections may be treated with daily aspirations rather than surgery. Infections of the hip joint must all be treated by prompt surgical drainage to prevent avascular necrosis. The knee joint frequently can be drained arthroscopically. Early motion after subsidence of the acute infection is important to prevent joint stiffness, and antibiotics usually are continued for 3–6 weeks.

Tuberculosis is now an uncommon infection in this country, but it can cause severe destruction of bone and joints. Most commonly the spine is involved, with destruction of adjacent vertebrae, kypho-

sis, and abscess formation. In peripheral joints, the subchondral bone is eroded and destroyed early, whereas the articular cartilage is relatively well preserved until late in the course. The end result is fibrous ankylosis of the joint. The clinical course may be insidious, and diagnosis depends on recovery of organisms from the bone or joint by biopsy or aspiration. Synovial fluid usually contains less than 20,000 leukocytes per deciliter. Patients are treated by surgical debridement of involved joints, supportive therapy, and triple-drug therapy (isoniazid, ethambutol, and rifampin) for 6 months to 1 year. Surgical arthrodesis of destroyed joints may be necessary. Tuberculous spondylitis (Pott's disease) is treated by anterior debridement, decompression, and fusion with rib grafts in conjunction with triple-drug therapy.

Gonococcal arthritis is more common in females. Symptoms start with migratory polyarthralgia, followed by localization in one or two joints. The knee, elbow, and wrist are the most common sites of involvement. Infection may be clinically subacute or chronic, and treatment is with aspiration and penicillin.

Lyme arthritis is a tick-borne illness caused by a spirochete, *Borrelia burgdorferi.* A skin eruption may herald the onset of a rheumatic syndrome resembling rheumatoid arthritis with oligoarticular presentation. Cardiac and neurologic symptoms also can occur. Penicillin or tetracycline therapy will eliminate the infection.

Rheumatoid arthritis is a systemic disease affecting many organs of the body, characterized especially by proliferative synovial destruction of multiple joints. The proliferative synovium that destroys the articular cartilage is called *pannus,* and radiographically, periarticular osteopenia and concentric joint space narrowing occur. Ninety percent of rheumatoid patients have the antigammaglobulin factor, called *rheumatoid factor,* measured by latex fixation test. Radiographs show soft tissue swelling, osteoporosis, and periarticular erosions, followed by complete joint destruction.

Medical management includes anti-inflammatory drugs (both steroidal and nonsteroidal), gold salts, methotrexate, and antimalarials. Surgical treatments include synovectomies of involved joints and tenosynovectomies to prevent tendon ruptures; joint replacements for end-stage disease [hip, knee, shoulder, elbow, wrist, metacarpophalangeal (MP), and proximal interphalangeal (PIP) joints]; metatarsal head resections (Hoffman procedure) for forefoot deformity; and various procedures on the hand for correction of deformity.

Osteoarthritis, or degenerative arthritis, is a noninflammatory form of progressive joint destruction. Cartilage wear is manifested by loss of proteoglycans, which then causes fibrillation of the articular surface. Marginal osteophytes form as part of the injury and

repair process, and the cartilage surface eventually becomes denuded to subchondral bone. Radiographs demonstrate asymmetric joint space narrowing, subchondral sclerosis, subchondral cysts, and osteophytes. Joints deranged by any process such as trauma, Legg-Calvé-Perthes disease, septic arthritis, gout, or hemophilia can undergo changes of osteoarthritis. Effusion tends to be minimal, and the arthritis is only slowly progressive. Treatment involves limitation of activities, anti-inflammatory medications, walking aids, osteotomy to correct deformity or realign joints, and as a last resort, joint arthrodesis or total joint replacement. Complications of total joint arthroplasty include infections, loosening, and periarticular heterotopic ossification. Recently, use of uncemented total joint implants, prompted by the long-term problems of loosening of prostheses at the bone-cement interface, has become popular, particularly in younger patients. These devices have porous metal coatings that allow ingrowth of bone to permanently anchor the prosthesis and have been demonstrated to give comparable clinical results to conventional cemented components.

Osteonecrosis of the femoral head can result from trauma, sickle cell anemia, or alterations of lipid metabolism (e.g., lipid storage diseases, alcoholism, corticosteroids). The articular surface can collapse during the revascularization phase, when bone resorption and mechanical weakness occur, and this in turn leads to rapid degenerative arthritis. MRI is the most sensitive method of early detection, and early surgical treatment by bone grafting or marrow decompression may prevent collapse.

Gout is a metabolic disease in which crystals of sodium urate are deposited in and around joints, with severe episodic arthritis, classically involving the metatarsophalangeal (MTP) joint of the great toe in males over age 30. Diagnosis can be confirmed by aspiration of the joint with demonstration of urate crystals by polarized light microscopy. Treatment is with colchicine or indomethacin acutely and chronically with allopurinol to decrease serum urate levels.

Pyrophosphate arthritis (pseudogout or chondrocalcinosis) is an episodic arthritis resembling gout and most commonly affects the knee or wrist. The diagnosis rests on finding pyrophosphate crystals in the synovial fluid; radiographs also may demonstrate calcification of menisci. Treatment is with anti-inflammatory medication.

Hemophilic arthritis results from acute recurrent bleeding into synovial joints, usually after minor injury. The knee, elbow, shoulder, and ankle may be involved. Contractures develop, with synovial thickening and hemosiderin deposition, and progressive destruction of the articular cartilage. Minimization of hemorrhages is

the key to preventive treatment, along with dynamic splinting for contractures. In end-stage disease, total joint reconstruction or arthrodesis may be necessary under protection of large infusions of factor VIII.

Synovial Lesions Pigmented villonodular synovitis is a proliferative inflammatory process of synovium of unknown cause. Patients have a thickened, brownish proliferation of synovium that causes progressive joint destruction. Effusions aspirated from the affected joint will be brown because of the hemosiderin content. Treatment consists of early synovectomy, by either arthrotomy or arthroscopy.

Synovial chondromatosis is a condition of cartilaginous metaplasia of synovium that may become detached and form loose bodies within the joint. This condition, like pigmented villonodular synovitis, is monarticular and slowly progressive and is best treated by synovectomy.

Toxic or transient acute synovitis of the hip occurs in childhood and mimics septic arthritis or Legg-Calvé-Perthes disease. It frequently follows a viral illness and usually presents with a limp or refusal of the child to walk. One must exclude septic arthritis, and hip aspiration is generally necessary to accomplish this. Treatment is symptomatic with bed rest, skin traction, and protected weight bearing until the condition resolves.

Slipped Capital Femoral Epiphysis This condition affects adolescents ages 10–15 years and is more common in males. It presents with hip pain and a limp and involves slippage of the epiphysis medially and posteriorly on the femoral neck. Patients have a loss of internal rotation of the hip and an antalgic gait. The condition is bilateral in 25 percent of patients. Diagnosis is by orthogonal radiographs of the hip. The condition is treated by pinning in situ (subacute or chronic slips) or by closed reduction and pinning (acute slips). Chondrolysis is a complication of this disease, more common in blacks and females. Patients can develop secondary degenerative changes later in life.

Neuropathic (Charcot) Joints A Charcot joint results from any denervating process affecting the extremities. Tabes dorsalis, syringomyelia, leprosy, diabetes, or spinal cord injury may lead to neuropathic joints. It is generally thought that joint destruction results from repeated trauma to joints with impaired sensation. The joint may undergo very rapid and severe destruction, with gross instability and swelling but minimal inflammation. Arthrodesis is difficult to achieve; usually conservative methods such as bracing are used.

TUMORS OF THE MUSCULOSKELETAL SYSTEM

Primary bone tumors are relatively rare, but a number of both benign and malignant types occur. Musculoskeletal neoplasms are characterized by initial centrifugal growth from a single focus, pseudoencapsulation, and a tendency to respect anatomic compartment boundaries during growth (bone, muscle fascia, joint capsules, neurovascular sheaths). Metastasis usually is hematogenous to lung or bone. The surgical staging system used for bone and soft tissue tumors is shown in Table 41-6. Diagnostic evaluation includes radiographs, MRI or CT scan of the lesion, bone scan, and lung CT scan, preferably before biopsy of the lesion. Biopsy incisions should be longitudinal and excisable en bloc at the time of definitive surgery, cortical bone windows oval and small, frozen sections and cultures obtained on all specimens, neurovascular structures avoided, meticulous hemostasis achieved, drains placed in line with incision, and contamination of uninvolved compartments avoided. Treatment for benign lesions involves resection or curettage and bone grafting. Malignant lesions usually are treated by a combination of surgery, radiation therapy, and

TABLE 41-6
SURGICAL STAGING SYSTEM FOR MUSCULOSKELETAL TUMORS (AFTER ENNEKING)

Stage	Characteristics	Metastases
Benign		
1	Latent	No
2	Active	No
3	Aggressive	No
Malignant		
IA	Low grade; intracompartmental	No
IB	Low grade; extracompartmental	No
IIA	High grade; intracompartmental	No
IIB	High grade; extracompartmental	No
III	Low or high grade; intra or extracompartmental	Yes

SOURCE: Modified from Enneking WF, Gearen PF: Fibrous dysplasia of the femoral neck: Treatment by cortical bone grafting. *J Bone Joint Surg* 68A: 1415, 1986, with permission.

chemotherapy depending on the tumor type. Technological advances in bone grafting and prosthetic devices in conjunction with better adjuvant radiation and chemotherapy regimens now allow limb salvage surgeries with tumor resection and preservation of function in the majority of cases of musculoskeletal sarcomas.

Primary bone-forming tumors are listed below:

1. *Osteoma:* This is a small, benign, sessile lesion of dense bone usually occurring in the skull bones and generally asymptomatic. No treatment is necessary.
2. *Osteoid osteoma:* A benign, sclerotic bone-forming tumor of children and young adults that is usually painful and less than 1 cm in diameter. Aspirin often relieves the pain, and adjacent bone may show sclerotic thickening. Excision must include the radiolucent central nidus of the lesion to prevent recurrence.
3. *Osteoblastoma:* A benign, bone-forming tumor of children and young adults, common in the spine, which is histologically identical to osteoid osteoma but larger in size. Curettage and bone grafting are the treatment.
4. *Osteosarcoma:* This is the most common aggressive malignant bone tumor, generally involving the metaphyses of long bones about the knee and predominantly found in adolescents. Pulmonary metastases are frequent, and treatment consists of amputation or radical resection with limb reconstruction, in conjunction with systemic chemotherapy. Occasionally seen in older patients as a secondary malignancy arising in Paget's disease or following radiation treatment. Parosteal osteosarcoma is a less aggressive variant arising extraosseously adjacent to the periosteum, usually near the knee in young adults.

Cartilaginous tumors include the following:

1. *Osteochondroma (exostosis):* A benign exophytic growth from the metaphyses of long bones with a cartilage cap. Multiple form is hereditary. Secondary malignant change can occur in older adults (chondrosarcoma). Simple excision when indicated is curative.
2. *Enchondroma:* A benign, sometimes expansile cartilaginous tumor of the metaphyses of long bones or the tubular bones of the hands that exhibits calcification radiographically. Pathologic fractures can occur, as can late secondary malignant change. Treatment, when necessary, consists of curettage and bone grafting.
3. *Chondroblastoma:* A benign tumor of the epiphyses of children that may cause joint pain or effusion and is treated by curettage and bone grafting.

4. *Chondrosarcoma:* A malignant tumor of cartilage, most commonly seen in the metaphyses of long bones and in the pelvis of adults age 30–60 years. Wide resection or amputation is needed, and chemotherapy or radiation is of little benefit. Secondary tumors can arise in older individuals from an enchondroma or osteochondroma.

Fibrous tumors of bone include

1. *Nonossifying fibroma (metaphyseal fibrous cortical defect):* A benign fibrous lesion of childhood that is usually an incidental radiographic finding. Large lesions may cause pathologic fractures. Lesions spontaneously regress at skeletal maturity.
2. *Fibrosarcoma:* An aggressive malignancy, rare as a primary tumor in bone. Radical surgical removal or amputation with radiation usually needed for treatment.

Other musculoskeletal tumors include

1. *Giant cell tumor (osteoclastoma):* An aggressive, destructive, benign epiphyseal tumor of young adults, with a high recurrence rate with local treatment. A small percentage are frankly malignant and can metastasize to the lungs. Treatment is with resection and limb reconstruction or thorough curettage and cementation with methyl methacrylate bone cement, which seems to reduce local recurrence incidence.
2. *Unicameral bone cyst:* This is a metaphyseal, expansile, benign lesion of childhood, most commonly seen in the upper humerus or femur, consisting of a fluid-filled cavity in the bone. Pathologic fractures are common, and the lesion resolves spontaneously after skeletal maturity is reached. Steroid injections into the lesion may effect healing, and occasionally curettage and bone grafting are necessary, but the recurrence rate is 50 percent.
3. *Ewing's sarcoma:* An aggressive malignancy of childhood affecting the diaphyses of long bones, with permeative bone destruction and periosteal reaction, which must be differentiated from solitary eosinophilic granuloma and osteomyelitis. Treatment is with systemic chemotherapy and radiation, with 50–70 percent 5-year survival.
4. *Reticulum cell sarcoma (primary histiocytic lymphoma of bone):* A malignant tumor of bone occurring in the diaphyses of long bones in patients aged 20–40 years. Treated by radiation unless metastases are present, in which case chemotherapy is used.
5. *Aneurysmal bone cyst:* An aggressive, benign, expansile lesion of the metaphyses in children or young adults. Lesion is

vascular, with blood-filled cystic spaces, and is treated by curettage or resection, except for inaccessible lesions in the spine or pelvis, which may respond to intermediate-dose radiation.

6. *Hemangioma:* A benign vascular tumor of bone that is usually asymptomatic and most commonly diagnosed as an incidental finding on spine films; generally, no treatment is needed.
7. *Adamantinoma:* A low-grade malignancy resembling an epithelial tumor arising in the diaphyses or metaphyses of long bones (usually the tibia) in young adults. Wide resection or amputation is the usual treatment.
8. *Chordoma:* A slow-growing malignancy derived from notochordal remnants usually occurring in the sphenooccipital or sacrococcygeal areas of middle-aged adults. Recurrence incidence is high after surgical resection.
9. *Soft tissue sarcomas:* Include fibrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, liposarcoma, neurofibrosarcoma, synovial sarcoma, and epithelioid sarcoma. All are treated by aggressive surgery or amputation, often in conjunction with radiation and chemotherapy.
10. *Metastatic tumors of bone:* A number of cancers that do not arise primarily in bone have a propensity to metastasize to bone, including breast, prostate, lung, kidney, and thyroid carcinoma and neuroblastoma. Patients may present with pain or pathologic fractures. The lesions generally are controlled by radiation treatment, and fractures are stabilized surgically with rods or plating and bone cement, followed by radiation treatment for the lesion.

For a more detailed discussion, see Rosier RN: Orthopaedics, chap. 41 in *Principles of Surgery,* 7th ed.

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CHAPTER

42

SURGERY OF THE HAND

GENERAL CONSIDERATIONS

Examination

Prior records and diagnostic images may precisely define the extent, limitations, and duration of the patient's disorder and the clinical course. The history should include information about relevant systemic disease such as diabetes, atherosclerosis, neurologic and psychiatric disorders, and other serious or chronic diseases. The examiner should use the patient's normal anatomy—the contralateral, uninvolved limb—to observe for differences in alignment, contour, and symmetry. Observing the hand and forearm at rest, in pronation and in supination, should reveal any swelling, masses, erythema, ulceration, atrophy, anhidrosis, or excoriation. The reproducibility of the patient's active participation in the examination process is important. Responses should be consistent; repeated efforts, such as in grip testing, should produce similar values.

Light palpation provides information concerning excessive or absent sweating associated with anxiety or insensibility in particular zones, nerve distributions, dermatomes, or body parts. Variations in skin contour, texture, color, temperature, capillary refill, and hair characteristics offer information regarding circulation, nerve supply, masses, and joint swelling. Abnormal, injured, and scarred soft tissues can restrain joint motion, produce skin blanching with attempted active function, or cause visible "dimpling" of adherent deep structures, such as injured, repaired, or adherent tendons.The nails and eponychial and paronychial tissues often mirror systemic disease as well as acute and chronic injury.

Nails have a limited range of biologic responses. Splitting and fissuring, onycholysis, and onychorrhexis may reflect loss of nail adherence to the bed matrix after trauma, aging, or malnutrition. The transverse posttraumatic nail crease that parallels the proximal nail fold and advances with growth (Beau's line) represents a single alteration of nail metabolism at the time of trauma, which is common after injury but does not include a poor prognosis. Multiple transverse grooves (Mee's lines) can occur with diseases such as

Hodgkin's disease, malaria, and psoriasis and are normal in the latter part of pregnancy. Pigmented longitudinal bands may occur in melanoma, glomus tumor, and carpal tunnel syndrome. Nail bed pigmentation can be found with systemic sepsis, subungual infection, and benign and malignant tumors. Motion should be recorded with a small goniometer and strength with a dynamometer (Fig. 42-1). Simple line sketches record sites of injury, swelling, part loss, or dysfunction and can precisely record and communicate findings.

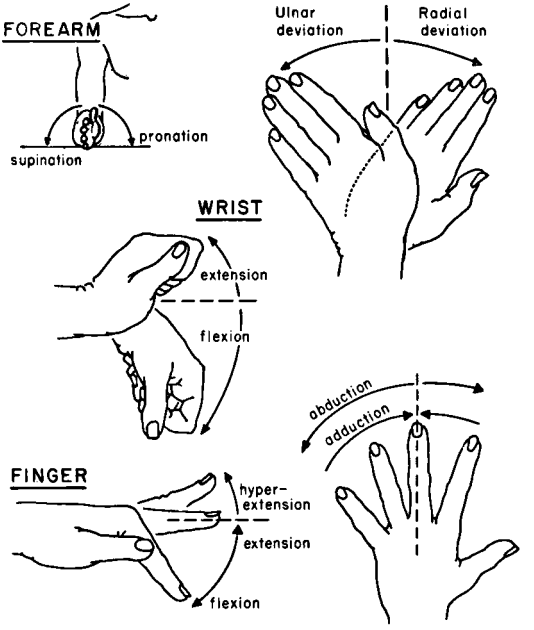
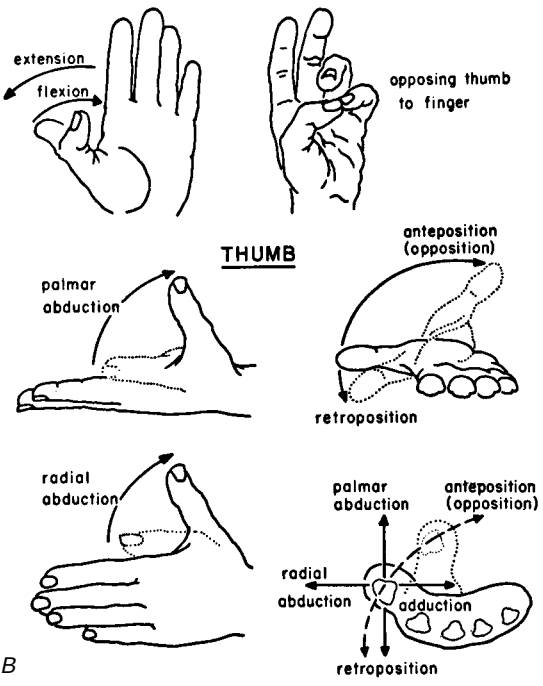
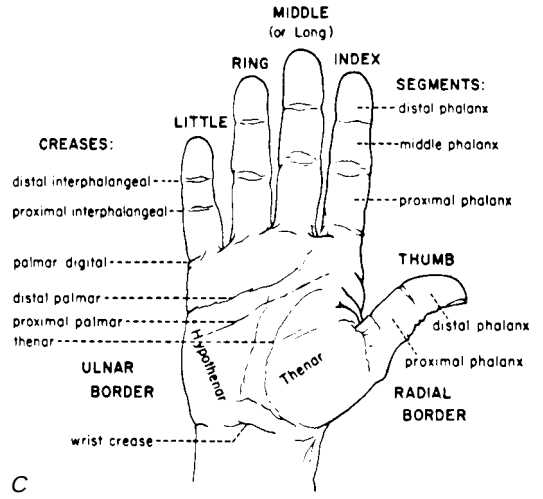


FIGURE 42-1 *A* and *B*. Common terminology used in describing hand mobility. *C*. The anatomy of the volar surface of the hand. (From: *American Society for Surgery of the Hand: The Hand: Examination and Diagnosis, 3d ed. New York, Churchill-Livingstone, 1990, with permission.)*


extension
flexion
opposing thumb to finger
THUMB
palmar abduction
anteposition (opposition)
retroposition
radial abduction
palmar abduction
anteposition (opposition)
radial abduction
adduction
retroposition
B


MIDDLE (or Long)
RING
INDEX
LITTLE
SEGMENTS:
distal phalanx
middle phalanx
proximal phalanx
CREASES:
distal interphalangeal
proximal interphalangeal
palmar digital
distal palmar
proximal palmar
thenar
THUMB
distal phalanx
proximal phalanx
Hypothenar
Thenar
ULNAR BORDER
RADIAL BORDER
wrist crease
C

Imaging Studies Diagnostic imaging includes traditional roentgenography, single- and multiple-phase technetium bone scans, computed tomography (CT), and magnetic resonance imaging (MRI). Most patients should receive plain radiographs in posteroanterior, lateral, and one or both oblique projections. Radiographs provide information with relatively intermediate sensitivity, high specificity, and reasonable cost. Diagnoses can be missed if only specialized and expensive evaluations such as trispiral tomography, CT, MRI, or bone scans are used.

TRAUMA

The best care is delivered initially, when tissues are fresh and potentially can be salvaged, revascularized, and directly repaired without the burdens of secondary scar tissue after delayed healing, osteoarticular degeneration, or infection. It is in the acute situation that success is greatest in achieving a functional and aesthetically satisfactory result.

Skeletal Trauma

Carpal Bone Fractures The eight carpal bones have a large proportion of their surfaces covered with articular cartilage, and this has two clinical implications. First, the limited periosteal attachment offers a tenuous blood supply; after fracture, one of the fragments is potentially at risk for avascular necrosis. Second, most carpal fractures are intraarticular injuries. The displaced fracture often needs surgical repair to avoid secondary arthritis from joint surface incongruity. The pattern of carpal fracture or fracture dissociation may not be clearly discernible on standard posteroanterior and lateral radiographs, and oblique views, carpal tunnel projection, and other views may be necessary. If results are still equivocal, trispiral tomography or CT should demonstrate the fracture patterns and fragment positions. A technetium bone scan 72 h after trauma usually is diagnostic when the question is whether or not a scaphoid fracture is present.

Scaphoid Fracture Nearly two-thirds of all carpal fractures are of the scaphoid, occurring most often in males 15–30 years of age. Scaphoid fractures occur most commonly through the middle third of the waist or at the juncture of the middle and proximal poles. Diagnosis requires clinical and imaging information. If initial radiographs are normal but the history and physical examination suggest the possibility of scaphoid fracture, continuous immobilization in a

thumb spica splint or cast is advised. Repeat radiographs in 2–3 weeks or a technetium bone scan after 72 h will make the diagnosis. Nondisplaced scaphoid fractures treated with adequate immobilization have a union rate of 90–95 percent. Displaced fractures, defined as displacement of 1.0 mm or more, are associated with avascular necrosis in one-half and nonunion in one-half of patients if not reduced and stabilized operatively.

Carpal Dislocations and Instabilities The radiocarpal and intercarpal articulations are not inherently stable on the basis of their osseous anatomy; it is the integration of osteoligamentous anatomy that secures the complex kinematics of wrist function. Most carpal dislocations are caused by an acute axial load with wrist hyperextension. The primary dislocation occurs at the midcarpal joint with dorsal displacement of the capitate. When the capitate displaces, the scaphoid must fracture or its ligaments will tear, allowing it to rotate from a horizontal position to one of vertical malalignment with the proximal pole rotating dorsally; this is called *dorsal perilunate dislocation.* These serious and unstable intraarticular injuries, with or without scaphoid or triquetral fracture, require careful reduction and internal fixation. The majority require open reduction. Direct trauma to the median nerve from impact, by secondary stretching resulting from dorsal displacement of the carpus, or from acute bleeding and swelling within the carpal tunnel should be identified by neurovascular examination. Carpal instabilities of all types should be treated aggressively to prevent chronic instability and dysfunction.

Metacarpal Fractures Because of their subcutaneous location and relatively rigid proximal articulations, the metacarpals represent one-third of hand and wrist fractures. Failure to reconstitute the metacarpals may lead to permanent functional deficit. Complication rates after extensive exposure for plate fixation can be high, and the risk of additional injury must be weighed against outcomes expected with conservative measures. The goal is early restoration of hand function to prevent stiffness. Whether internal or external immobilization is used is immaterial, as long as bone length and articular relationships are preserved and soft tissue management and therapy techniques can be instituted rapidly. A skin laceration caused by tooth impact often connotes an open fracture and mandates surgical treatment. Patients with human or animal bites require surgical irrigation of the fracture site or joint plus high-dose antibiotics. Rotational alignment of a metacarpal fracture is best assessed with the fingers flexed at the metacarpophalangeal joint. With an uncooperative juvenile patient or an unconscious

patient, the wrist can be passively flexed and extended, with the resulting extrinsic flexor and extensor effect on digital alignment observed. Malrotation on active flexion produces a degree of visible digital overlap. Malrotation and radial-ulnar angulation interfere with hand function and should be corrected. The metacarpal neck is the most common fracture site. As with displaced and angulated fractures, the cortex on the angulated side usually is comminuted. The normal pull of the intrinsic muscles further flexes the head fragment, making it difficult to maintain reduction. The degree of angulation and the metacarpal involved determine the best treatment for the specific fracture. Because the second and third carpometacarpal joints are rigid, no more than 10–15 degrees of palmar angulation of the distal fragment is acceptable. Considerably more angulation (30–50 degrees) may be acceptable in the neck of the fourth and fifth metacarpals. Closed reduction may be achieved through the combination of direct and counterpressure applied with the finger flexed. The hand should not be immobilized in the position depicted for manipulation. Open reduction usually is not necessary, but when the fracture is unstable and residual or recurring angulation is not acceptable, internal fixation is required. Metacarpal shaft fractures should be protected when position and angulation are acceptable but reduced when they are not. Spiral and oblique fractures undergo malrotation and displacement because of the normal forces of the flexor and extensor tendons and hand intrinsics. Those which are not initially displaced or rotated must be carefully observed. Internal fixation allows more rapid soft tissue mobilization and often can be treated with percutaneous intermetacarpal pin technique, local block anesthesia, and fluoroscopic monitoring. Some of these fractures require open reduction for fixation.

Phalangeal Fractures The goal of phalangeal fracture treatment is restoration of anatomy, bone healing, and full function. Dysfunctional angulation and rotation are not acceptable. Stabilized fracture anatomy must allow rapid mobilization. Each method of fracture care has relative advantages and risks. Less invasive methods may offer less stability, but they inflict less soft tissue damage. When operation is required, the least traumatic method should be used to avoid violation of gliding structures. The patient's active participation in a rehabilitation program encompassing supervised therapy, custom splinting, and home exercises is critical for recovery of function. Proximal interphalangeal joint motion, particularly extension, can be difficult to regain if an injured, swollen finger is immobilized in flexion. Scar can tether the extensor tendons or prevent the flexors from gliding, impairing grasp and manipulation

and preventing return to preinjury employment. When Kirschner wires are used, they may be buried, and they may then be retrieved in the outpatient setting under local anesthesia after 4 weeks. Sufficient fracture healing usually has occurred by then despite the delayed appearance of significant interfragmentary callus on radiographs. When Kirschner wires are left external to the skin, as in juveniles, pins must be capped and cared for meticulously. Small bone plates and screws need not be removed except to treat symptoms from the hardware.

Finger Ligament Injuries *Metacarpophalangeal (MP) Joint* MP joint dislocations can be managed by gentle reduction and splinting under local anesthesia. If significant residual collateral ligament instability in a particular finger is present, surgical repair is necessary. The small subgroup of irreducible fractures requires operative repair. Patients with acute collateral injuries may have a malrotated finger because of rotation about the intact ligament. Dorsal dislocations that are irreducible are characterized by dimpling of the palmar skin over a prominent metacarpal head. Interposed soft tissues can prevent joint reduction. In these patients, surgical treatment is required. Thumb MP joint injuries result from axial load and angular displacement. These injuries often occur when the patient jams the thumb into an object while falling. Disruption of the ulnar collateral ligament of the thumb is called *gamekeeper's thumb*, although the term was applied originally only to chronic ulnar collateral instability. Collateral laxity at the thumb MP joint is dysfunctional and painful and may lead to late arthritis. After plain radiographs fail to detect the presence of intraarticular fractures, the thumb is examined in about 30 degrees of MP flexion, gently and progressively stressing the suspect collateral ligament. Radiographs may be obtained simultaneously; the stress radiograph is best performed by the examining physician. Treatment of incomplete collateral ligament injuries without associated instability is best done closed, with cast immobilization for approximately 4 weeks, followed by custom-splint immobilization. Soreness may persist for several months. Complete disruption of the ulnar or radial collateral ligament of the thumb MP joint should be repaired and protected by temporary pin fixation of the joint, which is most likely to give a better result and shorter period of disability than secondary reconstruction.

Proximal Interphalangeal (PIP) Joint The tightly congruent osteoarticular contours of the proximal interphalangeal joint make restoration of stable alignment of disrupted or displaced structures essential. Stiffness, rather than instability, is the outcome that must

be avoided after trauma of the PIP joint. Most dorsal and lateral PIP dislocations can be treated by closed reduction and are stable. Immobilization for 10–15 days allows the patient to recover from the acute posttraumatic effects before a protected mobilization program is started with buddy tapes to an adjacent finger. Joints without an actual history of displacement, deformity, or reduction may have considerable swelling and stiffness if not mobilized early. Dislocations with fractures are more likely unstable. Postoperative immobilization that inadvertently stresses an osteoarticular fragment results in posttraumatic instability. The combination of joint surface impaction and ligament disruption has the worst prognosis. These fracture-dislocations have an outcome that is often unsatisfactory.

Palmar (Volar) PIP Dislocations In volar PIP dislocations the middle phalanx is displaced palmarward, sometimes resulting in serious instability. This PIP dislocation results from the combination of axial load and palmar vector force, most often during sports activities. Often unrecognized is that this trauma has an associated disruption of the central slip of the extensor tendon and one collateral ligament. Closed reduction and pinning or open reduction for the irreducible variant with prolonged postoperative therapy is the rule.

Distal Interphalangeal (DIP) Joint Collateral ligament injuries and dorsal or palmar dislocations may occur. Stable joints need not be pinned. In others, percutaneous fixation with maintenance of the pin fixation for 5 weeks allows the rest of the hand to be mobilized.

Fingertip Injuries Conservative treatment, such as healing by secondary intention of fingertip amputations, may result in painful scarring and deformity. However, with only a skin defect and of less than 25 percent of the pulp in adults and 50 percent of the pulp in children, conservative treatment (dressings) frequently gives the best result. There are several requirements for a satisfactory outcome after fingertip amputation: (1) Optimal functional finger length must be maintained, and additional shortening during or as a complication of treatment must be avoided. (2) The residual tip/pulp requires a resistant and resilient character like normal skin. (3) Excellent fingertip sensibility should be maintained to avoid "blinding" the finger. (4) Bone support for the nail is needed to minimize beaking deformity. For the thumb, every reasonable effort must be made to restore a sensate and durable pulp. Requirements for sensibility are more critical in the index and middle fingers, but they also are significant in the ulnar pulp of the small finger. Amputations can be clean and sharp, but the common

injury has a component of avulsion, crush, blast, and burn, as in explosions. Explosions cause extensive trauma to surrounding skin, soft tissue, and neurovascular tissue that requires debridement and, in some cases, staging of the closure. Treatment of partial amputations, crush injuries, and partial devascularizing injuries should be directed toward preserving soft tissues. Distal phalangeal fractures, including bursting or tuft fractures, frequently are associated with crush trauma and nail bed disruption or lacerations. Nail bed injuries are not always obvious, and subungual hematoma may be the only sign of nail bed injury. Nail bed injuries should be repaired to prevent permanent nail deformity. Nail bed repairs usually are done with fine 6-0 absorbable suture. After repair, the nail that was removed is replaced beneath the cuticle to splint the bed.

Bone Shortening and Primary Closure This is performed under local or regional anesthesia and consists of debriding enough bone so that the skin can be closed with a few 5-0 sutures without tension. This method affords coverage with soft tissues of normal sensibility, and this well-padded fingertip is not painful, but the cost is some length and at least a portion of the fingernail. Inadequate bone resection produces a fingertip with unpadded bone, resulting in pain during grasping.

Composite Pulp Reattachment Reapplication of the "composite" of skin and pulp or skin, pulp, and bone can be done when the mass of the amputated part is very small. This choice almost always should be reserved for young children. It is best to debride any residual bone. Superficial necrosis of the reapplied part should be expected. In most situations, the reapplied tissue is a temporary biologic dressing.

Skin Grafting Grafts are a means of coverage of skin defects. The major drawbacks are sensory loss in the graft area and inadequate padding if the graft is applied directly over periosteum on prehensile surfaces. The aesthetics of the graft are affected by the donor site. The best cosmetic result for the pulp surface is achieved in all races with split-thickness or full-thickness skin graft taken from the glabrous skin at the hypothenar eminence under local anesthesia. The defect covered with a skin graft should be a skin defect, and the recipient bed must have adequate subcutaneous tissues. Skin grafts to the palm from any area other than glabrous skin is hyperpigmented. Split grafts usually are inadequate for pressure and friction surfaces. Toe-to-finger and foot-instep-to-hand-pulp skin grafting can be performed, but the short-term disadvantages are obvious as compared with full-thickness hypothenar skin as the donor.

Local Flaps Local tissue transfer from more proximally on the injured finger affords vascularized, padded, and most often sensate tissue.

Regional and Distant Flaps Cross-finger, thenar, and other heterodigital flaps have been used since the early part of the twentieth century, generally for more extensive pulp loss and otherwise uncoverable bone and tendon. These flaps have the advantage of retaining finger length but carry the risk of posttraumatic deformity or dysfunction in an adjacent donor finger. Care must be taken to avoid dysfunction from immobilization of the injured or the donor part because of nonphysiologic positioning during flap healing and before pedicle detachment. Such flaps usually are not sensate.

Replantation and Microvascular Neurosensory Flaps Microsurgical advances have made finger- and hand-part reattachment possible and have allowed reconstruction by composite neurovascular pulp tissue from toes, with or without joints and tendons. The isolated single-digit amputation in the adult usually is not suitable for replantation, especially if proximal to the PIP joint, because the functional and aesthetic recovery usually does not justify the morbidity and costs of the replantation procedure. Multiple-digit amputations, subtotal hand amputations, amputations throughout the upper limb proximal to the hand, and most pediatric amputations should be evaluated for replantation or primary composite microvascular reconstruction.

Soft Tissue Trauma

Tendon Injuries *Flexor Tendons* Flexor mechanism injuries in the hand and fingers usually are treated early in most patients because direct primary and delayed primary repairs offer good to excellent results even when done in the middle of the digits. Satisfactory results are reported in 75–98 percent of patients in various series. Flexor tendon repair and functional rehabilitation are a challenge. Flexor tendons are not difficult to repair, but achieving good function of repaired tendons is difficult, particularly in zones in which multiple tendons of different excursion are in juxtaposition. Tendons must glide, and simultaneously they are restrained by ligaments, such as within the digital sheath and within the carpal canal. Getting flexor tendons to glide after repair is a problem. The critical operative principle in tendon repair is to achieve near-perfect anatomic alignment of the tendon ends. There should be no gaps at the repair site, and "bunching" of the repair zone should be avoided to permit the repaired tendon(s) to glide within a sheath or

pulley system. The zones of flexor tendons are defined by the number of tendons, restraints, and pulleys and the presence or absence of synovial membrane at that specific anatomic level. In the diagnosis of tendon disruption, the patient often presents with an open wound and loss of active motion. Observing the part at rest along with active, separate evaluation of the flexor digitorum profundus and flexor digitorum superficialis tendons makes the diagnosis. A high level of suspicion should be maintained with injuries that have loss of active flexion or extension when x-rays do not show skeletal disruption. Tendon avulsions may occur without attached bone. Closed, isolated flexor profundus avulsion is most common in the ring finger; the DIP joint will not flex, but the PIP joint does. For primary or delayed primary repair to be effective, early diagnosis is essential. Partial tendon lacerations, approximately up to two-thirds of the tendon's cross-sectional area, do not present serious risk of rupture, but the lacerated edge may catch on a nearby pulley, producing posttraumatic triggering. Lacerations involving 30–60 percent of the tendon's cross-sectional area may be treated by epitendinous suture alone. Division of 60 percent or more of cross-sectional area may be treated surgically as though division were complete.

Extensor Tendons The superficial location of the extensor tendons on the dorsum of the fingers and hand makes them vulnerable to injury, especially when the fingers are flexed. Trauma comes from lacerations, crush impacts, abrasions, and bites. Extensor tendon injuries are more common than those of flexors and often are treated casually in the emergency department. Extensor dysfunction may result in loss of active flexion from scar tethering and/or diminished active extension. The extensor system is more intricate and complex than the flexor system. The interconnections of the extrinsic digital extensor tendons from the muscles in the forearm and tendons in the hand, and the intrinsic tendons in which muscles and tendons are in the hand, are complex. The two sets of tendons collaborate to flex the MP joints and extend the IP joints. Because excursion of the extensor mechanism is limited over the finger joints, preservation of tendon length is more critical to maintain and restore tendon balance than with flexor tendon injury. The flexor tendons are thick, round, cordlike structures with spiraling fibers. The extensor tendons are thin and flat, and the longitudinal fibers of the extensors do not hold sutures well. The limited amount of soft tissues about these tendons also makes repairs prone to adherence and scarring. The extrinsic extensor tendon is the only MP joint extensor through aponeurotic sagittal fibers. Distally, the function of the intrinsic and extrinsic tendons together forms the dorsal tendon

apparatus in the fingers. The direct distal continuation of the intrinsic tendon is the lateral band that continues distally to reach a position dorsal to the center of axis of PIP joint motion before crossing over the distal third of the proximal phalanx, thereby making it an extensor tendon for both IP joints. At the metaphysis of the proximal phalanx and the base of the middle phalanx, the extrinsic and intrinsic tendons converge to become conjoined extensors. The central slip inserts into the dorsal lip of the middle phalanx as its direct extensor, but the conjoined lateral bands run along the dorsal lateral edge of the PIP joint and converge distally over the middle phalanx to become the terminal tendon that inserts into the dorsal lip of the distal phalanx, functioning as this last joint's only extensor. Because of the normal dorsolateral position of the lateral bands, in certain direct injuries to the dorsum of the finger at the PIP joint the lateral bands may subluxate volarly, hyperextending the terminal joint. This is called the *boutonnière deformity.* When the terminal tendon insertion at the DIP joint (zone 1) is avulsed or transected, the distal joint droops, and the secondary proximal and dorsal retraction of the lateral bands produces gradual hyperextension at the PIP joint level. This deformity is known as *mallet* or *baseball finger;* it progresses to the *swan-neck deformity* when PIP joint hyperextension is added.

Terminal tendon injury may occur by avulsion with or without attached bone fragment and by transection from laceration or crush. Closed and open injuries usually can be treated successfully by closed means. Splints that immobilize the DIP articulation in extension (6–8 weeks) but leave the PIP joint unrestrained usually are preferred.

Zone 2 Zone 2 is the area over the middle phalanx where the lateral bands fuse to form the terminal tendon. Direct repair and terminal joint pinning for 6–8 weeks are appropriate for open cases; closed splinting for closed injuries without significant fracture is effective.

Zone 3 (Boutonnière) Zone 3 is the area over the PIP joint where the central slip and lateral bands interconnect. Injury may include avulsion of the central slip, with or without a dorsal bone fragment. The latter injuries require accurate reduction of the joint, bone, and contiguous tendon mechanism. Pinning the PIP joint in extension allows early rehabilitation of the other joints. Closed splint or percutaneous pin management may be equally effective for pure tendon injuries.

Zone 4 Most tendon injuries in zone 4 are partial, and the cut tendon ends do not retract significantly. Only direct inspection can

confirm this diagnosis. If IP joint extension is normal, a partial tendon injury need not be repaired. Splinting the PIP joint for 3–4 weeks usually is adequate.

Zone 5 Lacerations and bite wounds are common at the MP joint. Bite wounds are serious contaminated injuries requiring primary surgical debridement, irrigation of the wound and joint, and aggressive intravenous antibiotics for 24–48 h. The incidence of complications is directly related to the delay in treatment. Radiographs are taken to rule out the presence of a foreign body such as a piece of tooth, an intraarticular fracture, or air in the joint, proving contamination. When caused by a bite, the wound is left open, and tendon repair is performed secondarily after healing by secondary intention. In a simple laceration, the tendon can be repaired directly. The more dorsal extrinsic extensor tendon and the sagittal band mechanism should be repaired to prevent subluxation of the extensor into the intermetacarpal valley. Primary repairs are preferable, using suture techniques described in Fig. 42-2. The wrist is immobilized in 30 degrees or less of extension, and the MP joint is

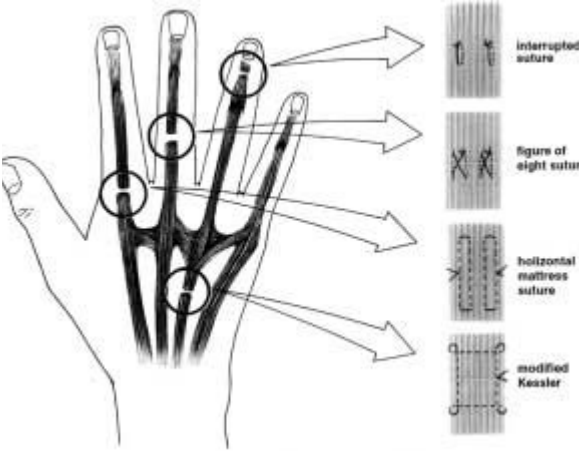


FIGURE 42-2 Suture techniques for the extensor tendons. Different techniques are chosen according to the size and quality of the tendon. The interrupted suture is used in zone 1, whereas core-type sutures can be used in thicker tendon tissue in zone 6.

splinted at 60–70 degrees or treated with a custom dynamic MP extension splint for early passive motion. The PIP and DIP joints are left free.

Zone 6 Zone 6 covers the dorsum of the hand. Single or partial tendon lacerations may not produce MP extension loss because forces are transmitted through the tendinous interconnections extending from adjacent extensors, such as the juncturae tendinum. The tendons are oval in cross section and thicker here than distally. Core sutures of the type used in flexor repairs are recommended (see Fig. 42–2). The wrist should be kept in about 30 degrees of extension and the MP joints fitted with proximal phalangeal extensor cuffs with the IP joints free, allowing active flexion and passive extension.

Zone 7 Zone 7 is the proximal wrist region under the extensor retinaculum, which should be preserved or repaired. Attrition ruptures should be repaired by tendon transfer or grafting. Direct repair is almost never possible because of the wide zone of tendon trauma that occurs before breakage.

Zone 8 Multiple adjacent muscles or tendons make it difficult to identify individual tendons. The priority of repair is to restore independent wrist and thumb extension and group extension of the fingers. For repair at this level, the suture line must include fascia or the intramuscular tendinous septa to prevent pullout and failure of operation. After repair, elbow flexion and wrist extension may be needed to reduce tension at the suture line.

Nerve Injury The upper extremity is innervated by the brachial plexus and several sensory branches arising from the plexus and intercostal nerves. Classification of nerve injuries is as follows: *Neurapraxia* describes paralysis/dysfunction in the absence of nerve degeneration. This dysfunction is often of some duration, though recovery is always achieved in a shorter time than would be required after complete transection and nerve degeneration and regeneration. Recovery is invariably complete. *Axonotmesis* includes damage to the nerve fibers of a severity that causes complete nerve degeneration. The epineurium and other supporting structures of the nerve are not disrupted, so the internal architecture is relatively well preserved. Spontaneous recovery is the rule, and generally it is of very good quality because the regenerating fascicles are guided into their paths via the intact sheaths. Recovery takes longer than for neurapraxia. *Neurotmesis* is when all nerve structures have been divided. Laceration produces neurotmesis, but physical gaps in the

nerve may occur even though the epineurial sheath appears in continuity, such as after traction or crush. At the site of damage, the nerve will be completely replaced by fibrous tissue, and there is complete loss of anatomic continuity. Recovery after nerve injury depends on successful reinnervation of sensory or motor end-organs. After denervation, muscles begin to lose their bulk; a loss of cross-sectional area without any loss in muscle fiber count begins within 1 week of denervation. Connective tissue surrounding the muscle undergoes degeneration and thickening. Interstitial fibrosis predominates over time, but passive exercises may delay or prevent this phenomenon. For function to be resumed, motor end plates must be reinnervated within 18 months of trauma. Sensory end-organs may be usefully reinnervated long after initial injury, but the quality of recovery diminishes with the passage of time. The result after repair depends on numerous factors: injury level and mechanism, associated bone and soft tissue loss, residual function, patient compliance and motivation, timing of repair, and supervised rehabilitation. Quantitative postoperative assessment of motor and sensory function should be documented. Repair should be done with microsutures with the aid of magnification to produce a spatially correct, tension-free suture line. Nerve grafts are used when direct repair after segmental loss or fibrosis would require tension at the repair site. Joint posturing into extreme flexion or extension to decrease tension at the nerve repair site should be avoided; nerve graft is substituted for such destructive splinting maneuvers. Primary or delayed primary repair should be done whenever appropriate conditions allow. The combination of group fascicular and epineurial nonreactive microsutures after identification of the internal topography should produce the best anatomic result. Repairs are protected by relaxed joint posturing for about 3 weeks, and the results of repair are maximized by beginning sensory and motor reeducation after reinnervation.

Vascular Trauma and Replantation Most upper extremity replantation surgery is based on microsurgical technique. A contaminated soft and bony tissue injury is healed by primary debridement and stabilization of open fractures, repair of extensor and flexor mechanisms, and microsurgical repair of nerves and vessels. Neither complete nor near-complete part amputation makes any patient an automatic candidate for revascularization or reattachment. Single-finger amputation in the adult, especially at a level proximal to the PIP joint, including both superficialis and profundus tendons and digital nerves, is not suitable for replantation in the vast majority of patients. Consideration should be given to replantation for thumb amputations at and proximal to the IP joint, for single-finger

amputations in children, and for partial hand and more proximal wrist, forearm, or arm amputations.

Handling of Amputated Parts The amputated part should be cleansed under saline solution, wrapped in a saline-moistened gauze, and placed in a plastic bag. The plastic bag containing the part should then be placed on, not packed in, a bed of ice in a suitable container. The part should not be immersed in nonphysiologic solution such as antiseptics or alcohols. The amputated part is never put in dry ice, it is not perfused, and it should not be allowed to freeze.

Preparing the Patient The patient is stabilized, and a compression dressing is applied to the stump before transport to the replantation center. Intravenous access lines should be started and blood samples drawn while awaiting transportation. If time permits, x-rays of the stump and also of the amputated part can be obtained. Most replantation centers request that the patient be given intravenous antibiotics, an aspirin suppository (325 mg), and 25–50 mL/h intravenous supplement of low-molecular-weight dextran in dextrose, the latter for antiaggregation platelet effects.

Complications of Trauma

Compartment Syndrome/Volkmann's Contracture In acute compartment syndrome, increased fluid pressure in the tissues contained within a fascial space or subcompartment increases to a level that reduces capillary blood flow below that necessary for continued tissue viability. When untreated, continued pressure elevation produces irreversible muscle and nerve damage because of ischemia, with secondary necrosis, fibrosis, contractures, and sensibility deficits or chronic pain. Acute compartment syndrome results from an increase in the volume of fluid within a compartment or limitations on the dimensions of an anatomic compartment. Posttraumatic edema or hemorrhage, hematoma, swelling from infection, or burns increase compartment fluid, as does revascularization. Other causes include venous obstruction and transiently strenuous exercise. Constrictive dressings and casts, excessively tight surgical closure, and prolonged direct limb pressure during unconsciousness from alcohol and drugs or during extended surgical procedures add to the limited dimensions of the anatomic compartment. Acute compartment syndrome is diagnosed clinically but can be confirmed by measurement of intracompartmental tissue pressure. Clinical findings include a swollen, tense, and tender

compartment with pain out of proportion to that expected from the originating injury, peripheral sensibility deficits, and finally, motor weakness or paralysis. Pain is accentuated by passive stretch of the affected muscle. Peripheral pulses usually remain intact because systolic arterial pressure usually is well in excess of the dangerously elevated intracompartmental pressure. While blood flow through the major arteries is not impeded, capillary perfusion is compromised by the elevated pressure (30–60 mmHg) within the compartment. Pressure measurement devices are confirmatory but not infallible, and in treatment decisions clinical concerns should outweigh specific pressure measurements. Threshold pressure measurements of 30 mmHg or more are consistent with compartment syndrome, and surgical decompression should be prompt. Because tissue perfusion is affected by systemic blood pressure, a lower threshold pressure for fasciotomy should be used in hypotensive patients. Treatment includes removal of all occlusive dressings, wraps, layers, and splints and splitting tight casts and cast padding down to the skin. If symptoms are not relieved rapidly, fasciotomy of the affected areas is required.

Neuromas Neuromas represent a normal physiologic response after nerve injury. All badly injured and severed nerves form neuromas, but only those neuromas which are exposed, superficial, and likely to be impacted become symptomatic. Only sensory fibers develop painful neuromas. Medical and surgical management of symptomatic neuromas may be difficult, but prevention is more important. A symptomatic neuroma is a therapeutic challenge. More than a hundred methods of surgical treatment have been described, but no method is universally successful. The symptomatic neuroma should be identified, isolated, and dissected intact. The scar bulb is kept in continuity with the nerve. The symptomatic nerve and its continuous neuroma are transposed to a deeper, more padded, and often more proximal location, beneath muscle if possible, but within bone when needed.

Reflex Sympathetic Dystrophy Reflex sympathetic dystrophy is a complex interaction of physiologic responses initiated by trauma and exacerbated by posttraumatic events. This process is staged by time and inflammatory phase with characteristic changes (Table 42-1) and by descriptive terminology (Table 42-2). The presumptive diagnosis is based on pain, which is often diffuse, burning, and hyperpathic, including allodynia (pain to light touch), hyperalgesia (painful response to nonpainful stimuli), dysesthesia (pins and needles following minor stimulus), and hyperesthesia

TABLE 42-1
STAGING OF REFLEX SYMPATHETIC DYSTROPHY

	Stage I Acute	Stage II Dystrophic	Stage III Atrophic
Time frame	0–3 months	3–6 months	6–>12 months
Symptoms	Allodynia Hypersensitive	Constant pain Cold intolerance	Constant pain Cold intolerance
Signs	Swelling (edema) Redness ↑Sweating	Tissue indurated Joint stiffness Dry skin	Thin, atrophic skin Dry skin Cool
Microvascular Assessment	↑Total flow ↓Nutritional flow	Nl to ↓ total flow ↓Nutritional flow	↓Total flow ↓Nutritional flow
X-ray findings	Mild to moderate osteopenia	Moderate to severe osteopenia	Severe osteopenia

TABLE 42-2
DEFINITIONS OF REFLEX SYMPATHETIC DYSTROPHY

From the International Association for the Study of Pain, Taxonomy, Adelaide Consensus Statement 1990

- RSD is a descriptive term for a complex disorder or group of disorders that may develop as a consequence of trauma affecting the limbs with or without obvious nerve lesions.
- RSD consists of pain and related sensory abnormalities, abnormal blood flow and sweating, abnormalities of the motor system, and changes in structure of both the superficial and the deep tissues (tropic changes).
- It is agreed that the term RSD is used in a descriptive sense and not to imply a specific underlying mechanism; not all components will exist at once.

From the Ad Hoc Committee on to the American Association for Hand Surgery

- RSD is a pain syndrome in which the pain is accompanied by loss of function and evidence of autonomic dysfunction.
- Neither pain without autonomic dysfunction nor autonomic dysfunction without pain is sufficient to define the syndrome.
- A more appropriate name for this syndrome may be *sympathetically maintained pain syndrome.*
- Diagnosis criteria include diffused pain, loss of function, and sympathetic dysfunction.

(increased sensitivity or pain with nonpainful stimuli). Patients with reflex sympathetic dystrophy often require chronic treatments, psychological support, including counseling and medication, and an extended, intensive, and closely monitored therapy program (Table 42-3). Early recognition and treatment prevent secondary stiffness from joint and tendon adhesions.

Burns

See Chap. 7.

TABLE 42-3
ORAL AND TOPICAL MEDICATIONS FOR REFLEX SYMPATHETIC DYSTROPHY

Drug	Usual Dosage	Mechanism	Major Short-term Disadvantage or Side Effects	Contraindications
Amitriptyline (Elavil)	25 mg tid or 50 mg qhs	Inhibits amine pump (decreases norepinephrine uptake)	Drowsiness: antimuscarinic side effects; orthostatic hypotension	With guanethidine sulfate or bretylium
Phenytoin	100 mg tid	Decreases resting membrane potential; inhibits amine pump; stabilizes synaptic membrane	Minimal drowsiness; serum levels suggested	Long-term use
Phenoxybenzamine hydrochloride (Dibezyline)	40–120 mg/day	Alpha-receptor blocking agent	Orthostatic hypotension	With late-stage RSD
Nifedipine (Procardia)	10 mg tid; may be increased slowly to 30 mg tid (30 mg XL for qd administration available)	Calcium-channel blocking agent; diminishes A–V shunting; increases nutritional flow	Headache; constipation	Concurrent use of beta-adrenergic blocking agents

Corticosteroids	20–80 mg qd prednisone equivalents × 5 – 40 days	Stabilizes membrane, increases nutritional flow	Adrenal suppression; avascular necrosis; pain (related to dose decreases)	
Carbamazepine (Tegretol)	400–1200 mg in 2 to 3 divided doses	Blocks neural discharges; sodium-channel blocker	Neurological; bone marrow suppression; hepatoxicity; suppresion; ataxia	History of bone marrow suppression; hypersensitivity suppression; to tricyclic compounds; concurrent monamine oxidase inhibitors
Clonidine (Catapres-TTS − 2, − 3)	0.2–0.3 mg patch	Affects adrenergic transmission with marked selectivity for presynaptic sites of vasomotor fibers; alpha-2 adrenergic agonist	Skin irritation; rash surrounding patch; passive absorption of drug varies	Renal disease; heart block; beta-blockers

SOURCE: From Koman LA, Ruch DS, Smith BP, Pollock FE, Poehling GG: Reflex sympathetic dystrophy after wrist surgery. In: Levin LS (ed): *Problems in Plastic and Reconstructive Surgery.* Philadelphia, JB Lippincott, 1992, pp 300–322.

INFECTION

Bacterial Infection

Skin infections most commonly derive from direct bacterial inoculation. Secondary spread from contiguous sites and hematogenous seeding are less likely. The most common infecting organisms are *Staphylococcus* and *Streptococcus* species; gram-negative, anaerobic, and mixed infections are seen, depending on the inoculation method, e.g., a tooth. Serious, deep infections require hospital admission and extended use of high-dose intravenous antibiotics. Wound and blood cultures are obtained before antibiotic therapy is started, and adjustments are made as indicated. Paronychial infections are common. These involve the nail and nail bed and constitute about 15 percent of hand infections. Occurrence is associated with hangnails, nail biting, finger sucking, and occupations requiring the hands to be damp frequently. Acute infection is always bacterial, creating a localized abscess, but chronic inflammation is most often yeast or fungal, requiring a different therapeutic approach. Herpetic whitlow is an infection of the soft tissues of the distal phalanx or paronychial area by the herpes simplex virus. It is characterized by intense pain and cutaneous vesicles or blisters. The vesicle fluid is clear at first but may become cloudy over a few days. It is important to distinguish this from bacterial infection. Herpetic whitlow is self-limited, generally resolving within 3–4 weeks. Felon is an expanding abscess within the finger pulp and represents up to one-quarter of hand infections. Felons also can be extremely painful, often reported as throbbing pulp pain.

Tenosynovitis Acute pyogenic digital tenosynovitis is most frequently a result of direct penetrating trauma. Kanavel's cardinal signs of tenosynovitis include (1) fusiform digital swelling, (2) semiflexed digital posture, (3) significant pain from passive extension of the finger, and (4) tenderness along the entire flexor sheath. Proper management for this closed-space tenosynovial abscess is surgical drainage and intravenous antibiotics. A high index of clinical suspicion is required for diagnosis. Aspiration of the sheath will confirm the diagnosis. In early cases, systemic antibiotics alone may be considered, but there must be profound resolution within 12–24 h; otherwise, prompt operative drainage is necessary.

Osteoarthritis and Osteomyelitis These may result from neglected soft tissue infections.

High-Pressure Injection Injuries These occur from paint and grease guns. Penetration along extended tissue planes occurs. These injuries require immediate mechanical debridement to prevent extensive loss.

Nonbacterial Infections

These include tuberculous and mycotic infections such as leprosy.

CHRONIC SYNDROMES

Tendinitis

De Quervain's Tenosynovitis Inflammation of the tendons in the first dorsal compartment and the abductor pollicis longus and extensor pollicis brevis became associated with de Quervain after his 1895 report of five cases. This tendon inflammation is one of the most common causes of pain along the radial side of the wrist and the proximal dorsoradial thumb. Injection with a steroid and local anesthetic combination is the best nonoperative treatment. As with other tendon inflammations, injection should relieve symptoms adequately and for a minimum of 4–6 months to merit repeating. When symptoms persist or recur, surgery is carried out.

Trigger Finger Chronic flexor tenosynovitis or tenovaginitis occurs most commonly in the middle and ring fingers and in the thumb and most often in postmenopausal females. The snapping phenomenon occurs as the flexor digitorum superficialis and profundus tendons or the flexor pollicis longus in the case of the thumb pulls through a tight A1 flexor pulley at the proximal edge of the sheath. There is debate as to whether tenosynovial inflammation or pulley thickening is the cause. Nonsurgical treatment should be offered except for patients with a fixed PIP joint flexion contracture that will not unlock after local anesthetic and steroid injection. Approximately 1–2 mL of steroid and local anesthetic is injected into the flexor sheath and pulley. Surgery routinely cures the problem for those unrelieved by steroid.

Neuropathies

Median Nerve The median nerve may be compressed anywhere along its course from the cervical roots to the fingertips, but the most common site is within the carpal tunnel, where it is dorsal to the transverse carpal ligament. All anatomic sites of compression must be considered and evaluated in the differential diagnosis of

this increasingly common peripheral neuropathy. Carpal tunnel syndrome results from increased pressure within the rigid carpal canal, producing median nerve ischemia and physiologic dysfunction. Symptoms include paresthesias and numbness in the radial three fingers, burning digital dysesthesias, and later in the course, hand weakness or awkwardness. Focal wrist and hand pain are not a part of the syndrome, whereas nocturnal presence of symptoms is a hallmark of this diagnosis.

All treatments are designed to reduce pressure within the canal and relieve nerve. There is debate as to the cause of the increased pressure. Some have postulated tenosynovitis, whereas other studies have shown collagen, amyloid deposits, and edema as causes. Eighty percent of carpal tunnel patients are over the age of 40 years. The female-to-male ratio varies from 4:1 for idiopathic cases to as low as 1.5:1 with occupational presentation. A direct connection between carpal tunnel syndrome and forceful or repetitive use of the hands has not been demonstrated conclusively. Carpal tunnel syndrome has been associated with endocrine disorders, including diabetes, myxedema, hyperthyroidism, acromegaly, pregnancy, and the postpartum state. Chronic infections and hematologic and autoimmune disorders also are associated with carpal tunnel syndrome. Space-occupying lesions such as lipomas, bone abnormalities of the radius or carpals, posttraumatic edema, and hematomas may induce increased pressure within the canal and compromise median nerve function.The diagnosis of carpal tunnel syndrome is clinical.

Classic symptoms include paresthesias, with a predominance of nocturnal or early morning onset, burning or numbness in the median sensory distribution, and awkwardness in use of the hand. On physical examination, direct digital pressure over the median nerve at the carpal tunnel reproduces symptoms within 30 s. In Phalen's maneuver, gravity-induced wrist flexion reproduces symptoms within a minute. When direct percussion of the nerve elicits and reproduces paresthesias in the median distribution, it is a positive Tinel's sign.

Examination of motor function includes observation for thenar loss and assessing abductor muscle resistance against force. Electrophysiologic studies provide important confirmatory and differential diagnostic information. Electrophysiologic studies alone do not form the basis for this diagnosis, but surgery should not be done without electrophysiologic evaluation. Underlying peripheral neuropathies and multifocal compressions that are otherwise unsuspected may be uncovered. Electrical studies provide a baseline for later comparison if the response to surgery is disappointing.

Evaluation may include studies of the median nerve as well as of a second nerve in the more symptomatic extremity. Comparison of median and ulnar or of median and radial sensory stimulation values at the wrist is useful in confirming the diagnosis. Studies are not necessarily of prognostic value for the response to surgery. Routine radiographs including the carpal tunnel view are recommended by the American Academy of Orthopaedic Surgery for evaluation and treatment of carpal tunnel syndrome. Radiographs are evaluated for carpal fractures, arthritis, Kienböck's disease, or other problems that could alter treatment. CT scans and MRI are seldom needed, but basic laboratory studies to screen for endocrine and hematologic disorders are helpful.

Predisposing medical diseases, such as thyroid dysfunction or rheumatoid arthritis, should be treated and frequently may improve or resolve the neuropathy without surgery. In pregnancy, carpal tunnel syndrome is treated by salt restriction, wrist splinting, analgesics, and occasionally, diuretics. Local injection may be needed in the third trimester. Most patients recover within about 6 months of delivery. For acute posttraumatic carpal tunnel syndrome associated with swelling or hemorrhage, loosening of constrictive bandages and moving the wrist from a position at the extreme of flexion or extension may suffice to reverse or significantly improve symptoms. Pressure studies and early surgery may be appropriate for those who do not respond. Splints and nonsteroidal anti-inflammatory medications are widely used. Splints should fit comfortably and position the wrist in neutral to minimal extension. Splints are worn at night if nocturnal symptoms are a major complaint. Night splinting may be all that is required. With activity-induced symptoms, daytime splint use during provoking tasks may be needed. Oral nonsteroidal anti-inflammatory agents may be helpful, with monitoring for possible gastrointestinal and systemic side effects. Although subclinical vitamin B_6 deficiency is a possible cause of carpal tunnel syndrome, no prospective study has demonstrated the efficacy of pyridoxine, but it is nontoxic. Local steroid injection results in improvement in 80–90 percent of patients, but there is gradual deterioration over the next 12–24 months. As with other sites, injections should not be repeated more than two or three times annually. Inadvertent injection directly into the median nerve will worsen symptoms. Surgical treatment requires complete division of the transverse carpal ligament for the entire length of the carpal tunnel under direct vision. Surgical failure is most often associated with incorrect diagnosis or incomplete ligament division. Internal neurolysis, flexor tenosynovectomy, concomitant ulnar nerve decompression in Guyon's canal, or carpal ligament

reconstruction is not indicated with primary release and may be harmful. Open and endoscopic release can effectively divide the transverse carpal ligament and increase canal volume. If the patient continues to have symptoms after surgery, appropriate clinical and adjunctive diagnostic investigations should be undertaken. Incomplete ligament division or inaccurate preoperative diagnosis is the most frequent problem, but patients with hidden agendas of a nonanatomic nature may experience prolonged wound discomfort and limited recovery. In such situations, the value of preoperative electrodiagnostics becomes evident.

Ulnar Nerve Ulnar nerve compression at the elbow, the cubital tunnel syndrome, has been known for more than a century. It has been called *posttraumatic ulnar neuritis* and *tardy ulnar nerve palsy* to emphasize the traumatic causation. Distal compression in the canal of Guyon (the ulnar tunnel) at the wrist is a less common problem and more often caused by a space-occupying lesion or direct trauma. All sites of nerve compression must be considered. The differential diagnosis must include medial epicondylitis and its coexistence with ulnar nerve irritation. Some patients have the mechanical problem of a hypermobile or subluxating ulnar nerve. Ulnar traction neuritis with elbow flexion and anterior nerve subluxation reproduce radiating paresthesias in the ulnar two fingers. Patients who have actual motor weakness, and especially the subgroup with intrinsic muscle atrophy and electrophysiologic changes, have a guarded prognosis after delayed decompression. Patients presenting with medial epicondylitis should be treated for that problem, but the presence of secondary coexisting nerve irritation must be addressed. Those who do not respond to conservative measures as outlined for the carpal tunnel should be treated surgically. There is no clear advantage of one technique over the other in most patients. Ulnar tunnel decompression at the wrist must include the management of space-occupying lesions that complicate this diagnosis. Ulnar tunnel syndrome is far less frequent than compromise of the median nerve in the carpal tunnel syndrome.

ACQUIRED DYSFUNCTION

Dupuytren's Contracture

Although this disorder is associated with the nineteenth-century French surgeon Baron Guillaume Dupuytren, he was not the first to describe it. John Hunter, in 1777, and Sir Astley Cooper, in 1822, described the disease, and Cooper recommended subcutaneous fas-

ciotomy. The pathologic proliferation is primarily of the longitudinal portion of the palmar fascia and its digital expansions palmar and dorsal to the neurovascular bundles. There is no proven relationship to trauma, occupation, handedness, or repetitive use in work or sports. Dupuytren's contracture is seen most commonly in Caucasian males of northern European descent who are in their sixth decade or older. Hand dominance and trauma are not causes; the male-to-female ratio varies from 2:1 to 10:1. Dupuytren's contracture is familial and is inherited as an autosomal dominant trait but with variable penetrance. There are significant associations with a number of diseases and conditions, the most prominent of which are diabetes and alcoholism. Human immunodeficiency virus (HIV) infection may be a risk factor. There is no effective nonsurgical treatment for Dupuytren's contracture. Operation should be reserved for those whose disease is complicated by contracture. When the patient can no longer place the hand flat on the table, the Huston tabletop test, operation is indicated. Contracture correction at the MP joint is easier than at the PIP joint. Operating on a patient with Dupuytren's contracture requires a detailed knowledge of normal hand anatomy, palmar fascial structure, and location of the pathology as it applies to the deformity, including pathologic displacement of the neurovascular bundles, which puts them at risk of injury during even the most careful of surgical release procedures. Most patients have the ulnar palm affected first and most significantly. In decreasing order, the fourth, fifth, third, second, and first rays are most frequently involved. The most effective technique is digital fasciectomy as opposed to fasciotomy. The results deteriorate with time, however; surgery does not cure the disease but treats joint deformities, contracture, and dysfunction. Fasciectomy is performed under loupe magnification and exsanguinated pneumatic tourniquet control. In addition to wound infection and skin slough, secondary swelling is a serious but uncommon complication. Prolonged pain leading to reflex sympathetic dystrophy is a difficult problem for patient, therapist, and physician. Digital nerves can be injured during operation no matter how expertly the procedure is performed, but such injury must be recognized and repaired.

Arthritis

Inflammatory Arthropathies The hand is a mirror of many inflammatory arthropathies, not just gout or rheumatoid arthritis (Table 42-4).

Adult and Juvenile Rheumatoid Arthritis Primary consideration should be given to arthritis because of worldwide prevalence and

TABLE 42-4
INFLAMMATORY ARTHROPATHIES AFFECTING THE HANDS

Systemic autoimmune diseases
Rheumatoid arthritis (RA)
Polymyalgia rheumatica
Systemic lupus erythematosus (SLE)
Systemic sclerosis (scleroderma)
Vasculitis
Polymyositis and dermatomyositis
Adult-onset Still's disease
Remitting, seronegative, symmetrical synovitis with pitting edema (RS_3PE)

Spondyloarthropathies
Ankylosing spondylitis (AS)
Reiter's syndrome
Psoriatic arthritis
Inflammatory bowel disease-associated
Reactive arthritis

Rheumatic Fever

Crystal arthropathies
Gout
Calcium pyrophosphate dihydrate (CPPD) deposition disease
Apatite crystal deposition disease

Miscellaneous
Infectious arthritis
Sarcoidosis
Leukemia and lymphoma

the severe disability if untreated or, occasionally, when treated aggressively. Rheumatoid arthritis is a chronic systemic disorder of unknown cause whose major manifestation is inflammatory synovitis with secondary bone and tendon invasion and destruction. There may be late tendon dysfunction through nodularity and locking or scarring, joint subluxation, and pain. In most cases, synovitis deformities are symmetrical. Rheumatoid arthritis affects the elbows, wrists, and MP joints. Proximal IP joint involvement is less

common but may be significant in a given patient. On radiographs, the hands and feet show some of the earliest signs of periarticular osteopenia, demineralization. The earliest erosions occur along the radial-palmar aspects of the metacarpal heads, at the proximal phalanges, and in the prestyloid recess of the ulna. Operative intervention is best limited to patients who, despite medical management, have persistent dysfunction because of pain, stiffness, or instability or those who have progressively worsened function and increased deformities.

Scleroderma or Systemic Sclerosis This is a generalized vasculitis affecting the skin, gastrointestinal tract, kidneys, and hands, resulting in thickened, dense, and inelastic skin and connective tissues. Pathologic joint involvement occurs in up to 80 percent of the patients. Vasculitis and secondary small joint deformity may combine to produce unstable skin, chronic ulcerations that cannot heal, and secondary infections and painful loss of use.

Noninflammatory Arthropathies *Osteoarthritis* Osteoarthritis is the most common upper extremity arthropathy. Although classically defined as noninflammatory, osteoarthritis is a cartilage disease with at least intermittent low to moderate levels of inflammation. Its incidence increases with age. There is a significant hereditary component, especially for women. Patients may demonstrate progressive loss of articular cartilage, seen on radiographs first as diminished joint space, with secondary subchondral sclerosis and marginal bone spurs or lipping. Joint enlargement as a result of lipping usually occurs. The prevalence of DIP joint nodularity, Heberden's nodes, is up to 10 times greater in women, especially for those with a family history. Secondary posttraumatic mechanical osteoarthritis is more common in individuals whose occupations expose them to injuries or repetitive load, motion, and impact. The inflammatory variant often affects the hands, particularly the IP joints, and can be clinically and radiographically aggressive. The IP joints (particularly the terminal IP joints of the index finger and thumb), the trapeziometacarpal, thumb basilar joint, and the pantrapezial and radioscaphoid articulations are most frequently affected. Focal small joint deformities are best treated with arthroplasty, especially in MP joints and for the less active, older patient or patients with arthrodesis at selected limited intercarpal and IP joints. For successful arthrodesis, selection of operative method is not as important as meticulous, precise technique. Stabilized continuous bone contact over the entire surface to be fused, in the presence of good bone stock with durable soft tissue

coverage, produces a positive outcome. Thumb basilar arthroplasty yields functional, aesthetic results.

CONGENITAL DEFORMITIES

Failures of development, separation, and segmentation and intrauterine injury such as amniotic bands or congenital constriction ring syndrome affect mobility, facility, and self-image. Abnormalities of the shoulder and humerus, elbow, forearm, wrist, and hand produce important but different impairments, and all diminish hand facility to different degrees. Among the most common congenital afflictions in the hand are syndactyly and polydactyly. Consideration of repair should begin when the patient is 3–6 months of age.

Congenital trigger thumb may present to the primary pediatric caregiver as a snapping that may or may not be painful, but it often presents as a fixed flexion of the terminal thumb joint. Surgical release of the pulley is almost always curative.

TUMORS

Principles Localized masses are common in the hand and upper limb, but most are benign. Most have characteristics that assist in making the diagnosis. The relative rarity of malignant tumors of the musculoskeletal system distal to the elbow can lead to misdiagnosis and undermanagement. Every mass, particularly those which are atypical in appearance or location, should be diagnosed with staging and imaging procedures leading to careful incisional biopsy. Hand masses tend to present earlier, when smaller, because of their superficial location. Enlarging, symptomatic masses are evaluated with history, laboratory studies, imaging by plain films, ultrasonography, scintigraphy, CT scans, or MRI. Biopsy is the last step in diagnosis, and only very small lesions or lesions that are typical should be excised initially. Surgical staging and treatment for true malignant tumors is outlined in Tables 42-5 and 42-6.

Specific Tumors

Ganglion Joint and tendon ganglions are among the most common benign soft tissue tumor masses in the upper extremity, representing up to 50–75 percent of reported tumors. Although potentially located anywhere, the majority of ganglions are in specific sites: the middorsal wrist, the volar radial wrist, the flexor sheath

TABLE 42-5
SURGICAL STAGING FOR SARCOMA

Stage	Grade	Site
IA	Low (G_1)	Intracompartmental (T_1)
IB	Low (G_1)	Extracompartmental (T_2)
IIA	High (G_2)	Extracompartmental (T_1)
IIB	High (G_2)	Extracompartmental (T_2)
III	Regional or distant metastasis (M); any (G); any (T)	

at the metacarpal flexion crease and at the dorsum of the DIP joint, and nail base. Aspiration and steroid instillation may be of value, particularly when the expanding lesion has not been diagnosed or is associated with discomfort. Generally, surgical excision is preferred.

Giant Cell Tumor of the Tendon Sheath This is the most common soft tissue tumor of the hand. It is more frequent in women between the ages of 30 and 60 years. It is firm, nodular, nontender, and usually on the palmar surface. Treatment is complete excision.

Enchondroma This is the most common cartilaginous tumor of bone and occurs in the small tubular bones of the hand. Treatment is through curretage.

TABLE 42-6
MUSCULOSKELETAL ONCOLOGIC SURGICAL PROCEDURES

Margin	Local	Amputation
Intracapsular	Currettage/ debulking	Debulking amputation
Marginal	Marginal excision	Marginal amputation
Wide	Wide local excision	Through bone amputation
Radical	Radical local excision	Disarticulation of extremity

SURGICAL PRINCIPLES

Anesthesia Regional anesthesia for upper limb surgery offers effective pain control and the avoidance of mental confusion or other side effects from sedatives and general anesthesia. Regional anesthesia is not risk-free or always fully satisfactory; systemic and local reactions may be serious. Appropriate monitoring is mandatory. Forearm or axillary tourniquet is used for most hand surgery, but patients without axillary, intravenous regional, or inhalation anesthesia often are not able to tolerate continuous pneumatic tourniquet applications for more than 30 min. Distal peripheral blocks in the upper extremity always should be done without epinephrine added to the anesthetic solution. The injection technique is based on infiltration of anesthetic around the nerve and not directly into nerve substance. Although inadvertent needle entry into nerves is common, without epinephrine in the injection solution and with the use of a fine-gauge needle, it should present no problem. Should a patient complain of paresthesias, the needle is withdrawn and redirected. Intraneural injection with epinephrine-containing solutions may result in extended intraneural ischemia and secondary fibrosis as well as peripheral vascular compromise, particularly in the digital end-arterial circulation.

Digital Nerve Block The ulnar, radial, and median nerves can be blocked selectively at varying levels. The fingers receive their sensory supply from the common digital nerve branches of the median and ulnar nerves. Digital anesthesia can be achieved by injecting the anesthetic into the looser web tissues about the common digital nerves, which is preferable to a ring block in the base of the finger. The so-called ring block technique risks vascular compromise from volume compression when a solution is injected circumferentially about the base of the finger. Digital anesthetic solution should not include epinephrine because any resulting digital vessel spasm may compromise finger circulation. Anesthetic is injected retrograde from the web, advancing about 1 cm proximally into the palm, where 2 mL of anesthetic is injected after aspiration. The needle can be withdrawn and turned into the dorsal subcutaneous tissues of the web to ensure anesthesia of the dorsal branch of the digital nerve with another 1–2 mL of anesthesia. The technique is repeated on the opposite side of the finger or sequentially in several digits as needed. No more than 5–7 mL total of anesthetic solution should be injected for any one finger with this technique.

Tourniquet The use of tourniquets dates to Roman times, but the device acquired its name from surgical application in eighteenth-

century France (from *tourner*, meaning "to turn"). Hand surgery is performed using an axillary or forearm pneumatic tourniquet. Fingertip procedures can be done using a digital tourniquet made from a ¼-in rubber drain hose or with the finger cut from a sterile surgical glove; the tip of the finger sleeve is pierced, and the sleeve is placed over the patient's finger and rolled proximally, simultaneously exsanguinating and achieving a tourniquet effect. In the absence of proximal anesthetic blockade, the maximum tourniquet time a patient will tolerate is 30–60 min. Except in the presence of infections and suspected aggressive and malignant tumors, the arm should be exsanguinated before tourniquet inflation; limb elevation may be used for partial exsanguination.

Incisions and Exposures Skin incisions can be linear, curved, or angled. They may be oriented in a longitudinal or transverse direction relative to the limb. Ideally, elective wounds are placed to lie in and about the soft tissue skin creases. Hand incisions are not made perpendicular to joint creases so that iatrogenic contracture and unsightly scars are prevented. A sterile skin-marking pen is used to draw out the incisions. Cross-hatching the incision at regular intervals assists in realigning the skin edges for closure. Angles, pedicles, and turns in incisions should not be so narrow as to risk vascular compromise by creating a narrow skin peninsula.

Dressings and Splints The hand dressing is an intrinsic part of the surgical procedure. The dressing and splint are frequently as important to the outcome as the operation. The generic position for hand immobilization includes splinting the wrist at about 30 degrees of extension, the MP joints at 70 degrees of flexion, and the IP joints at 0–5 degrees of flexion.

Postoperative Hand Therapy Hand therapy is begun early and depends on the specific diagnosis, procedure, and patient. Operative goals include minimizing the time of immobilization, enhancing internal stabilization, preferably with minimal invasion, and allowing early mobilization of skin, joints, and tendons. Exercises appropriate for the condition and surgery performed are prescribed, and a therapist instructs the patient in these exercises. Exercises should be gentle, not painful, and should take the patient to the limit of potential motion at that time. The therapy program should emphasize soft tissue mobilization and a decrease in edema. When doing therapy for the hand, mobility in the forearm, elbow, and shoulder should be included, especially in older patients. The use of whirlpools is limited to patients with special needs, such as those with burns and those whose wounds require periodic debridement.

Heating the tissues is rarely, if ever, done acutely; ice is often more appropriate for posttraumatic conditions. Use of warm-water or paraffin baths is reserved for chronic conditions of systemic inflammation and periarticular stiffness. After injury, tissue swelling often increases proportionally to heat, worsening the prospects of rehabilitation in those swollen parts.

For a more detailed discussion, see Peimer CA: Surgery of the Hand, chap. 42 in *Principles of Surgery*, 7th ed.

CHAPTER

43

PLASTIC AND RECONSTRUCTIVE SURGERY

BASIC PRINCIPLES

Skin Incisions

Incisions should be planned parallel to the skin lines. Elliptical incisions have a long axis three to four times the length of the short axis to prevent standing cones at the ends of the incision.

Wound Closure

Wound preparation includes debridement of the skin edges and the use of noncrushing instruments. Excess tension produces a wide scar. Undermining and subcutaneous absorbable sutures help reduce wound tension. Early suture removal reduces scarring. Facial sutures should be removed at 3–5 days to prevent suture marks.

Skin Grafting

Split-thickness skin grafts include epidermis and a portion of the dermis. Full-thickness skin grafts include the epidermis and the entire dermis. "Take" of a skin graft requires an adequately vascularized recipient bed. Skin grafts will "take" on paratenon and periosteum but not bare tendon or bone.

Skin grafts may be stored for up to 21 days soaked in sterile saline at 4°C. Meshing of a skin graft allows an increased area to be covered, irregular contours to be covered more easily, and escape of fluid that would normally accumulate under the graft and could compromise graft survival. Grafts to the face and hands should not be meshed. Not meshing a graft will require fluid to be removed by syringe and needle as it accumulates under the graft.

Grafted areas must be kept immobilized, since motion may disrupt the graft. Grafts to the extremities require elevation of the extremity.

Grafts "take" by plasmatic imbibition (48 h), followed by capillary ingrowth (2–5 days). Wounds with greater than 10^5 bacteria per gram of tissue will not support a graft.

Composite grafts contain several tissue layers, such as ear skin and cartilage grafted to the nose. "Take" usually is accomplished if no portion of the graft is more then 1 cm from the vascular bed.

Flaps

Random Flaps Z-plasty, advancement, rotation, transposition, and interpolation flaps are based on the dermal-subdermal vascular plexus and are used for covering adjacent defects.

Axial Flaps Forehead flaps, deltopectoral flaps, and omental flaps are examples of axial flaps. They are based on specific vessels within the flap. They are better vascularized and more reliable than random flaps.

Fasciocutaneous Flaps These include the underlying fascia as well as the subcutaneous tissues. A good vascular supply allows greater length to the flap.

Muscle or Myocutaneous Flaps These include a muscle with its blood supply and may include its overlying skin.

Free Tissue Transfer

Many myocutaneous and some fasciocutaneous flaps have a consistent vascular pedicle, which may be divided and reanastomosed to recipient vessels at a distant site.

Tissue Expansion

Tissue expanders are inflatable devices placed under the skin and subcutaneous tissue. The tissue expander is filled with sterile saline over a number of weeks. Once enough tissue is expanded, the tissue expander is removed, and the defect is closed with transposition of the expanded skin.

Liposuction

Through one or more small incisions, a metal cannula is inserted into the area of excess fat deposition. The cannula cuts the fat, which is then aspirated via a vacuum device attached to the cannula.

RECONSTRUCTIVE SURGERY

Breast

Macromastia This is an abnormal enlargement of the breast. Reduction is achieved with resection of the redundant breast tissue and nipple preservation by pedicle or full-thickness nipple-areola graft. Risks include nipple necrosis, decreased sensation of the nipple, and an inability to lactate or breast-feed.

Ptosis Ptosis occurs when the nipple has descended below the inframammary crease. Repair involves nipple repositioning with reduction or placement of implants depending on the cause of the ptosis.

Hypomastia Hypomastia is insufficient volume in one or both breasts. Augmentation is performed with a prosthesis placed in either the submuscular or subglandular position.

Reconstruction after Mastectomy This can be accomplished with tissue expanders and subsequent prosthesis or myocutaneous flap (e.g., latissimus dorsi or rectus abdominis). Repair may be immediate or delayed until after radiation therapy or chemotherapy. There is no known increased risk of recurrence or failure to identify recurrence after reconstruction. Reconstruction may be needed on the nonmastectomy breast to obtain symmetry.

Gynecomastia This is an enlargement of the male breast secondary to increased ductal tissue. The most common form is idiopathic and occurs in adolescence. Treatment in adolescence is expectant, since the process usually resolves spontaneously within 2 years. For excessive enlargement or enlargement of greater than 2 years' duration, excision through a circumareolar incision is the treatment of choice.

Chest and Abdominal Wall

Defects may be secondary to trauma, tumor resection, radiation necrosis, infection, or congenital abnormalities. Repair usually is accomplished with one of several myocutaneous flaps (e.g., latissimus dorsi or deltopectoral). Pressure sores often appear small externally and usually are located over a bony prominence. Their presence may indicate a more extensive involvement of underlying subcutaneous tissue, fascia, and muscle.

Lymphedema

This may be secondary to regional lymph node dissection or congenital malformation. Nonoperative treatment consists of elevation and compression. Surgical management (for those failing medical therapy) includes excision of involved tissue either under skin flaps or with split-thickness or full-thickness skin grafts. Microvascular lymphaticovenous anastomosis has inconsistent results.

Lower Extremity Defects

Small tissue defects, those less than 1 cm, can be expected to heal on their own. Venous stasis ulcers need treatment of venous disease before reepithelialization or split-thickness skin grafting. Large defects, such as compound tibial fractures with soft tissue injury, are best managed with fasciocutaneous, muscle, or musculocutaneous flaps. Local muscle transposition usually is the preferred treatment except for wounds in the distal third of the tibia, where free muscle transfer is used most often.

AESTHETIC SURGERY

Facial Aging

Rhytidectomy (Face Lift) This involves an incision in the hairline at the lateral aspect of the forehead, continued in front of the ear, inferior and then posterior to the lobe. The skin is undermined from the frontalis muscle to the platysma in order to free it from the underlying structures. The skin is then advanced toward the ear and secured to the fascia anterior to the ear. The redundant tissue is excised. Rhytidectomies may be performed more than once.

Dermabrasion This improves fine wrinkling.

Chemical Face Peel This tightens skin and flattens fine wrinkles.

Eyelid Bagging of the eyelids or ptosis can be corrected by blepharoplasty (excision of redundant lid skin and fat) and/or brow lift.

Nose Rhinoplasty, performed under local or general anesthesia, can be done with incisions hidden inside the nose to minimize visible scarring.

Abdomen, Thighs, Buttocks, and Upper Arm

Redundant skin secondary to aging or significant weight loss may be surgically excised; however, resulting scars are often fairly prominent.

HEAD AND NECK SURGERY

Congenital Deformities

Cleft Lip These deformities may be unilateral or bilateral and incomplete (skin bridge connecting the cleft and noncleft sides) or complete (no skin bridge). Repair usually is timed according to the "rule of tens": at least 10 weeks of age, 10 lb, and a hemoglobin level of 10 g. Unilateral repairs are often done in one stage, whereas bilateral clefts may be done in one or two stages. Associated nasal deformities may be repaired at the same time or at a later date.

Cleft Palate This occurs when fusion of the two palatial processes is incomplete. Repair usually is performed by the age of 6–18 months. Late repair may affect speech development; early repair may affect facial growth.

Craniofacial Anomalies Craniosynostosis—Apert syndrome and Crouzon syndrome—involves premature closure of one or more cranial sutures and associated facial deformity. Repair involves separation and repositioning of the involved bone and the use of bone grafts, interosseous wiring, and miniplates for support.

Maxillomandibular Disproportion Abnormal size, shape, and position of the mandible or maxilla can result in malocclusion. Less severe disproportioning can be corrected with orthodontia. More severe disproportioning—micrognathia, retrognathia, and prognathia—requires surgical correction by splitting, advancing, or resecting a portion of the mandible depending on the specific deformity. Small chin not associated with any malpositioning can be treated with silicone prosthesis or sliding genioplasty to improve projection. Repair of severe maxillary deformities—hypoplasia or hyperplasia—involves surgical fracturing of the maxilla with repositioning.

Ear Deformities *Microtia* These are congenitally small, malformed ears; they are repaired in stages beginning at the age of 5–6 years. Rib cartilage is used for the structural framework.

Prominent Ears These are corrected by elevating and excising a portion of the skin from the posterior aspect of the ear and scoring the underlying cartilage, recreating the anthelix. Closure results in a more normal contour.

Hemangioma and Lymphangioma *Capillary Hemangiomas* These are abnormal collections of small vessels. They become prominent at 1–3 weeks of age, often increase in size over the first 6 months, and usually disappear spontaneously over the next several years. Surgical excision may be performed for compromised vision or respiration or for failure to resolve spontaneously.

Cystic Hygroma Most often this involves the head and neck. Swelling often accompanies upper respiratory infections and may compromise the airway. Should surgical excision be required, partial excision may be all that is possible in order to preserve local vital structures.

Acquired Deformities

Skull and Scalp Deformities Avulsions of the scalp may be closed by microvascular replantation, split-thickness skin grafting, or multiple scalp flaps transposed into the defect. Loss of scalp and calvarium requires early coverage to decrease the risk of infection. Transposition flaps can cover small defects. Free tissue transfer or split-thickness skin grafting may be necessary to cover larger areas of loss.

Eyelid and Eyebrow Reconstruction Loss of one-fourth or less of either lid can be closed directly. Larger defects in the upper lid are closed with composite tissue from the lower lid. Local flaps from a portion of the upper lid or the cheek can be used to reconstruct the lower lid. Loss of the hair-bearing eyebrow can be replaced using hair-bearing tissue from the scalp.

Eyelid Ptosis Moderate ptosis is managed by resection of a portion of the levator aponeurosis. Severe forms are treated by suspension of the eyelid by a portion of the frontalis muscle.

Nasal Reconstruction This is done after loss of part or all of the nose, as from skin cancer; the support framework is supplied by bone graft, and skin coverage is provided by nasolabial, forehead, or scalp flaps.

Lip Reconstruction Full-thickness lip defects usually are reconstructed with various local lip flaps.

Facial Palsy Lacerated or resected facial nerves should be repaired or grafted promptly. Long-standing palsy traditionally was treated with static suspension of the cheek and/or eyelid. Newer techniques include muscle transfers and nerve grafts.

Parotid Duct Laceration This may be repaired over a stent or can be tied off proximally.

Facial Fractures

Examination Examination proceeds from the upper to the lower face and includes an ophthalmologic examination, intraoral as well as extraoral examination of the mandible and maxilla, evaluation of dental occlusion, and assessment of midface stability by grasping the upper incisors and gently attempting to displace the structures anteriorly and posteriorly.

Radiographic Studies Fractures are diagnosed by visible fractures, blood in the sinuses, or subcutaneous air on computed tomographic (CT) scan and plain films.

Mandibular Fractures The mandible is often fractured in more than one place, and displacement is common secondary to the pull of the muscles of mastication. Treatment is early reduction and restoration of normal dental occlusion and firm immobilization. These may be managed by intermaxillary fixation or open reduction and internal fixation using plates and screws. Antibiotics should be given in open fractures.

Zygomatic Fractures These are often displaced. Significant deformities require mandatory open reduction and internal fixation and correction of orbital floor fracture.

Orbital Fractures "Blowout" fractures may trap the inferior rectus muscle and often are associated with double vision. Surgical repair involves returning of the herniated tissue to the orbit and reinforcing the orbital floor with alloplastic sheeting or bone graft.

Nasal Fractures Obvious deformities are corrected immediately. With nasal edema, reduction of the nasal fracture is delayed several days until the swelling subsides. Septal hematomas should be drained and the nose packed.

Maxillary Fractures These are classified as *Le Fort I* (transverse)—separation of the lower maxilla, hard palate, and pterygoid processes from the rest of the maxilla; *Le Fort II* (pyramidal)—

separation along the nasofrontal suture, floor of the orbit, zygomaticomaxillary sutures, and the pterygoid processes; and *Le Fort III* (craniofacial disjunction)—separation of the midface from the rest of the cranium by fracture through the zygomaticofrontal sutures, nasofrontal sutures, and the floor of the orbit. Treatment for Le Fort fractures is open reduction and internal fixation and intermaxillary fixation.

Reconstruction after Tumor Excision

Intraoral Defects Many can be managed with split-thickness skin grafting. Larger defects can be closed with forehead, deltopectoral, platysma, sternocleidomastoid, and pectoral flaps or free tissue transfers.

Bony Deficits These may be managed with bone grafts or composite bone and soft tissue grafts (e.g., fibula, scapula, and ilial crest).

Reconstruction of the Cervical Esophagus This can be achieved by numerous musculocutaneous flaps, gastric transposition, or intestinal interposition with microvascular anastomosis.

For a more detailed discussion, see Wood RJ, Jurkiewicz MJ: Plastic and Reconstructive Surgery, chap. 43 in *Principles of Surgery*, 7th ed.

CHAPTER

44

MINIMALLY INVASIVE SURGERY

PHYSIOLOGY

Laparoscopy The pneumoperitoneum required for laparoscopic surgery deserves special physiologic considerations. CO_2 is used because it is not combustible and it is rapidly absorbed. Absorption of this can create a respiratory acidosis once body buffers are exhausted. With normal respiratory function, increases in minute ventilation can easily compensate. Pressure effects from insufflation also are important. Reverse Trendelenburg position, combined with inferior vena cava compression by insufflation, can cause loss of venous return from the lower half of the body, most significant in the hypovolemic patient. Most common arrhythmia is bradycardia, vagally induced. This is managed with atropine and desulfation. Decreased lower extremity venous return also increases risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). Subcutaneous heparin and sequential compression stockings usually are preventive. Increased intraperitoneal pressures also (1) is transmitted to the thoracic cavity and (2) decreases renal blood flow. Other consequences include gas embolus, which should be suspected when sudden hypotension develops during insufflation. Treat with head-down, left lateral decubitus position and central venous pressure (CVP) catheter to aspirate air from the right ventricle.

Alternatives to insufflation include bulky, difficult-to-use abdominal wall lift devices. The stress hormone response to laparoscopic surgery is very similar to that of open surgery except that there is more rapid normalization after operation.

Thoracoscopy This is different from laparoscopy because it is not necessary to use insufflation because of the bony thorax. However, double-lumen endotracheal tubes are needed to collapse the lung on the operative side.

Other Procedures Extracavitary insufflation can cause subcutaneous emphysema with carbon dioxide and metabolic acidosis.

Anesthetic Management Most important are carbon dioxide ventilation and rapid venous return at the end of the procedure when the pneumoperitoneum is released and the patient is laid flat. Little intravenous fluid should be used during the operation.

GENERAL PRINCIPLES OF ACCESS

Thoracoscopic access is similar to a chest tube. Trocars are inserted over the top of a rib. The lung is collapsed with a double-lumen endotracheal tube. Insufflation is unnecessary.

Laparoscopic access requires maintenance of a pneumoperitoneum. This may be begun by direct puncture (Veress needle) or direct peritoneal access technique (Hasson, cutdown). Both require a pressure-limited carbon dioxide insufflator to maintain a pressure of 15 mmHg. The latter access method is used in patients who have had previous abdominal surgery and adhesions. Additional trocars are then placed under direct vision using the first trocar. Lower abdominal trocar sites 10 mm and larger must be closed to prevent herniation.

For retroperitoneal procedures, balloon dissection of this anatomic space is accomplished through a Hasson trocar. Pressures should not go above 10 mmHg for the subsequent insufflation. Subcutaneous access (i.e., saphenous vein harvesting) uses 5-mm scopes with lighted holding retractors. Gas insufflation can cause subcutaneous emphysema.

IMAGING SYSTEMS

Flexible endoscopy uses CCD camera chips on the end of flexible endoscopes. Laparoscopy and thoracoscopy use rigid telescopes with a camera head attached to the external end. The scope lens may be flat (0 degrees) for a head on view or angled (30 degrees) for a wider field and a top-down or side-in view. Cameras may be single-chip or three-chip. Three-chip cameras have separate red, green, and blue CCDs (RGB), with the greatest resolution and color fidelity. Laparoscopic imaging is limited to two dimensions. Three-dimensional systems that add depth of field are being developed but are not in practical use yet.

ENERGY SOURCES

Most common is radiofrequency (RF) electrosurgical for coagulation and desiccation, either by monopolar or bipolar delivery. Argon

beam coagulation also is available. This uses an ionized argon gas jet. It is good for diffusely bleeding surfaces. The abdomen must be vented during laparoscopic argon beam use! Lasers also are used, less so for laparoscopic procedures than for endoscopic procedures. Ultrasonic energy is being used for coagulation and division of small blood vessels (harmonic scalpel or laparoscopic coagulation shears) with a minimal amount of lateral damage. It is good for short gastric division during fundoplications.

BALLOONS AND STENTS

Endoluminal balloons are used during endoscopic procedures to dilate strictures. Once dilatation is accomplished, stenting is used to maintain patency. Stents are plastic or expandable metal. Metal stents have tissue ingrowth that may cause future obstruction.

INSTRUMENTATION

Most instruments replicate standard instruments but are 20–45 cm (standard 30 cm) long and 3–10 mm (standard 5 mm) wide. Cautery often is incorporated into instruments. Unique laparoscopic instruments have been designed, such as the electrocautery hook.

ROOM SETUP

For upper abdominal procedures, two video units, one at each upper corner of the field, are used. For pelvic procedures, the video monitor is placed at the patient's foot with the surgeon facing that end. The ideal trocar placement is procedure-dependent but should form an equilateral triangle between the surgeon's hands and the laparoscope, with the hand trocars at least 10 cm apart.

MINIMALLY INVASIVE SURGICAL PROCEDURES

Laparoscopic Cholecystectomy "Lap chole" revolutionized general surgical laparoscopy. It greatly reduced length of stay and recovery time from this common operation. The most important operative point is lateral retraction of the infundibulum and cephalic retraction of the fundus to "open up" the triangle of Calot to provide optimal visualization and minimize bile duct injury.

Laparoscopic Appendectomy This is useful in patients with right-sided pelvic pain of uncertain etiology; it is also useful in obese patients. The appendix is removed based on standard surgical principals (as in open technique). This requires three ports: (1) camera, (2) suprapubic for retraction, and (3) left lower quadrant for dissection and endo-GIA division of the appendiceal base and mesentery.

Inguinal Hernia Repair This is the most controversial minimally invasive procedure. The transperitoneal mesh onlay approach has all but been abandoned. Approaches today are: (1) TAPP, or transabdominal preperitoneal, and (2) TEP, or totally extraperitoneal. The TEP repair is preferred, especially for recurrent hernias. Bilateral hernias also are a good indication. Overall, the recurrence rate is approximately 5 percent. The procedure uses three trocars. A balloon is used to open the space anterior to the posterior rectus sheath. This opens Hesselbach's triangle posteriorly. The cord is then dissected free from the sac. The sac is ligated, and a 10×15 cm mesh is affixed to Cooper's ligament, the public tubercle, the posterior rectus muscle, and laterally to the transversalis fascia.

Fundoplication Antireflux surgery has been demonstrated to be superior to medical therapy for the treatment of severe gastroesophageal reflux disease (GERD), and the laparoscopic approach provides the same results as the open technique. Workup should include endoscopy and biopsy of esophagitis, 24-h pH probe, barium swallow, and esophageal motility studies. Gastric emptying should be studied in diabetes. For those with diminished esophageal motility, a partial wrap (Toupet) should be performed instead of a full wrap (Nissen). For trocar placement, see Fig. 44-1.

Laparoscopic Assisted Colectomy Indications are benign or premalignant diseases of the colon. The use of laparoscopy for malignant disease of the colon is being evaluated under a prospective, randomized protocol to assess the true incidence of trocar site malignant implantation, which seems to be twice that of the open technique.

Splenectomy Most common indication is idiopathic thrombocytopenic purpura (ITP). This should be limited to spleens less than 500 g. The patient is placed in the left lateral decubitus position with the spleen "hanging." Major vessels are controlled with individual ligation or a linear stapler. Short gastrics are divided in a similar fashion or with the harmonic scalpel. Finally, the spleen is

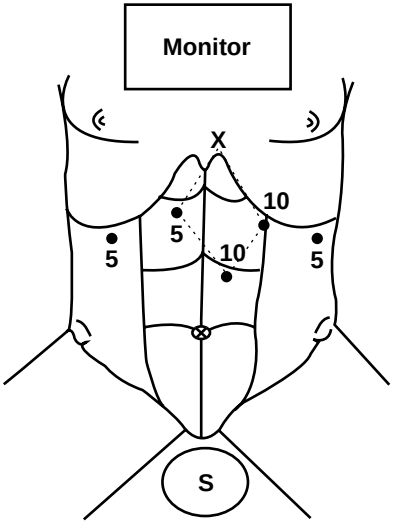


FIGURE 44-1 Laparoscopic Nissen fundoplication, with the "baseball diamond" positions of trocar, target, monitor, and surgeon (X = location of gastroesophageal junction; S = location of surgeon). (*From Hunter JG: Advanced laprascopic surgery. Am J. Surg 173:14–18, 1977, with permission.*)

placed in a retrieval bag, morcellated, and removed through the neck of the bag, avoiding any spillage.

For a more detailed discussion, see Hunter JG: Minimally Invasive Surgery, chap. 44 in *Principles of Surgery,* 7th ed.

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