Chapter 39

Anesthetic Implications of Concurrent Diseases

LEE A. FLEISHER • MICHAEL MYTHEN

Acknowledgment: The editors and the publisher would like to thank Dr. Michael F. Roizen, who was a contributing author to this topic in the prior edition of this work. It has served as the foundation for the current chapter.

Key Points

- The history and physical examination most accurately predict the risks of anesthesia and the likelihood of required changes in monitoring or therapy.
- For diabetic patients, end-organ dysfunction and the degree of glucose control in the perioperative and periprocedural periods are the critical issues with regard to risk.
- The keys to managing blood glucose levels in diabetic patients perioperatively are to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.
- Obesity is associated with multiple comorbid conditions, including diabetes, hyperlipidemia, and cholelithiasis, but the primary concern is derangements of the cardiopulmonary system.
- Obstructive sleep apnea is important to recognize because of the increased sensitivity to and the consequence of the depressive effects of hypnotics and opioids on airway muscle tone and respiration, as well as the difficulty with laryngoscopy and mask ventilation.
- Although no controlled, randomized prospective clinical studies have been performed to evaluate the use of adrenergic receptor blocking drugs in patients undergoing resection of pheochromocytoma, the preoperative use of such drugs is generally recommended.
- For patients with hypertension, the routine administration of all drugs preoperatively is recommended, except angiotensin-converting enzyme inhibitors and angiotensin II antagonists.
- Evaluation of a patient with cardiovascular disease depends on clinical risk factors, the extent of surgery, and exercise tolerance.
- In patients with pulmonary disease, the following should be assessed: dyspnea, coughing and the production of sputum, recent respiratory infection, hemoptysis, wheezing, previous pulmonary complications, smoking history, and physical findings.
- In patients with pulmonary disease, several strategies have been suggested, including cessation of smoking 8 weeks or more preoperatively.
- Risk factors for perioperative renal dysfunction include advanced age, congestive heart failure, previous myocardial revascularization, diabetes, and increased baseline blood creatinine concentration.
- One of the primary objectives for a patient with renal disease is ensuring that the renal dysfunction is not augmented and thereby increasing the chance for renal failure, coma, and death.
- Mild perioperative anemia may be clinically significant only in patients with ischemic heart disease.
- Careful management of long-term drug administration should include questions about the effects and side effects of alternative as well as prescription drugs.
This chapter reviews many conditions requiring special preoperative and preprocedure evaluation, intraoperative or intraprocedure management, or postprocedure care. Patients undergoing surgical procedures move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon, radiologist, or obstetrician-gynecologist contribute to ensure the best outcome possible. No aspect of medical care requires greater cooperation among physicians than does performance of a surgical operation or a complex procedure involving multiple specialists and the perioperative care of a patient. Moreover, nowhere else can counseling make so huge a difference in so many lives. The preoperative evaluation also represents a time when education on tobacco cessation, physical inactivity, and poor food choices can be discussed (see also Chapter 38). The importance of integrating physicians’ expertise is even greater within the context of the increasing life span of our population. As the number of older adults and very old adults (those >85 years old) grows, so does the need of surgical patients for preoperative consultation to help plan for comorbidity and multiple drug regimens, knowledge of which is crucial to successful patient management (see also Chapter 80). At a time when medical information is encyclopedic, it is difficult, if not impossible, for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative or periprocedure patient management. This chapter reviews such issues with primary emphasis on the anesthesiologist providing preoperative evaluation and care, rather than transferring these responsibilities to other providers.

As with “healthy” patients (see also Chapter 38), the history and physical examination most accurately predict not only the associated risks but also the likelihood that a monitoring technique or change in therapy will be beneficial or necessary for survival. This chapter emphasizes instances in which specific information should be sought in history taking, physical examination, or laboratory evaluation. Although controlled studies designed to confirm that optimizing a patient’s preoperative or preprocedure physical condition would result in a less frequent rate of morbidity have not been performed for most diseases, it is logical to assume that such is the case. That such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious environment.

Minimally invasive procedures such as cataract extraction, magnetic resonance imaging (MRI), or diagnostic arthroscopy, performed in conjunction with the best current anesthetic practices, may pose no greater risk than daily living and thus may not be considered an opportunity for special evaluation. Nevertheless, the preoperative evaluation may identify conditions that could change perioperative management and that may improve both throughput of surgery and the speed of recovery. Examples include the following: ensuring the administration of long-term medications such as a β-adrenergic blocking drug, aspirin for patients with coronary stents, or a statin (or any combination); administering a histamine type 2 (H₂) antagonist 1 to 2 hours before entry into the operating room; ensuring the availability of equipment to measure blood glucose levels; obtaining a history of the patient’s diabetic course and treatment from the primary care physician, as well as from the patient; and performing a fiberoptic laryngoscopic examination or procuring additional skilled attention.

The following conditions are discussed in this chapter:

1. Diseases involving the endocrine system and disorders of nutrition (discussed first because of its increasing importance to care)
2. Diseases involving the cardiovascular system
3. Disorders of the respiratory and immune system
4. Diseases of the central nervous system (CNS), neuromuscular diseases, and mental disorders
5. Diseases involving the kidney, infectious diseases, and disorders of electrolytes
6. Diseases involving the gastrointestinal (GI) tract or the liver
7. Diseases involving hematopoiesis and various forms of cancer
8. Diseases of aging or those that occur more commonly in older adults, as well as chronic and acute medical conditions requiring drug therapy (see also Chapter 80)

**ROLE OF THE PRIMARY CARE PHYSICIAN OR CONSULTANT**

The roles of the primary care physician or consultant are not to select and suggest anesthetic or surgical methods but rather to optimize the patient’s preoperative and preprocedure status regarding conditions that increase the morbidity and mortality associated with surgery and to alert the anesthesia care team about these conditions.

Quotations and a box in a Medical Knowledge Self-Assessment Program published by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant:

**Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation [Box 39-1]. The consulting internists’ role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery. Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.**

Optimizing a patient’s preoperative and preprocedure condition and, in settings with a preoperative clinic, counseling a patient about needed future lifestyle changes such as walking, food choices, and tobacco cessation are cooperative ventures between the anesthesiologist and the internist, pediatrician, surgeon, or family physician (see also Chapter 38). If available, the primary...
care physician should affirm that the patient is in the very best physical state attainable (for that patient), or the anesthesiologist and primary care physician should do what is necessary to optimize that condition. Statements that describe the preoperative and preprocedure physical condition of the patient (e.g., “This patient is in optimum shape” and “I believe the mitral stenosis is more severe than the slight degree of mitral insufficiency”) are much more useful to the anesthesiologist than statements that suggest overall clearance (“cleared for surgery”) or perioperative procedures (“prevent hypoxia and hypotension”).

Primary care physicians can prepare and treat a patient to provide optimal conditions for daily life. However, they often do not have the depth of understanding of the anesthesiologist regarding the physiologic changes brought on by surgery and the manipulations in function that must be made to facilitate surgery and procedures and to optimize perioperative and periprocedure outcomes. One example is the induction of some degree of prerenal azotemia in a patient with congestive heart failure (CHF) by the primary care physician. The intravascular volume depletion associated with prerenal azotemia may make a patient with a cardiac condition more comfortable in daily life but would predispose that patient to hypovolemic problems during and after surgery and complex procedures. The preoperative clinic should collaborate with the primary care physician to start the process of preparing the patient for the needs of surgery or complex procedures (see Chapter 38). Although such education is more readily available and of better quality than in previous decades and although cardiologic organizations have provided considerable data on the importance of this aspect of care, the primary care physician’s training, knowledge, and ability must be verified when he or she is part of the preoperative evaluation process. Without understanding the physiologic changes that occur perioperatively, appropriate therapy is difficult to prescribe. It is therefore part of the anesthesiologist’s job to instruct the patient’s consultants about the type of information needed from the preoperative and preprocedure consultation.

### Guidelines for Consultation Practice

- Complete a prompt, thorough, generalist-oriented evaluation.
- Respond specifically to the question or questions posed.
- Indicate clearly the perioperative importance of any observations and recommendations outside the area of initial concern.
- Provide focused, detailed, and precise diagnostic and therapeutic guidance.
- Emphasize verbal communication with the anesthesiologist and surgeon, particularly to resolve complex issues.
- Avoid chart notations that unnecessarily create or exacerbate regulatory or medicolegal risk.
- Use frequent follow-up visits in difficult cases to monitor clinical status and compliance with recommendations.


### DISEASES INVOLVING THE ENDOCRINE SYSTEM AND DISORDERS OF NUTRITION

#### PANCREATIC DISORDERS

**Diabetes Mellitus**

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute lack of insulin. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, by diffuse microvascular lesions, and by long-term end-organ complications. The diagnosis of diabetes is made with a fasting blood glucose level greater than 110 mg/dL (6.1 mmol/L), and impaired glucose tolerance is diagnosed if the fasting glucose level is less than 110 mg/dL (6.1 mmol/L) but greater than 100 mg/dL (5.5 mmol/L). Diabetes can be divided into two very different diseases that share these end-organ abnormalities. Type 1 diabetes is associated with autoimmune diseases and has a concordance rate of 40% to 50% (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the other twin would have diabetes is 40% to 50%). In type 1 diabetes, the patient is insulin deficient and susceptible to ketoacidosis if insulin is withheld. In type 2 diabetes, the concordance rate is 100% (i.e., genetic material is both necessary and sufficient for the development of type 2 diabetes). How markedly the aging and end-organ effects of these genes are expressed is based on lifestyle choices of food and physical activity. These patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance. Patients with non–insulin-dependent (type 2) diabetes now account for most (>90%) of the diabetic patients in Europe and North America. These individuals tend to be overweight, relatively resistant to ketoacidosis, and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. Plasma insulin levels are normal or increased in type 2 diabetes but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease. Gestational diabetes develops in more than 3% of all pregnancies and increases the risk of type 2 diabetes by 17% to 63% within 15 years.

Type 1 and type 2 diabetes differ in other ways as well. Contrary to long-standing belief, a patient’s age does not allow a firm distinction between type 1 and type 2 diabetes; type 1 diabetes can develop in an older person, and clearly, type 2 diabetes can develop in overweight children. Type 1 diabetes is associated with a 15% prevalence of other autoimmune diseases, including Graves disease, Hashimoto thyroiditis, Addison disease, and myasthenia gravis.

Over the next decade, the prevalence of diabetes is expected to increase by 50%. This growth is primarily the result of the increase in type 2 diabetes caused by excessive weight gain in adults (see also Chapter 71) and now also in the pediatric population (see also Chapter 93). Large clinical studies show that long-term, strict control of blood glucose levels and arterial blood pressure, along with regular physical activity, results in a major delay in microvascular complications and perhaps indefinite postponement of type 2 diabetes in patients.
The common orally administered drugs can be classified into six major groups: acarbose, meglitinide (e.g., repaglinide or nateglinide), metformin, sulfonylureas (e.g., glibenclamide, glipizide, glimepiride, gliucone), thiazolidinediones (e.g., pioglitazone), and dipeptidyl peptidase-4 (DPP-IV) inhibitors (e.g., sitagliptin, saxagliptin, vildagliptin). Physicians advocating tight control of blood glucose levels usually give insulin to “maturity-onset” insulin-dependent diabetic patients twice a day or even more frequently.

Patients with insulin-dependent diabetes tend to be young, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or not measurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the postmidnight hours, which may result in early morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose use reflect nocturnal surges in secretion of growth hormone (GH). Physiologically normal patients and diabetic patients taking insulin have steady-state levels of insulin in their blood. (Unfortunately, traditional values for insulin pharmacokinetics are derived from studies designed as though the diabetic patient received only one shot of insulin in a lifetime.) Absorption of insulin is highly variable and depends on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, attainment of a steady state depends on periodic administration of the preparations received by the patient. Thus, it seems logical to continue the combinations of preparations perioperatively that the patient had been receiving on a long-term basis after examining the patient’s blood glucose monitoring logbook for the degree of control.

The major risk factors for diabetic patients undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitation in neck extension,7 poor wound healing), inadequate granulocyte production, and neuropathies.8-15 Thus, a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal preoperative and preprocedure conditions. Poor preoperative glucose control, as measured by the hemoglobin A1c (glycosylated hemoglobin) level, is an independent predictor of worse perioperative outcome.16-18

Glucotoxicity

Long-term tight control of blood glucose has been motivated by a theoretic concern about three potential glucotoxicities, in addition to the results from major randomized outcome studies involving diabetic patients.5-13

1. Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions that lead to the formation of abnormal proteins. These proteins may weaken endothelial junctions and decrease elasticity, which is responsible for the stiff joint syndrome (and difficult intubation secondary to fixation of the atlanto-occipital joint), as well as decrease wound healing tensile strength.

2. Furthermore, elevations in glucose may increase macroglobulin production by the liver (which would increase blood viscosity) and promote intracellular swelling by favoring the production of nondiffusible, large molecules (e.g., sorbitol). Some drug therapies (e.g., aldose reductase inhibitors) endeavor to decrease intracellular swelling by inhibiting the formation of such large molecules.

3. Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic blood pressure. A glycosylated hemoglobin level of 8.1% is the threshold at which the risk for microalbuminuria increases logarithmically. A person with type 1 diabetes who has microalbuminuria of greater than 29 mg/day has an 80% chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5% to 9.0% (12.5 mmol/L or 225 mg/dL), and that for cardiovascular disease is an average blood glucose value of 5.4 mmol/L (96 mg/dL). Thus, different degrees of hyperglycemia may be required before different vascular beds are damaged, or certain degrees of glycemia are associated with other risk factors for vascular disease. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. For instance, diabetic patients in whom microalbuminuria develops are more resistant to insulin, insulin resistance is associated with microalbuminuria in first-degree relatives of patients with type 2 diabetes, and persons who are normoglycemic but subsequently have clinical diabetes are at risk for atherogenesis before the onset of disease.

Diabetes itself may not be as important to perioperative outcome as are its end-organ effects. Epidemiologic studies segregated the effects of diabetes itself on the organ system from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Even in patients requiring intensive care unit (ICU) management, long-standing diabetes does not appear to be as important an issue as the end-organ dysfunction that exists and the degree of glucose control in the perioperative or periprocedure and ICU periods.5-13

The World Health Organization’s surgical safety checklist bundle suggests control with a target perioperative blood glucose concentration of 6 to 10 mmol/L (acceptable range, 4 to 12 mmol/L).19 Poor perioperative glycemic control has a significant impact on the risk of postoperative infection across a variety of surgical specialties.20 Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the greater the risk of hypoglycemia. Therefore, debate regarding optimal control during the perioperative period has been extensive. Tight control retards all these glucotoxicities and may have other benefits in retarding the severity of diabetes itself.5-13,21 Management of intraoperative glucose may be influenced by specific situations, such as the following: the type of operation, pregnancy, expected global CNS insult, the bias of the patient’s primary care physician, or the type of diabetes.

Much of the research on perioperative control is derived from studies in the ICU, as opposed to the operating...
PART IV: Anesthesia Management

The first major trial demonstrating the benefit of tight glucose control was in medical ICU patients in Leuven, Belgium. The most recent trial was from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) group. In this randomized controlled trial, the investigators examined the associations between moderate and severe hypoglycemia (blood glucose, 41 to 70 mg/dL [2.3 to 3.9 mmol/L] and ≤40 mg/dL [2.2 mmol/L, respectively) and death among 6026 critically ill patients in ICUs. Intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death. The association exhibits a dose-response relationship and is strongest for death from distributive shock. The optimal perioperative management has been reviewed elsewhere. Guidelines have been developed on the use of insulin infusions in the critical care unit to achieve these goals (Table 39-1).

### TABLE 39-1 RECOMMENDED GLUCOSE TARGET RANGES FOR INTENSIVE CARE PATIENTS AND RELATED SUBGROUPS

<table>
<thead>
<tr>
<th>Society, Guideline</th>
<th>Patient Group</th>
<th>Trigger Blood Glucose Value to Start Insulin Infusion (mM [mg/dL])</th>
<th>Target range, (mM [mg/dL])</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>General recommendation</td>
<td>8.3 (150)</td>
<td>5.6-8.3 (100-150)</td>
<td>Decreased risk for deep sternal wound infection and death</td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Cardiac surgical patients</td>
<td>&lt;8.3 (150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Critically ill trauma patients</td>
<td>8.3 (150)</td>
<td>&lt;10 (180)</td>
<td></td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Patients with traumatic brain injury</td>
<td>8.3 (150)</td>
<td>&lt;10 (180)</td>
<td></td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Neurologic ICU patients Ischemic stroke</td>
<td>8.3 (150)</td>
<td>&lt;10 (180)</td>
<td></td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Intraparenchymal hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Society of Critical Care Medicine’s clinical practice guideline</td>
<td>Aneurysmal subarachnoid hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Diabetes Association guidelines</td>
<td>General recommendation</td>
<td>10 (180)</td>
<td>7.8-10 (140-180)</td>
<td>Adjust to lower target range in documented low rate of severe hypoglycemia</td>
</tr>
<tr>
<td>American Diabetes Association guidelines</td>
<td>Adaptation</td>
<td>6.1-7.8 (110-140)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>General recommendation</td>
<td>7.8-10 (140-180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>Surgical patients</td>
<td></td>
<td>Lower range</td>
<td>Only in units showing low rates of hypoglycemia</td>
</tr>
<tr>
<td>Surviving Sepsis Campaign</td>
<td>General recommendation</td>
<td>10 (180)</td>
<td>&lt;10 (180)</td>
<td>Based on the NICE-SUGAR study</td>
</tr>
<tr>
<td>Surviving Sepsis Campaign</td>
<td>General recommendation</td>
<td>7.8-11.1 (140-200)</td>
<td></td>
<td>If insulin infusion is applied; however, guideline does not recommend intensive insulin therapy</td>
</tr>
<tr>
<td>Clinical Practical Guideline from the American College of Physicians</td>
<td>General recommendation</td>
<td>&lt;8.3 (150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish Society of Intensive Care Medicine and Coronary Units</td>
<td>General recommendation</td>
<td>10 (180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Society of Anaesthesia and Intensive Care</td>
<td>General recommendation</td>
<td>7.8-10 (140-180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Society of Anaesthesia and Intensive Care</td>
<td>Surgical patients</td>
<td>&lt;6.1 (110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Society of Anaesthesia and Intensive Care</td>
<td>Cardiac patients</td>
<td>&lt;6.1 (110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Society of Anaesthesia and Intensive Care</td>
<td>Cardiac surgical patients</td>
<td>&lt;10 (180) except &lt;8.3 (150) for those with devices in place</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes and Accelerated Physiologic Aging

Adverse perioperative outcomes have repeatedly and substantially correlated with the age of the patient\(^2,3,27-30\) and diabetes does cause physiologic aging. When one translates the results of the Diabetes Control and Complications Trials into age-induced physiologic changes, a patient with type 1 diabetes who has poor control of blood glucose ages approximately 1.75 years physiologically for every chronologic year of the disease and 1.25 years if blood glucose has been controlled tightly.\(^27-29\) A patient with type 2 diabetes ages approximately 1.5 years for every chronologic year of the disease and approximately 1.06 years with tight control of blood glucose and blood pressure.\(^6,27-29,31\) Thus, when providing care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically; the physiologic age of a diabetic patient is considerably older than that person’s calendar age just by virtue of having the disease.\(^1\)

The pervasiveness of obesity and the lack of physical exercise seem to be major contributors to the increased prevalence of type 2 diabetes. As with type 1 diabetes, tight control of blood glucose, increased physical activity, and reduction in weight appear to reduce the accelerated aging associated with type 2 diabetes and even to delay the appearance of the disease and aging from it substantially.\(^27-29,31\) Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

The key to managing blood glucose levels perioperatively in diabetic patients is to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.

Other Conditions Associated With Diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathy, autonomic dysfunction, and infection. Diabetic patients are often treated with angiotensin-converting enzyme (ACE) inhibitors, even in the absence of gross hypertension, in an effort to prevent the effects of disordered autoregulation, including renal failure.\(^5,6,32\)

Preoperatively, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as assessment of the diabetic patient’s current overall metabolic status. The preoperative evaluation of diabetic patients is also discussed in Chapter 38.

The presence of autonomic neuropathy likely makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy may be routinely sought before the surgical procedure. Patients with diabetic autonomic neuropathy are at increased risk for gastroparesis (and consequent aspiration of gastric contents) and for perioperative cardiorespiratory arrest. Diabetic patients who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very frequent incidence of painless myocardial ischemia.\(^15,33\) as well as gastroparesis. Administration of metoclopramide, 10 mg preoperatively to facilitate gastric emptying of solids, may be helpful (Fig. 39-1). Interference with respiration or sinus automaticity by pneumonia or by anesthetic agents, pain medications, or sedative drugs is likely the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between the maximum and minimum heart rate on deep inspiration is normally 15 beats/minute, but it is 5 beats/minute or less in all patients who subsequently sustain cardiorespiratory arrest.\(^15,33\)

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in arterial blood pressure of more than 30 mm Hg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetic patients with significant autonomic neuropathy may have impaired respiratory responses to hypoxia and are particularly susceptible to the action of drugs that have depressant effects. These patients may warrant very close, continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although such logical treatment has not been tested in a rigorous, controlled trial.\(^15\) In the absence of autonomic neuropathy, outpatient surgery is preferred for a diabetic patient if possible (see Table 39-1).

Emergency Surgery

Many diabetic patients requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis (see also Chapter 81). Frequently, little time is available to stabilize the patient, but even a few hours may be sufficient for correction of any fluid and electrolyte disturbances that are potentially life-threatening. It is futile to delay surgery in an attempt...
to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if intravascular volume depletion and hypokalemia are at least partially treated.

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily if one divides the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight [body mass index ≥35]). The actual amount of insulin administered is less important than is regular monitoring of glucose, potassium, and arterial pH. Because the number of insulin binding sites is limited, the maximum rate of decline in glucose is fairly constant and averages 75 to 100 mg/dL/hour, regardless of the dose of insulin. During the first 1 to 2 hours of fluid resuscitation, the glucose level may decrease more precipitously. When serum glucose reaches 250 mg/dL, the intravenous fluid should include 5% dextrose.

The volume of intravenously administered fluid required varies with the overall deficit; it ranges from 3 to 5 L and may be as large as 10 L. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Factitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by approximately 1.6 mEq/L for every 100 mg/dL increase in plasma glucose greater than normal. Initially, normal saline solution is infused at a rate of 250 to 1000 mL/hour, depending on the degree of intravascular volume depletion and cardiac status. Some measure of left ventricular volume should be monitored in diabetic patients who have a history of myocardial dysfunction. Approximately one third of the estimated fluid deficit is corrected during the first 6 to 8 hours and the remaining two thirds over the next 24 hours.

The degree of acidosis is determined by analysis of arterial blood gases and detection of an increased anion gap (see also Chapter 60). Acidosis with an increased anion gap (≥16 mEq/L) in an acutely ill diabetic patient may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three disorders. In ketoacidosis, plasma levels of acetoacetate, β-hydroxybutyrate, and acetone are increased. Plasma and urinary ketones are measured semiquantitatively with Ketostix and Accetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial. Myocardial function and respiration are known to be depressed at a blood pH lower than 7.0 to 7.10, yet rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. These alterations may be caused by (1) paradoxical development of cerebrospinal fluid and CNS acidosis from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin, β-hydroxybutyrate levels decrease rapidly, whereas acetoacetate levels may remain stable or even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose, β-hydroxybutyrate, and acetoacetate levels have returned to normal; the result is continuing ketonuria. Persistent ketosis with a serum bicarbonate level less than 20 mEq/L in the presence of a normal glucose concentration is an indication of the continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total-body potassium. Deficits range from 3 to 10 mEq/kg body weight. Serum potassium levels decline rapidly and reach a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular space with insulin as the acidosis is corrected. Potassium is also excreted in urine because of the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis as a result of tissue catabolism, impaired cellular uptake, and increased urinary losses may give rise to significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight. Replacement is needed if the plasma concentration decreases to less than 1.0 mg/dL.

Anticipated Newer Treatments of Diabetes

At least three major changes in the care of diabetic patients have made it to the clinical trial stage:

- Implanted (like a pacemaker) glucose analyzer with electronic transmission to a surface (watch) monitor
- New islet transplantation medication that makes islet cell transplants much more successful and rejection medication less hazardous
- Medications such as INGAP (islet neogenesis–associated protein) peptide, which may cause regrowth of normally functioning islet cells (without the need for transplantation)

Some of these treatments may radically change the therapies used in the perioperative period. If regrowth of islet cells becomes common, type 1 diabetes could all but disappear; if implanted minute-to-minute glucose reading is possible, tight control may be much easier and more expected.

Insulinoma and Other Causes of Hypoglycemia

Hypoglycemia in persons not treated for diabetes is rare. Hypoglycemia in nondiabetic patients can be caused by such diverse entities as pancreatic islet cell adenoma or carcinoma, large hepatoma, large sarcoma, alcohol ingestion, use of β-adrenergic receptor blocking drugs, haloperidol therapy, hypopituitarism, adrenal insufficiency, altered physiology after gastric or gastric bypass surgery, hereditary fructose intolerance, ingestion of antidiabetic drugs, galactosemia, or autoimmune hypoglycemia. The last four entities cause postprandial reactive hypoglycemia. Because restriction of oral intake prevents severe hypoglycemia, the practice of keeping the patient NPO (nothing by mouth) and infusing small amounts of a solution containing 5% dextrose greatly lessens the
posibility of perioperative postprandial reactive hypoglycemia. The other causes of hypoglycemia can cause serious problems during the perioperative period.35

Symptoms of hypoglycemia fall into one of two groups: adrenergic excess (tachycardia, palpitations, tremulousness, or diaphoresis) or neuroglycopenia (headache, confusion, mental sluggishness, seizures, or coma). All these symptoms may be masked by anesthesia, so blood glucose levels should be determined frequently in such patients to ensure that hypoglycemia is not present. Because manipulation of an insulinoma can result in massive insulin release, this tumor should probably be operated on only at centers equipped with a mechanical pancreas. Perioperative use of the somatostatin analogue octreotide, which suppresses insulin release from such tumors, makes the perioperative period a logarithm safer in anecdotal experience.

DISORDERS OF NUTRITION, INCLUDING OBESITY

Hyperlipoproteinemia, Hyperlipidemia, and Hypolipidemia

Hyperlipidemia may result from obesity, estrogen or corticoid therapy, uremia, diabetes, hypothyroidism, acromegaly, alcohol ingestion, liver disease, inborn errors of metabolism, or pregnancy. Hyperlipidemia may cause premature coronary or peripheral vascular disease or pancreatitis.

Coronary events can be decreased by treating individuals with even normal levels of low-density lipoprotein (LDL) cholesterol with the “statins” (3-hydroxy-3-methylglutaryl–coenzyme A [HMG-CoA] reductase inhibitors)—drugs that increase high-density lipoprotein (HDL) and decrease LDL cholesterol levels. This approach has markedly decreased the rate of myocardial infarction in high-risk patients.36-38 Secondary prevention efforts were successful when these high-risk patients stopped smoking, reduced their arterial blood pressure, controlled stress, increased physical activity, and used aspirin, folate, β-blocking drugs, angiotensin inhibitors, diet, and other drugs to reduce their levels of LDL and increase their levels of HDL.

Although controlling the diet remains a major treatment modality for all types of hyperlipidemia, the drugs fenofibrate and gemfibrozil, which are used to treat hypertriglyceridemia, can cause myopathy, especially in patients with hepatic or renal disease; clofibrate is also associated with an increased incidence of gallstones. Cholestyramine binds bile acids, as well as oral anticoagulants, digitals, drugs, and thyroid hormones. Nicotinic acid causes peripheral vasodilation and should probably not be continued through the morning of the surgical procedure. Probucol (Lorelco) decreases the synthesis of apoprotein A-1; its use is associated on rare occasion with fetid perspiration or prolongation of the QT interval, or both, and sudden death in animals.

The West of Scotland Coronary Prevention Study and its congeners produced convincing evidence that drugs in the statin class prevent the morbidity and mortality related to arterial aging and vascular disease, as well as their consequences, such as coronary artery disease (CAD), stroke, and peripheral vascular insufficiency.37 Thus, the statins—lovastatin (Mevacor), pravastatin (Pravachol), simvastatin, fluvastatin, atorvastatin (Lipitor), and rosuvastatin (Crestor)—are mainstays of therapy.

However, the report of Downs and co-workers from the Air Force/Texas Coronary Atherosclerosis Prevention Study went further.37 This report showed a 37% reduction in the risk for first acute major coronary events in patients who had no risk factors and normal (average) LDL cholesterol levels. In this study lovastatin did not alter mortality rates, but that had been true for many early short-term trials with the statins. Although much of the effect of the statins has been attributed to their lipid-lowering effects, statins also influence endothelial function, inflammatory responses, plaque stability, and thrombogenicity. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a new clinical practice guideline for the treatment of blood cholesterol in people at high risk for cardiovascular diseases.39 They now advocate statin therapy for the following:

• Patients who have cardiovascular disease
• Patients with an LDL, or “bad” cholesterol, level of 190 mg/dL or higher
• Patients with type 2 diabetes who are between 40 and 75 years old
• Patients with an estimated 10-year risk of cardiovascular disease of 7.5% or higher who are between 40 and 75 years old (the report provides formulas for calculating 10-year risk)

Statins are drugs that block HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Their use is occasionally accompanied by liver dysfunction, CNS dysfunction, and severe depression not related to the high cost of each drug and its congeners. Based on the available evidence, statin therapy should be continued in patients already taking these drugs.40 Other drugs that reduce LDL and increase HDL cholesterol and decrease triglycerides are docosahexaenoic acid (an ω-3 fatty acid) and niacin. Statins also provide the substantial benefit of reversing inflammation in arteries, as evidenced by their ability to decrease highly specific C-reactive protein and pull cholesterol from plaque.41

Hypolipidemic conditions are rare diseases often associated with neuropathy, anemia, and renal failure. Although anesthetic experience with hypolipidemic conditions has been limited, some specific recommendations can be made: continuation of caloric intake and intravenous administration of protein hydrolysates and glucose should be continued throughout the perioperative period.

Obesity

Although many conditions associated with obesity (diabetes, hyperlipidemia, cholelithiasis, gastroesophageal reflux disease, cirrhosis, degenerative joint and disk disease, venous stasis and thrombotic or embolic disease, sleep disorders, and emotional and altered body image disorders) contribute to chronic morbidity in obese patients, the main concerns for the anesthesiologist have been the same since the 1970s—derangements of the cardiopulmonary system (see also Chapter 71).

Morbid obesity with minimal or no coexisting pulmonary conditions (e.g., no obesity-hypoventilation
syndrome or chronic obstructive pulmonary disease (COPD)) is referred to here as “simple” obesity. In simple obesity, the pathophysiology of mild alterations in daytime gas exchange and pulmonary function may also result from compression and restriction of the chest wall and diaphragm by excess adipose tissue. Typically, in obese patients, the expiratory reserve volume and functional residual capacity are most affected and are reduced to 60% and 80% of normal, respectively.

**Other Eating Disorders: Anorexia Nervosa, Bulimia, and Starvation**

Many endocrine and metabolic abnormalities occur in patients with anorexia nervosa, a condition characterized by starvation to the point of 40% loss of normal weight, hyperactivity, and a psychiatrically distorted body image. Many anorectic patients exhibit impulsive behavior, including suicide attempts, and intravenous drug use is much more common than in the general population. Acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hyperthermia, diabetes insipidus, and severe endocrine abnormalities mimicking panhypopituitarism need attention before patients undergo anesthesia and surgery. Similar problems occur in bulimia (bulimorexia), a condition that may affect as many as 50% of female college students and is even unintentionally present in many older adults. As in severe protein deficiency (kwashiorkor), anorexia nervosa and bulimia may be accompanied by the following: alterations on the electrocardiogram (ECG), including a prolonged QT interval, atrioventricular (AV) block, and other arrhythmias; sensitivity to epinephrine; and cardiomyopathy. Total depletion of body potassium makes the addition of potassium to glucose solutions useful; however, fluid administration can precipitate pulmonary edema in these patients. Esophagitis, pancreatitis, and aspiration pneumonia are more frequent in these patients, as is delayed gastric emptying. One review reported that in patients with severe anorexia with a body mass index less than 13 kg/m², marked hypoglycemia or leukocytopenia lower than 3.0 × 10⁹/L, or both, potentially fatal complications frequently occur. Accordingly, patients need strict nutritional support to avoid refeeding syndrome until the surgical procedure. Intraoperatively, glucose or catecholamine administration may lead to disturbance of electrolytes or fatal arrhythmia. Intensive care and early feeding as soon as possible postoperatively are important to prevent surgical site infection.

**HYPERALIMENTATION (TOTAL PARENTERAL OR ENTERAL NUTRITION)**

Hyperalimentation (i.e., total parenteral nutrition [TPN]) consists of concentrating hypertonic glucose calories in the normal daily fluid requirements (see also Chapter 106). The solutions contain protein hydrolysates, soybean emulsions (i.e., Intralipid), or synthetic amino acids (or any combination of these ingredients). The major benefits of TPN or enteral nutrition have been fewer complications postoperatively and shorter hospital stays for patients scheduled to have no oral feeding for 7 days or who were malnourished preoperatively. Starker and colleagues found that the response to TPN, as monitored by serum albumin levels, predicted the postoperative outcome. The group of patients demonstrating an increase in serum albumin concentrations from TPN had diuresis, weight loss, and fewer complications (1 of 15 patients) than did the group that gained weight and had a decrease in serum albumin (8 of 16 patients had 15 complications) (Fig. 39-2). The Veterans Administration (former name for Veterans Affairs [VA used for both]) studies also found that the serum albumin level was one of the most powerful predictors of perioperative outcome.

The major complications of hyperalimentation are sepsis and metabolic abnormalities. The central lines used for TPN require application with an absolutely aseptic technique and should not be used routinely as an intravenous route for drug administration. Major metabolic complications of TPN relate to deficiencies and the development of hyperosmolar states. Complications of hypertonic dextrose can develop if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar or if insulin resistance occurs (e.g., because of uremia, burns, or sepsis).

A gradual decrease in the infusion rate of TPN prevents the hypoglycemia that can occur on abrupt discontinuance. Thus, the infusion rate of TPN should be decreased the night before anesthesia and surgery or should be continued throughout the operation at its current rate. The main reason for slowing or discontinuing TPN before anesthesia is to avoid intraoperative hyperosmolarity secondary to accidental rapid infusion of the solution or hypoglycemia if the infusion is discontinued because of high levels of endogenous insulin and lower levels of glucose present in the usual crystalloid solutions. Hypophosphatemia is a particularly serious complication that results from the administration of phosphate-free or phosphate-depleted solutions for hyperalimentation.

**Figure 39-2.** The response to hyperalimentation (A, repletion), as measured by variation in serum albumin levels, predicted the outcome of surgery. Patients who responded (B) to nutritional support with increased albumin levels had a significantly better outcome than did those whose albumin level did not increase (C). See the text for a more complete explanation. (Modified from Starker PM, et al: Serum albumin levels as an index of nutritional support, Surgery 91:194, 1982.)
The low serum phosphate level causes a shift of the oxygen dissociation curve to the left. The resulting low 2,3-diphosphoglycerate and adenosine triphosphatase levels mean that cardiac output must increase for oxygen delivery to remain the same. Hypophosphatemia of less than 1.0 mg/dl of blood may cause hemolytic anemia, cardiac failure, tachypnea, neurologic symptoms, seizures, and death. In addition, long-term TPN is associated with deficiencies in trace metals such as copper (refractory anemia), zinc (impaired wound healing), and magnesium.

ADRENOCORTICAL MALFUNCTION

Three major classes of hormones—androgens, glucocorticoids, and mineralocorticoids—are secreted by the adrenal cortex. For each class, an excess or a deficiency of hormone produces a characteristic clinical syndrome. The widespread use of steroids can also make the adrenal cortex unable to respond normally to the demands placed on it by surgical trauma and subsequent healing. The increase in unindicated (scanning) computed tomography (CT) abdominal imaging procedures has meant that many adrenal masses have unfortunately been discovered only incidentally. These adrenal “incidentalomas,” as they are termed because they were initially thought a nuisance discovered by unindicated body scans, have proved more serious. As many as 30% are hormonally active; in a review of 2000 such masses, 82% were not hormonally active, 5.3% proved to be cortisone-secreting adenomas, 5.1% were pheochromocytomas, 4.7% were adrenal carcinomas, 2.5% were unsuspected metastatic disease, and 1% were aldosterone-secreting adenomas. Incidentalomas may therefore require serious pursuit. Several points relative to adrenal cortical management deserve attention.

Controlled comparisons of the perioperative management of patients who have disorders of adrenal function are lacking, although steroids are used more and more commonly, with the results of some controlled trials available for specific uses. However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable physicians to improve the perioperative care of patients with adrenal abnormalities.

Physiologic Properties of Adrenocortical Hormones

Androgens. Androstenedione and dehydroepiandrosterone, weak androgens arising from the adrenal cortex, constitute major sources of androgen in women (and have gained prominence for their use or abuse by base-ball players seeking to hit more home runs). Excess secretion of androgen causes masculinization, pseudopuberty, or female pseudohemaphroditism. With some tumors, androgen is converted to an estrogenic substance, in which case feminization results. No special anesthetic evaluation is needed for such patients. Some congenital enzyme defects that cause androgen abnormalities also result in glucocorticoid and mineralocorticoid abnormalities that should be evaluated preoperatively. Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and consequently require supplementation of these hormones perioperatively (see later).

**TABLE 39-2 RELATIVE POTENCIES AND EQUIVALENT DOSES FOR COMMONLY USED GLUCOCORTICOIDS**

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Relative Glucocorticoid Potency</th>
<th>Equivalent Glucocorticoid Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (hydrocortisone)</td>
<td>1.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Intermediate Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Long Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Data from Axelrod L: Glucocorticoid therapy, Medicine (Baltimore) 55:39, 1976.
primarily in the liver and is excreted as 17-hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into urine. The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (>30 mg/day), cortisol and cortisone bind to mineralocorticoid receptor sites and cause salt and water retention and loss of potassium and hydrogen ions. When these steroids are administered in maintenance doses of 30 mg/day or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect (see Table 39-2).

Secretion of glucocorticoids is regulated by pituitary adrenocorticotropic hormone (ACTH). ACTH is synthesized from a precursor molecule (pro-opiomelanocortin) that is metabolized to form an endorphin (β-lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm that is normally greatest during the early morning hours in men and later in women and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor (CRF) from the hypothalamus. (An abnormality in the diurnal rhythm of corticoid secretion has been implicated as a cause of so-called jet lag.) Cortisol and other glucocorticoids exert negative feedback at both the pituitary and hypothalamic levels to inhibit the secretion of ACTH and CRF. If the CRF- or ACTH-producing cells are destroyed, the adrenal gland takes more than 30 days to atrophy to the point at which short-term administration of exogenous ACTH will cause almost no adrenal responsiveness.

Mineralocorticoids. Aldosterone, the major mineralocorticoid secreted in humans, comes from the zona glomerulosa of the adrenal cortex and causes reabsorption of sodium and secretion of potassium and hydrogen ions, thereby contributing to electrolyte and volume homeostasis. This action is most prominent in the distal renal tubule but also occurs in the salivary and sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. Renin transforms the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in the lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by an increased potassium concentration and, to a lesser degree, by ACTH.

Adrenocortical Hormone Excess

Glucocorticoid Excess. Glucocorticoid excess (Cushing syndrome) resulting from either endogenous oversecretion or long-term treatment with glucocorticoids at higher than physiologic doses produces a moon-faced plethoric individual with a centripetal distribution of fat (truncal obesity and skinny extremities), thin skin, easy bruising, and striae. Muscle wasting is common, but the heart and diaphragm are usually spared. A test for this syndrome is to ask the patient to get up from a chair without using the hands. An inability to do so indicates proximal muscle weakness consistent with Cushing syndrome. These patients often have osteopenia as a result of decreased formation of bone matrix and impaired absorption of calcium. Fluid retention and hypertension (because of increases in renin substrate and vascular reactivity caused by glucocorticoid) are common. Such patients may also have hyperglycemia and even diabetes mellitus from inhibition of peripheral use of glucose, as well as antiinsulin action and concomitant stimulation of gluconeogenesis (Table 39-3).

The most common cause of Cushing syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies. In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the preoperative and preprocedure period) by secreting more steroid. Thus, additional glucocorticoids may be required perioperatively (see the later section “Patients Taking Steroids for Other Reasons”). Spontaneous Cushing syndrome may be caused by pituitary production of ACTH (65% to 75% of all spontaneous cases), which is usually associated with pituitary microadenoma, or by nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus). Ten percent to 20% of cases of spontaneous Cushing syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.

Special preoperative and preprocedure considerations for patients with Cushing syndrome include regulating diabetes and hypertension and ensuring that intravascular fluid volume and electrolyte concentrations are normal. Ectopic ACTH production may cause marked hypokalemic alkalosis. Treatment with the aldosterone antagonist spironolactone stops the potassium loss and helps mobilize excess fluid. Because of the high incidence of severe osteopenia and the risk of fractures, meticulous attention must be paid to positioning of the patient. In addition,
glucocorticoids are lympholytic and immunosuppressive and thus increase the patient’s susceptibility to infection. The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by the topical administration of vitamin A.

Specific considerations pertain to the surgical approach for each cause of Cushing syndrome. For example, nearly three fourths of cases of spontaneous Cushing disease result from a pituitary adenoma that secretes ACTH. In the experience of Dr. Michael Roizen, a previous author of this chapter in earlier editions, perioperative treatment of patients who have Cushing disease and a pituitary microadenoma differs from that of patients who have a pituitary adenoma associated with amenorrhea and galactorrhea. A patient with Cushing disease is inclined to bleed more easily and (on the basis of anecdotal evidence) tends to have higher central venous pressure (CVP). Thus, during transsphenoidal tumor resection in such patients, routine practice is to monitor CVP and maintain it at the low end of the normal range. In other cases of transsphenoidal resection of microadenoma, such monitoring is needed only infrequently.

Ten percent to 15% of patients with Cushing syndrome exhibit adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. If either unilateral or bilateral adrenal resection is planned, the physician should begin administering glucocorticoids at the start of resectioning of the tumor. Despite the absence of definitive studies, 100 mg of hydrocortisone hemisuccinate or hydrocortisone phosphate every 24 hours intravenously is reasonable. This amount can be reduced over a period of 3 to 6 days until a maintenance dose is reached. Beginning on day 3, the surgeon may also give a mineralocorticoid, 9α-fluorocortisol (0.05 to 0.1 mg/day). In certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For a patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. The incidence of pneumothorax in open adrenal resection approach can be as high as 20%; the diagnosis of pneumothorax is sought and treatment is initiated before the wound is closed. The use of the laparoscopic technique has markedly decreased this complication.

Bilateral adrenalectomy in patients with Cushing syndrome is associated with a high incidence of postoperative complications and a perioperative mortality rate (higher than that of even cardiac surgery) of 5% to 10%; this procedure often results in permanent mineralocorticoid and glucocorticoid deficiency. Ten percent of patients with Cushing syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After cortisol concentrations are decreased by adrenalectomy, the pituitary tumor will likely enlarge. These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation.

Approximately 85% of adrenal tumors are discovered incidentally during screening CT scans. Nonfunctioning adrenal adenomas are found in patients on autopsy, ranging from 1% to 32% in different series. Functioning adenomas are generally treated surgically; often, the contralateral gland resumes functioning after several months.

Frequently, however, the effects of carcinomas are not cured surgically. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (α,α-DDD[2,2-bis(2-chlorophenyl)-4-chlorophenyl]-1,1-dichloroethane), may ameliorate some symptoms but may not improve survival. These drugs and specific aldosterone antagonists may aid in reducing symptoms in the case of ectopic ACTH secretion if the primary tumor proves unresectable. Patients given these adrenal suppressants are also prescribed long-term glucocorticoid replacement therapy (i.e., the goal of therapy is complete adrenal suppression). These patients should be considered to have suppressed adrenal function, and glucocorticoid replacement should be increased perioperatively.

Mineralocorticoid Excess. Excess mineralocorticoid activity (common with glucocorticoid excess because most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. These symptoms constitute primary hyperaldosteronism, or Conn syndrome (a cause of low-renin hypertension because renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5% to 1% of hypertensive patients who have no other known cause of hypertension. Primary hyperaldosteronism most often results from unilateral adenoma, although 25% to 40% of patients have been found to have bilateral adrenal hyperplasia. Intravascular fluid volume, electrolyte concentrations, and renal function should be restored to within normal limits preoperatively by administering the aldosterone antagonist spironolactone. The effects of spironolactone are slow in onset and increase for 1 to 2 weeks. A patient who has a serum potassium level of 2.9 mEq/L may have a total-body potassium deficit of as little as 40 mEq or as much as 400 mEq. Frequently, a period of at least 24 hours is required to restore potassium equilibrium. A normal serum potassium level does not necessarily imply correction of a total-body deficit of potassium. In addition, patients with Conn syndrome have a high incidence of hypertension and ischemic heart disease; hemodynamic monitoring should be appropriate for the degree of cardiovascular impairment.

A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when arterial blood pressure and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive drugs were used. However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly established. We have assumed that gradual restoration of a normal condition is good medicine and that it would decrease perioperative morbidity and mortality.

Adrenocortical Hormone Deficiency

Glucocorticoid Deficiency. Withdrawal of steroids or suppression of synthesis by steroid therapy is the leading cause of underproduction of corticosteroids. Management of this type of glucocorticoid deficiency is discussed in the later section “Patients Taking Steroids for Other
Reasons”. Other causes of adrenocortical insufficiency include the following: defects in ACTH secretion and destruction of the adrenal gland by autoimmune disease, tuberculosis, hemorrhage, or cancer; some forms of congenital adrenal hyperplasia (see previous discussion); and administration of cytotoxic drugs.

Primary adrenal insufficiency (Addison disease) is associated with local destruction of all zones of the adrenal cortex and results in both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral; common symptoms and signs are listed in Table 39-3. Autoimmune disease is the most common cause of primary (nonexogenous) bilateral ACTH deficiency in the United States, whereas tuberculosis is the most common cause worldwide. Tuberculosis is associated with decreased adrenal function but large adrenal glands, as is also common in sarcoidosis, histoplasmosis, amyloidosis, metastatic malignant disease, and adrenal hemorrhage. Destruction or partial destruction by trauma and by human immunodeficiency virus (HIV) and other infections, such as cytomegalovirus, mycobacteria, and fungi, is being recognized more frequently.

An increasingly common cause of adrenal insufficiency associated with large adrenal glands is heparin-induced thrombocytopenia, which may be considered in every patient who has received heparin and has hypotension.

Autoimmune destruction of the adrenal glands may be associated with other autoimmune disorders, such as some forms of type 1 diabetes and Hashimoto thyroiditis. Enzymatic defects in cortisol synthesis also cause glucocorticoid insufficiency, compensatory elevations in ACTH, and congenital adrenal hyperplasia. Because adrenal insufficiency usually develops slowly, such patients are subject to marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (apparently secondary to chronic hypotension).

Secondary adrenal insufficiency occurs when ACTH secretion is deficient, often because of a pituitary or hypothalamic tumor. Treatment of pituitary tumors by surgery or radiation therapy may result in hypopituitarism and subsequent adrenal failure.

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress is present (e.g., upper respiratory infection). Preparation of such a patient for anesthesia and surgery should include treatment of hypovolemia, hyperkalemia, and hypotension. Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids (=200 mg hydrocortisone/70 kg body weight/day) perioperatively. However, Symreng and colleagues gave 25 mg of hydrocortisone phosphate intravenously to adults at the start of the operative procedure, followed by 100 mg intravenously over the next 24 hours. Because using the minimum drug dose that would produce an appropriate effect is desirable, this latter regimen seems attractive. Such a regimen has proved to be as successful as a regimen using maximum doses (=300 mg hydrocortisone/70 kg body weight/day—see the later section “Patients Taking Steroids for Other Reasons”). Thus, we now recommend giving 100 mg of hydrocortisone phosphate intravenously every 24 hours.

**Mineralocorticoid Deficiency.** Hypoaldosteronism, a less common condition, can be congenital or can occur after unilateral adrenalectomy or prolonged administration of heparin. In addition, it can also be a consequence of long-standing diabetes and renal failure. Nonsteroidal inhibitors of prostaglandin synthesis may also inhibit renin release and exacerbate this condition in patients with renal insufficiency. Plasma renin activity is lower than normal and fails to increase appropriately in response to sodium restriction or diuretic drugs. Most symptoms are caused by hyperkalemic acidosis rather than hypovolemia; in fact, some patients are hypertensive. These patients can have severe hyperkalemia, hyponatremia, and myocardial conduction defects. These defects can be treated successfully by administering mineralocorticoids (9α-fluorocortisol, 0.05 to 0.1 mg/day) preoperatively. Doses must be carefully titrated and monitored to avoid an increase in hypertension.

**Patients Taking Steroids for Other Reasons**

**Perioperative Stress and the Need for Corticoid Supplementation.** The adrenal responses of normal patients to the perioperative period, as well as those responses of patients taking steroids for other diseases, indicate the following:

1. Perioperative stress is related to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia delays the usual intraoperative glucocorticoid surge to the postoperative period.
2. A few patients with suppressed adrenal function will have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively.
3. Although a patient who takes steroids on a long-term basis may become hypotensive perioperatively, glucocorticoid or mineralocorticoid deficiency is rarely the cause.
4. Acute adrenal insufficiency rarely occurs, but it can be life-threatening.
5. Giving these patients steroid coverage equivalent to 100 mg of hydrocortisone hemisuccinate perioperatively has little risk.

In a well-controlled study of glucocorticoid replacement in nonhuman primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement. An alternative dose regimen has altered management methods that will likely improve patients’ safety. In this study, adrenalectomized primates and sham-operated controls were given physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (one tenth of the normal cortisol production), physiologic, or supraphysiologic (10 times the normal cortisol production) doses of cortisol for 4 days preceding abdominal surgery (cholecystectomy). Hemodynamic variables were measured by means of arterial and pulmonary artery catheters. The animals were maintained on their randomized dosage schedules during and after the surgical procedures. The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. Death rates
for the physiologic and supraphysiologic replacement groups were the same and did not differ from the rate for sham-operated controls. Death in the subphysiologic replacement group was related to severe hypotension associated with a significant decrease in systemic vascular resistance and a reduced left ventricular stroke work index. Filling pressures of the heart were unchanged when compared with those in control animals. No evidence of hypovolemia or severe CHF was observed. Despite the low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented interaction of glucocorticoids and catecholamines and thus suggest that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing involving accumulation of hydroxyproline. All treatment groups, including the group given supraphysiologic doses of glucocorticoids, had the same capacity for wound healing. Furthermore, perioperative administration of supraphysiologic doses of corticosteroids produced no adverse metabolic consequences.

This well-conducted study confirms several longstanding intuitive impressions concerning patients who have inadequate adrenal function as a result of either underlying disease or administration of exogenous steroids. Inadequate replacement of corticosteroids perioperatively can lead to addisonian crisis and death. Administration of supraphysiologic doses of steroids for a short time perioperatively caused no discernible complications. However, at least theoretic negative consequences can occur when large doses of steroids are given (see later). It is clear that inadequate corticosteroid coverage can cause death. What is not so clear is what dose of steroid should be recommended for replacement therapy. Yong and colleagues reviewed the randomized controlled trials for a Cochrane Systemic Review and reported only 2 trials involving 37 patients that met the inclusion criteria.51 These studies reported that supplemental perioperative steroids were not required during surgery for patients with adrenal insufficiency, but neither study reported any adverse effects or complications in the intervention and control groups. The authors concluded that they were unable to support or refute the use of supplemental perioperative steroids for patients with adrenal insufficiency during surgery. Because the risk is low, physicians should consider providing supplementation for any patient who has received steroids within a year.48,50 Data indicate that topical application of steroids (even without the use of occlusive dressings) can suppress normal adrenal responses for as long as 9 months to 1 year (Table 39-4).

How can one determine when adrenal responsiveness has returned to normal? The morning plasma cortisol level does not reveal whether the adrenal cortex has recovered sufficiently to ensure that cortisol secretion will increase adequately to meet the demands of stress. Inducing hypoglycemia with insulin has been advocated as a sensitive test of pituitary-adrenal competence, but it is impractical and is probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of greater than 25 μg/dL assuredly (and a value >15 μg/dL probably) indicates normal pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 μg of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. An increase in plasma cortisol of 6 to 20 μg/dL or more is normal.52,53 A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.

It is unusual for laboratory data defining pituitary-adrenal adequacy to be available preoperatively. Rather than delay surgery or test most patients, we assume that any patient who has taken steroids at any time during the preceding year has suppressed pituitary-adrenal function and will require perioperative supplementation.

Under perioperative conditions, the adrenal glands secrete 116 to 185 mg of cortisol daily. Under maximum stress, they may secrete 200 to 500 mg/day. Good correlation exists between the severity and duration of the operation and the response of the adrenal gland. “Major surgery” would be represented by procedures such as laparoscopic colectomy and “minor surgery” by procedures such as herniorrhaphy. In a study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 μg/dL (range, 22 to 75 μg/dL). Values remained higher than 26 μg/dL for a maximum of 72 hours postoperatively. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 μg/dL (range, 10 to 44 μg/dL).

<table>
<thead>
<tr>
<th>Recovery Time (mo)</th>
<th>Plasma 17-Hydroxycorticoid Values</th>
<th>Plasma ACTH Values</th>
<th>Adrenal Response to Exogenous ACTH</th>
<th>Response to Metyrapone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low†</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>2-5</td>
<td>Low</td>
<td>High†</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>6-9</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>&gt;9</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>


ACTH, Adrenocorticotropic hormone.

*Various subjective manifestations of mild adrenal insufficiency occur during this stage.

†The diurnal rhythm of plasma concentrations is qualitatively normal during this stage.
Although the precise amount required has not been established, we usually intravenously administer the maximum amount of glucocorticoid that the body manufactures in response to maximal stress (i.e., approximately 200 mg/day of hydrocortisone phosphate/70 kg body weight). For minor surgical procedures, we usually give hydrocortisone phosphate intravenously, 100 mg/day/70 kg body weight. Unless infection or some other perioperative complication develops, we decrease this dose by approximately 25% per day until oral intake can be resumed. At this point, the usual maintenance dose of glucocorticoids can be administered.

**Risks of Supplementation.** Rare complications of perioperative steroid supplementation include aggravation of hypertension, fluid retention, induction of stress ulcers, and psychiatric disturbances. Two common complications of short-term perioperative supplementation with glucocorticoids are abnormal wound healing and an increased rate of infections. This evidence is inconclusive, however, because it relates to short-term glucocorticoid administration and not to long-term administration of glucocorticoids with increased doses at times of stress. In contrast to a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study involving primates suggested that large doses of glucocorticoids, administered perioperatively, do not impair sensitive measures of wound healing.48 An overall assessment of these results suggests that short-term perioperative supplementation with steroids has a small but definite deleterious effect on wound healing that is perhaps partially reversed by topical administration of vitamin A.

Information on the risk of infection from perioperative glucocorticoid supplementation is also unclear. In many studies of long-term use by patients and supplementation, no increased risk of serious infections was reported with long-term use of steroids alone. Data indicate that the risk of infection in a patient taking steroids on a long-term basis is real, but whether perioperative supplementation with steroids increases that risk is not clear.

**Adrenal Cortex Function in Older Adults**

Production of androgens by the adrenal gland progressively decreases with age; this change has no known implications for anesthesia (see also Chapter 80). Plasma levels of cortisol are unaffected by increasing age. Levels of CBG are also unaffected by age, a finding suggesting that a normal fraction of free cortisol (1% to 5%) is present in older patients. Older patients have a progressively impaired ability to metabolize and excrete glucocorticoids. In normal individuals, the quantity of 17-hydroxycorticosteroids excreted is reduced by half by the seventh decade. This decreased excretion undoubtedly reflects the reduced renal function that occurs with aging. When excretion of cortisol metabolites is expressed as a function of creatinine clearance, the age difference disappears. Further reductions in cortisol clearance may reflect impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30% slower in older adults. This reduced secretion may be an appropriate compensatory mechanism for maintaining a normal cortisol level in the presence of decreased hepatic and renal clearance of cortisol. The reduced cortisol production can be overcome during periods of stress, and even extremely old patients (>100 years old) display an entirely normal adrenal response to the administration of ACTH and to stresses such as hypoglycemia.

Both underproduction and overproduction of glucocorticoids are generally considered diseases of younger individuals. The highest incidence of Cushing disease of either pituitary or adrenal origin occurs during the third decade of life. The most common cause of spontaneous Cushing disease is benign pituitary adenoma. However, in patients older than 60 years in whom Cushing disease develops, the most likely cause is adrenal carcinoma or ectopic ACTH production from tumors usually located in the lung, pancreas, or thymus.

**ADRENAL MEDULLARY SYMPATHETIC HORMONE EXCESS: PHEOCHROMOCYTOMA**

Less than 0.1% of all cases of hypertension are caused by pheochromocytomas, or catecholamine-producing tumors derived from chromaffin tissue.54 Nevertheless, these tumors are clearly important to the anesthesiologist inasmuch as 25% to 50% of hospital deaths in patients with pheochromocytoma occur during induction of anesthesia or during operative procedures for other causes.55 Although usually found in the adrenal medulla, these vascular tumors can occur anywhere, such as in the right atrium, the spleen, the broad ligament of the ovary, or the organs of Zuckerkandl at the bifurcation of the aorta. Malignant spread, which occurs in less than 15% of pheochromocytomas, usually proceeds to venous and lymphatic channels with a predisposition for the liver. This tumor is occasionally familial or part of the pluriglandular-neoplastic syndrome known as multiple endocrine adenoma type IIa or type IIb and is manifested as an autosomal dominant trait. Type IIa consists of medullary carcinoma of the thyroid, parathyroid adenoma or hyperplasia, and pheochromocytoma. What used to be called type IIb is now often called pheochromocytoma in association with phakomatoses such as von Recklinghausen neurofibromatosis and von Hippel–Lindau disease with cerebellar hemangioblastoma. Frequently, bilateral tumors are found in the familial form. Localization of tumors can be achieved by MRI or CT, metaiodobenzylguanidine (MIBG) nuclear scanning, ultrasonography, or intravenous pyelography (in decreasing order of combined sensitivity and specificity).

Symptoms and signs that may be solicited before surgery or procedures and are suggestive of pheochromocytoma are as follows: excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities. In fact, the occurrence of combined symptoms of paroxysmal headache, sweating, and hypertension is probably a more sensitive and specific indicator than any one biochemical test for pheochromocytoma.
specificity (%) 40% to 60% when adrenergic receptor blockade is introduced as preoperative and preprocedure therapy. These drugs probably reduce the complications of hypertensive crisis, the wide arterial blood pressure fluctuations during manipulation of the tumor (especially until venous drainage is obliterated), and the myocardial dysfunction that occurs perioperatively. Mortality decreased with resection of pheochromocytoma (from 40% to 60% to the current 0% to 6%) when adrenergic receptor blockade is introduced as preoperative and preprocedure preparatory therapy for such patients.56-60

- Adrenergic receptor blockade with prazosin or phenoxybenzamine restores intravascular plasma volume by counteracting the vasoconstrictive effects of high levels of catecholamines. This reexpansion of intravascular fluid volume is often followed by a decrease in hematocrit. Because some patients may be very sensitive to the effects of phenoxybenzamine, this drug should initially be given in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/day. The efficacy of therapy should be judged by the reduction in symptoms (especially sweating) and stabilization of arterial blood pressure. For patients who have carbohydrate intolerance because of inhibition of insulin release mediated by adrenergic receptor stimulation, -adrenergic receptor blockade may reduce fasting blood glucose levels. For patients who exhibit ST-T changes on the ECG, long-term preoperative and preprocedure -adrenergic receptor blockade (1 to 6 months) has produced ECG and clinical resolution of catecholamine-induced myocarditis.56,57,59-63

- Adrenergic receptor blockade with propranolol is suggested for patients who have persistent arrhythmias or tachycardia56,57,59-63 the reason being that these conditions can be precipitated or aggravated by -adrenergic receptor blockade. -Adrenergic receptor blockade should not be used without concomitant -adrenergic receptor blockade lest the vasoconstrictive effects of the latter go unopposed and thereby increase the risk of dangerous hypertension.

The optimal duration of preoperative therapy with phenoxybenzamine has not been studied. Most patients require 10 to 14 days, as judged by the time needed to stabilize arterial blood pressure and ameliorate symptomatology. Because the tumor spreads slowly, little is lost by waiting until medical therapy has optimized the patient’s preoperative condition. The following criteria are reasonable for assessing the adequacy of treatment:

1. No in-hospital arterial blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours preoperatively. We often measure arterial blood pressure every minute for 1 hour in a stressful environment (our postanesthesia care unit). If no blood pressure reading is higher than 165/90 mm Hg, this criterion is considered satisfied.

2. Orthostatic hypotension is acceptable as long as arterial blood pressure when the patient is standing is not less than 80/45 mm Hg.

3. The ECG should be free of ST-T changes that are not permanent.

4. No more than one premature ventricular contraction (PVC) should occur every 5 minutes.

Other drugs, including prazosin, calcium channel blocking drugs, clonidine, dexmedetomidine, and magnesium, have also been used to achieve suitable degrees of -adrenergic blockade preoperatively. Multiple case series have confirmed the clinical utility of this approach in adults before tumor excision, including in a hemodynamic catecholamine crisis.64 Magnesium therapy has shown efficacy for the resection of pheochromocytoma or paraganglioma during pregnancy. The dosing of magnesium for the management of pheochromocytoma has been reviewed elsewhere.65

The key clinical components of ideal patient care include optimal preoperative preparation, gentle (slow) induction of anesthesia, and good communication between the surgeon and the anesthesiologist. Virtually all anesthetic drugs and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, fentanyl, and regional anesthesia) have been used with success. In fact, all drugs studied are associated with a high rate of transient intraoperative arrhythmias.59

Because of ease of use, the preference is to give phenylephrine hydrochloride (Neo-Synephrine) or dopamine for hypotension and nitroprusside or theoretically, clevidipine, for hypertension. Phentolamine (Regitine) has too long an onset and duration of action. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have pheochromocytoma. This response is caused by release of catecholamines from nerve endings that

### Table 39-5: Characteristics of Tests for Pheochromocytoma

<table>
<thead>
<tr>
<th>Test/Symptoms</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Result</th>
<th>Negative Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanillylmandelic acid excretion</td>
<td>81</td>
<td>97</td>
<td>27.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Catecholamine excretion</td>
<td>82</td>
<td>95</td>
<td>16.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Metanephrine excretion</td>
<td>83</td>
<td>95</td>
<td>16.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Abdominal computed tomography</td>
<td>92</td>
<td>80</td>
<td>4.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Concurrent paroxysmal hypertension, headache, sweating, and tachycardia</td>
<td>90</td>
<td>95</td>
<td>18.0</td>
<td>0.10</td>
</tr>
</tbody>
</table>


†The ratio representing the likelihood of a negative result is obtained by subtracting the sensitivity from 1 and the dividing by the specificity.

‡Data for concurrent paroxysmal symptoms are best estimates from available data.
are “loaded” by the reuptake process. Such stresses may result in catecholamine levels of 200 to 2000 pg/mL in normal patients. For a patient with pheochromocytoma, even simple stress can lead to blood catecholamine levels of 2000 to 20,000 pg/mL. However, infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products, can result in blood levels of 200,000 to 1,000,000 pg/mL—a situation that should be anticipated and avoided (ask for a temporary stay of surgery, if at all possible, while the rate of nitroprusside infusion is increased). Once the venous supply is secured and if intravascular volume is normal (as measured by pulmonary wedge pressure or echocardiography), normal arterial blood pressure usually results. However, some patients become hypotensive and occasionally require massive infusions of catecholamines. Vasopressin has also been used for hemodynamic rescue in catecholamine-resistant vasoplegic shock after resection of a massive pheochromocytoma.\(^{55}\) On rare occasion, patients remain hypertensive intraoperatively. Postoperatively, approximately 50% of patients remain hypertensive for 1 to 3 days—and initially have markedly increased but declining plasma catecholamine levels—at which time all but 25% will become normotensive. Other family members should be advised to inform their future anesthesiologist about the potential for such familial disease.

**HYPOFUNCTION OR ABERRATION IN FUNCTION OF THE SYMPATHETIC NERVOUS SYSTEM (DYSAUTONOMIA)**

Disorders of the sympathetic nervous system include Shy-Drager syndrome, Riley-Day syndrome, Lesch-Nyhan syndrome, Gill familial dysautonomia, diabetic dysautonomia, and the dysautonomia of spinal cord transection.

Although individuals can function well without an adrenal medulla, a deficient peripheral sympathetic nervous system occurring late in life poses major problems for many facets of life; nevertheless, perioperative sympathectomy or its equivalent is often recommended.\(^{57-73}\) A primary function of the sympathetic nervous system appears to be regulation of arterial blood pressure and intravascular fluid volume during changing of body position. Common features of all the syndromes of hypothfunication of the sympathetic nervous system are orthostatic hypotension and decreased beat-to-beat variability in heart rate. These conditions can be caused by deficient intravascular volume, deficient baroreceptor function (as also occurs in carotid artery disease\(^{74}\)), abnormalities in CNS function (as in Wernicke or Shy-Drager syndrome), deficient neuronal stores of norepinephrine (as in idiopathic orthostatic hypotension\(^{75}\) and diabetes), or deficient release of norepinephrine (as in traumatic spinal cord injury\(^{76}\)). These patients may have an increased number of available adrenergic receptors (a compensatory response) and an exaggerated response to sympathomimetic drugs. In addition to other abnormalities, such as retention of urine or feces and deficient heat exchange, hypothf unicating of the sympathetic nervous system is often accompanied by renal amyloidosis. Thus, electrolyte and intravascular fluid volume status should be evaluated preoperatively. Because many of these patients have cardiac abnormalities, intravascular fluid volume may be assessed preoperatively with a Swan-Ganz catheter or intraoperatively via tranesophageal echocardiography rather than measurement of CVP.

Because the functioning of the sympathetic nervous system is not predictable in these patients, gentle induction of anesthesia and treatment of sympathetic excess or deficiency by infusing drugs that directly constrict (phenylephrine) or dilate (nitroprusside) blood vessels or that stimulate (isoproterenol) or depress (esmolol) the heart rate are suggested. A 20% perioperative mortality rate for 2600 patients after spinal cord transection has been reported, thus indicating that such patients are difficult to manage and deserve particularly close attention.

After reviewing 300 patients with spinal cord injuries, Kendrick and co-workers concluded that autonomic hyperreflexia syndrome does not develop if the lesion is below spinal dermatome T7.\(^{77}\) If the lesion is above that level (splanchnic outflow), 60% to 70% of patients experience extreme vascular instability. The trigger to this instability, or a mass reflex involving noradrenergic and motor hypertonus, can be a cutaneous, proprioceptive, or visceral stimulus (a full bladder is a common initiator). The sensation enters the spinal cord and causes a spinal reflex, which in normal persons is inhibited from above.

Sudden increases in arterial blood pressure are sensed in the pressure receptors of the aorta and carotid sinus. The resulting vagal hyperactivity produces bradycardia, ventricular ectopia, or various degrees of heart block. Reflex vasodilation may occur above the level of the lesion and result in flushing of the head and neck. Two newer techniques to help reduce acute injury or aid in repair (high-dose docosahexaenoic acid and acute cooling) may also have anesthetic implications, but reports of these effects, if any, have not been published.

Depending on the length of time since spinal cord transection, other abnormalities may occur. In the short term (i.e., <3 weeks from the time of spinal injury), retention of urine and feces is common and, by elevating the diaphragm, may impair respiration. Disimpaction of the intestine alleviates this respiratory problem. Hyperesthesia is present above the lesion; reflexes and flaccid paralysis are present below the lesion. The intermediate period (3 days to 6 months) is marked by a hyperkalemic response to depolarizing drugs.\(^{78}\) The chronic phase is characterized by return of muscle tone, Babinski sign, and, frequently, the occurrence of hyperreflexia syndromes (e.g., mass reflex [see earlier]).

Thus, in addition to meticulous attention to perioperative intravascular volume and electrolyte status, the anesthesiologist should know—by history taking, physical examination, and laboratory data—the status of the patient’s myocardial conduction (as revealed by the ECG), the status of renal function (by noting the ratio of creatinine to blood urea nitrogen [BUN]), and the condition of the respiratory muscles (by determining the ratio of forced expiratory volume in 1 second [FEV\(_1\)] to forced vital capacity [FVC]) (see also Chapter 44). The anesthesiologist may also obtain a chest radiograph if atelectasis or pneumonia is suspected on the basis of history taking or the physical examination. Temperature control, the presence of bone fractures or decubitus ulcers, and normal
functioning of the urination and defecation systems must be assessed. Confirmation of the latter prevents postoperative pneumonia or atelectasis caused by high positioning of the diaphragm.

THYROID DYSFUNCTION

The major thyroid hormones are thyroxine (T₄), a prohormone product of the thyroid gland, and the more potent 3,5,3-triiodothyronine (T₃), a product of both the thyroid and extrathyroidal enzymatic deiodination of T₄. Under normal circumstances, approximately 85% of T₃ is produced outside the thyroid gland. Production of thyroid secretions is maintained by secretion of thyroid-stimulating hormone (TSH) in the pituitary, which in turn is regulated by secretion of thyrotropin-releasing hormone (TRH) in the hypothalamus. Secretion of TSH and TRH appears to be negatively regulated by T₄ and T₃. Many investigators believe that all effects of thyroid hormones are mediated by T₃ and that T₄ functions only as a prohormone.

Because T₃ has greater biologic effect than does T₄, one would expect the diagnosis of thyroid disorders to be based on levels of T₃. However, this is not usually the case. The diagnosis of thyroid disease is confirmed by one of several biochemical measurements: levels of free T₄ or total serum concentrations of T₃ and the “free T₄ estimate.” This estimate is obtained by multiplying total T₄ (free and bound) by the thyroid-binding ratio (formerly called resin T₃ uptake) (Table 39-6). Free T₄ can be accurately measured by many laboratories. Direct measurement of free T₄ obviates the need to account for changes in binding protein synthesis and affinity caused by other conditions. The T₃-binding ratio measures the extra quantity of serum protein-binding sites. This measurement is necessary because thyroxine-binding globulin (TBG) levels are abnormally high during pregnancy, hepatic disease, and estrogen therapy (all of which would elevate the total T₄ level) (Box 39-2). Reliable interpretation of measurements of the total hormone concentration in serum necessitates data on the percentage of bound hormone. The thyroid hormone-binding ratio test provides this information. In this test, iodine-labeled T₃ is added to a patient’s serum and is allowed to reach an equilibrium binding state. A resin is then added that binds the remaining radioactive T₃. Resin uptake is greater if the patient has fewer TBG-binding sites. In normal patients, resin T₃ uptake (the thyroid hormone–binding ratio) is 25% to 35%. When serum TBG is elevated, the thyroid hormone–binding ratio is diminished (see Table 39-6). When serum TBG is diminished, as in nephrotic syndrome, in conditions in which glucocorticoids are increased, or in chronic liver disease, the thyroid hormone–binding ratio is increased.

The free T₄ estimate and the free T₃ estimate are frequently used as measures of a patient’s serum T₄ and T₃ hormone concentrations, respectively. To obtain these estimates, the concentration of total serum T₄ or total serum T₃ is multiplied by the measured thyroid hormone–binding ratio. Values of these two indices are normal in the event of a primary alteration in binding but not with an alteration in secretion of thyroid hormone.

Hyperthyroidism can be diagnosed by measuring levels of TSH after the administration of TRH. Although administering TRH normally increases TSH levels in blood, even a small increase in the T₄ or T₃ level in blood abolishes this response. Thus, a subnormal or absent serum TSH response to TRH is a very sensitive indicator of hyperthyroidism. In one group of disorders involving hyperthyroidism, serum TSH levels are elevated in the presence of elevated levels of free thyroid hormone.

Measurement of the α-subunit of TSH has been helpful in identifying the rare patients who have a pituitary

<table>
<thead>
<tr>
<th><strong>Examples of Normal Thyroid Status</strong></th>
<th>FT₄E</th>
<th>T₄</th>
<th>THBR</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.19</td>
<td>0.6</td>
<td>31%</td>
<td>0.2</td>
</tr>
<tr>
<td>During use of oral contraceptives</td>
<td>0.19</td>
<td>1.3</td>
<td>15%</td>
<td>0.3</td>
</tr>
<tr>
<td>During use of corticosteroids</td>
<td>0.18</td>
<td>0.3</td>
<td>60%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*FT₄E is the free T₄ (thyroxine) estimate. It is usually obtained by multiplying the total T₄ concentration (the free amount and the amount bound to protein) by the thyroid hormone–binding ratio (THBR, formerly called the resin T₃ uptake). THBR is a measure of the bound thyroid hormone–binding protein. TSH is the thyroid-stimulating hormone secreted by the pituitary in the negative feedback loop. (TSH increases when FT₄E is low in hypothyroidism.)
neoplasm and who usually have increased α-subunit concentrations. Some patients are clinically euthyroid in the presence of elevated levels of total T₄ in serum. Certain drugs, notably gallbladder dyes, propranolol, glucocorticoids, and amiodarone, block the conversion of T₄ to T₃ and thereby elevate T₃ levels. Severe illness also slows this conversion. Levels of TSH are often high in situations in which the rate of conversion is decreased. In hyperthyroidism, cardiac function and responses to stress are abnormal; return of normal cardiac function parallels the return of TSH levels to normal.

Hyperthyroidism

Although hyperthyroidism is usually caused by the multinodular diffuse enlargement in Graves disease (also associated with disorders of the skin or eyes, or both), it can also occur with pregnancy, thyroiditis (with or without neck pain), thyroid adenoma, choriocarcinoma, or TSH-secreting pituitary adenoma. Five percent of women have thyrotoxic effects 3 to 6 months postpartum and tend to have recurrences with subsequent pregnancies. Major manifestations of hyperthyroidism are weight loss, diarrhea, warm and moist skin, weakness of large muscle groups, menstrual abnormalities, osteopenia, nervousness, jitteriness, intolerance to heat, tachycardia, cardiac arrhythmias, mitral valve prolapse, and heart failure. When the thyroid is functioning abnormally, the entity most threatened is the cardiovascular system. When diarrhea is severe, dehydration should be corrected preoperatively. Mild anemia, thrombocytopenia, increased serum alkaline phosphatase, hypercalcemia, muscle wasting, and bone loss frequently occur in hyperthyroidism. Muscle disease usually involves the proximal muscle groups; it has not been reported to cause respiratory muscle paralysis. In the apathetic form of hyperthyroidism (seen most commonly in persons >60 years old), cardiac effects dominate the clinical picture. Signs and symptoms include weight loss, anorexia, and cardiac effects such as tachycardia, irregular heart rhythm, atrial fibrillation (in 10%), heart failure, and occasionally, papillary muscle dysfunction.

Although β-adrenergic receptor blockade can control the heart rate, its use is fraught with hazard in a patient already experiencing CHF. However, a decreasing heart rate may improve heart-pumping function. Thus, hyperthyroid patients who have fast ventricular rates, who are in CHF, and who require emergency surgery are given short-acting β-blockers guided by changes in pulmonary artery wedge pressure and their condition. If slowing the heart rate with a small dose of esmolol (50 μg/kg) does not aggravate the heart failure, the physician should administer more esmolol. Antithyroid medications include propylthiouracil and methimazole, both of which decrease the synthesis of T₄ and may enhance remission by reducing TSH receptor antibody levels (the primary pathologic mechanism in Graves disease). Propylthiouracil also decreases the conversion of T₄ to the more potent T₃. However, the literature indicates a trend toward preoperative preparation with propranolol and iodides alone.79 This approach is quicker (i.e., 7 to 14 days versus 2 to 6 weeks); it shrinks the thyroid gland, as does the more traditional approach; it decreases conversion of the prohormone T₄ into the more potent T₃; and it treats symptoms but may not correct abnormalities in left ventricular function. Regardless of the approach, antithyroid drugs should be administered on a long-term basis and on the morning of the surgical procedure. If emergency surgery is necessary before the euthyroid state is achieved, if subclinical hyperthyroidism progresses without adequate treatment, or if hyperthyroidism is out of control intraoperatively, intravenous administration of esmolol, 50 to 500 μg/kg, could be titrated to restore a normal heart rate (assuming the absence of CHF) (see earlier). In addition, intravascular fluid volume and electrolyte balance should be restored. However, administering propranolol or esmolol does not invariably prevent “thyroid storm.”

No specific anesthetic drug is preferred for surgical patients who are hyperthyroid. Anticholinergic drugs (especially atropine) are sometimes not used because they interfere with the sweating mechanism and cause tachycardia; yet atropine has been given as a test for the adequacy of antithyroid treatment. Because patients are now subjected to operative procedures only (or almost only) when euthyroid, the traditional “steal” of a heavily premedicated hyperthyroid patient in the operating room has vanished.

A patient with a large goiter and an obstructed airway can be managed in the same way as any other patient with a problematic airway (see also Chapter 55). In this type of case, reviewing CT scans of the neck preoperatively may provide valuable information regarding the extent of compression. Maintenance of anesthesia usually presents little difficulty. Postoperatively, extubation of the trachea should be performed under optimal circumstances for reintubation in the event that the tracheal rings have been weakened and the tracheal collapses.

Of the many possible postoperative complications (nerve injury, bleeding, and metabolic abnormalities), thyroid storm (discussed in the next section), bilateral recurrent nerve trauma, and hypocalcemic tetany are the most feared. Bilateral recurrent laryngeal nerve injury (secondary to trauma or edema) causes stridor and laryngeal obstruction as a result of unopposed adduction of the vocal cords and closure of the glottic aperture. Immediate endotracheal intubation is required, usually followed by tracheostomy to ensure an adequate airway. This rare complication occurred only once in more than 30,000 thyroid operations at the Lahey Clinic. Unilateral recurrent nerve injury often goes unnoticed because of compensatory overadduction of the unaffected cord. However, we often test vocal cord function before and after this operation by asking the patient to say “e” or “moon.” Unilateral nerve injury is characterized by hoarseness and bilateral nerve injury by aphonia. Selective injury to the adductor fibers of both recurrent laryngeal nerves leaves the abductor muscles relatively unopposed, and pulmonary aspiration is a risk. Selective injury to the abductor fibers leaves the adductor muscles relatively unopposed, and airway obstruction can occur. Bullous glottic edema, an additional cause of postoperative respiratory compromise, has no specific cause or known preventive measure.

The intimate involvement of the parathyroid gland with the thyroid gland can result in inadvertent...
hypocalcemia during surgery for thyroid disease. Complications related to hypocalcemia are discussed in the later section on this disorder.

Because postoperative hematoma can compromise the airway, neck and wound dressings are placed in a crossing fashion (rather than vertically or horizontally) and should be examined for evidence of bleeding before a patient is discharged from the recovery room.

**Thyroid Storm**

Thyroid storm is the name for the clinical diagnosis of a life-threatening illness in a patient whose hyperthyroidism has been severely exacerbated by illness or surgery. Thyroid storm is characterized by hyperpyrexia, tachycardia, and striking alterations in consciousness. It clinically manifests in a manner similar to that of malignant hyperthermia, pheochromocytoma, and neuroleptic malignant syndrome. No laboratory tests are diagnostic of thyroid storm, and the precipitating (nonthyroidal) cause is the major determinant of survival. Therapy can include blocking the synthesis of thyroid hormones by administering antithyroid drugs and the release of preformed hormone with iodine. Blocking the sympathetic nervous system with reserpine, α- and β-receptor antagonists, or α2 drugs may be exceedingly hazardous and requires skillful management and constant monitoring of the critically ill patient.

Thyroid dysfunction, either hyperthyroidism or hypothyroidism, develops in more than 10% of patients treated with the antiarrhythmic agent amiodarone. Approximately 35% of the drug’s weight is iodine, and a 200-mg tablet releases approximately 20 times the optimal daily dose of iodine. This iodine can lead to reduced synthesis of T4 or increased synthesis. In addition, amiodarone inhibits the conversion of T4 to the more potent T3.

Patients receiving amiodarone may be considered to be in need of special attention preoperatively and intraoperatively, not just because of the arrhythmia that led to such therapy but also to ensure that no perioperative dysfunction or surprises result from unsuspected thyroid hyperfunction or hypofunction. Many patients with amiodarone-induced thyrotoxicosis receive steroids for a period, another area of questioning that may be triggered by the use of amiodarone in a preoperative patient.

**Hypothyroidism**

Hypothyroidism is a common disease that has been detected in 5% of a large population in Great Britain, in 3% to 6% of a healthy older population in Massachusetts, and in 4.5% of a medical clinic population in Switzerland. The apathy and lethargy that often accompany hypothyroidism frequently delay its diagnosis, so the perioperative period may be the first opportunity to spot many such hypothyroid patients. However, hypothyroidism is usually subclinical, serum concentrations of thyroid hormones are in the normal range, and only serum TSH levels are elevated. The normal range of TSH is 0.3 to 4.5 milliunits/L, and TSH values of 5 to 15 milliunits/L are characteristic of this entity. In such cases, hypothyroidism may have little or no perioperative significance. However, a retrospective study of 59 mildly hypothyroid patients found that more hypothyroid patients than control subjects required prolonged postoperative intubation (9 of 59 versus 4 of 59) and had significant electrolyte imbalances (3 of 59 versus 1 of 59) and bleeding complications (4 of 59 versus 0 of 59). Because only a few charts were examined, these differences did not reach statistical significance. In another study, overt hypothyroidism later developed in a high percentage of patients with a history of subclinical hypothyroidism. Thus, a previous history of subclinical hypothyroidism may be a clue to the possibility of overt hypothyroidism.

Overt hypothyroidism may cause slow mental functioning, slow movement, dry skin, arthralgias, carpal tunnel syndrome, periorbital edema, intolerance to cold, depression of the ventilatory responses to hypoxia and hypercapnia, impaired clearance of free water with or without hyponatremia, “hung-up reflexes,” slow gastric emptying, sleep apnea, and bradycardia. In extreme cases, cardiomegaly, heart failure, and pericardial and pleural effusions manifest as fatigue, dyspnea, and orthopnea. Hypothyroidism is often associated with amyloidosis, which may produce an enlarged tongue, abnormalities of the cardiac conduction system, and renal disease. Hypothyroidism decreases the anesthetic requirement slightly. The tongue may be enlarged in a hypothyroid patient even in the absence of amyloidosis, and such enlargement may hamper endotracheal intubation.

An increasing TSH level is the most sensitive indicator of failing thyroid function. Ideal preoperative and preprocedure management of hypothyroidism consists of restoring normal thyroid status: the physicians should consider administering the normal dose of levothyroxine the morning of the surgical procedure, even though these drugs have long half-lives (1.4 to 10 days). Reduced GI absorption of levothyroxine may occur with the coadministration of cholestyramine or aluminum hydroxide, iron, a high-bran meal, or sucralfate or colestipol. For patients in myxedema coma who require emergency surgery, liothyronine can be given intravenously (with fear of precipitating myocardial ischemia, however) while supportive therapy is undertaken to restore normal intravascular fluid volume, body temperature, cardiac function, respiratory function, and electrolyte balance.

In hypothyroidism, respiratory control mechanisms do not function normally. However, the response to hypoxia and hypercapnia and clearance of free water become normal with thyroid replacement therapy. Drug metabolism is anecdotally reported to be slowed, and awakening times from sedatives are reported to be prolonged by hypothyroidism. However, few formal studies and none in humans of the pharmacokinetics and pharmacodynamics of sedatives or anesthetic drugs have been published. These concerns disappear when thyroid function is normalized preoperatively. Addison disease (with its relative steroid deficiency) is more common in hypothyroidism, and some endocrinologists routinely treat patients with noniatrogenic hypothyroidism with stress doses of steroids perioperatively because both conditions are commonly caused by autoimmune responses. The possibility that this steroid deficiency exists should be considered if the patient becomes hypotensive perioperatively. Body heat mechanisms are inadequate in hypothyroid patients, so temperature should be monitored and
maintained, especially in patients requiring emergency surgery. Because of an increased incidence of myasthenia gravis in hypothyroid patients, it may be advisable to use a peripheral nerve stimulator to guide administration of muscle relaxants.

**Thyroid Nodules and Carcinoma**

More than 90% of thyroid nodules are benign, yet identifying malignancy in a solitary thyroid nodule is a difficult and important procedure. Male patients and patients with previous radiation therapy to the head and neck have an increased likelihood of malignant disease in their nodules. Often, needle biopsy and scanning are sufficient for the diagnosis, but occasionally excisional biopsy is needed. Papillary carcinoma accounts for more than 70% of all thyroid carcinomas. Simple excision of lymph node metastases appears to be as efficacious as radical neck procedures for the patient’s survival. Follicular carcinoma accounts for approximately 15% of thyroid carcinomas, is more aggressive, and has a less favorable prognosis.

Medullary carcinoma, the most aggressive form of thyroid carcinoma, is associated with a familial occurrence of pheochromocytoma, as are parathyroid adenomas. For this reason, a history may be obtained from patients who have a surgical scar in the thyroid region so that the possibility of occult pheochromocytoma can be excluded.

**DISORDERS OF CALCIUM METABOLISM**

The three substances that regulate serum concentrations of calcium, phosphorus, and magnesium—parathyroid hormone (parathyrin, PTH), calcitonin, and vitamin D—act on bone, kidney, gut, and their own receptors (the last has led to an important advance in treatment). Calcium excess in blood is caused by either malignant disease or hyperparathyroidism in more than 90% of patients.85 PTH stimulates bone resorption, inhibits renal excretion of calcium, and increases conversion to active vitamin D, three conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphates, and magnesium from the gut and facilitates the bone resorptive effects of PTH. Secretion of PTH is modulated through the calcium-sensing receptor on the cell surface of parathyroid cells. An increase in ionized calcium stimulates this receptor and thus causes a decrease in PTH secretion. Recognition of this effect has led to reevaluation of the therapy for hyperparathyroidism inasmuch as a drug up-regulating this receptor’s sensitivity reduces PTH levels.86

**Hyperparathyroidism and Hypercalcemia**

Primary hyperparathyroidism occurs in approximately 0.1% of the population, most commonly begins in the third to fifth decades of life, and occurs two to three times more frequently in women than in men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always develops.

Calcium is the chief mineral component of the body; it provides structure to the skeleton and performs key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1000 g of calcium present in the average human body is stored in the bone mineral reservoir. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories. Fifty percent to 60% is bound to plasma proteins or is complexed with phosphate or citrate. The value depends on the albumin level, with a decline of 0.8 mg/dL for each 1 g/dL drop in albumin. Binding of calcium to albumin depends on pH: binding decreases with acidic pH and increases with alkaline pH. Serum calcium, not ionized calcium, decreases with reductions in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, PTH and vitamin D3 work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent of which involve the renal, skeletal, neuromuscular, and GI systems—anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, formation of renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates or regulates muscle contraction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60% to 70% of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica, simple diffuse osteopenia, and osteoporosis. The rate of bone turnover is five times higher in patients with hyperparathyroidism than in normal controls. Patients may have a history of frequent fractures or may complain of bone pain, especially pain in the anterior margin of the tibia.

Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter signaling, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately one third of all hypercalcemic patients are hypertensive, but the hypertension usually resolves with successful treatment of the primary disease. Neither hypertension nor minimally invasive surgery seems to alter the perioperative risk associated with surgery in such patients in comparison with the usual hypertensive patients.87,88 Even octogenarians with asymptomatic hyperparathyroidism can be operated on without
mortality and with morbidity no different from that in younger individuals, thus encouraging the use of parathyroidectomy as preventive therapy. Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidneys. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.

The most useful confirmatory test for hyperparathyroidism is radioimmunoassay for PTH. In fact, two changes have radically reduced anesthesia involvement in the care of patients with primary hyperparathyroidism. One, use of the calcimimetic drug class, which modulates the calcium-sensitive PTH cell receptor and thereby decreases calcium levels, discussed earlier, has been emphasized in older individuals (see later). The other change is use of minimally invasive approaches after imaging procedures with just local anesthesia or a cervical plexus block—as with thyroidectomy. Most surgeons now performing minimally invasive parathyroid removal monitor PTH levels intraoperatively to determine whether the causative adenoma has been resected. The baseline PTH level should be determined before induction of anesthesia because even monitored anesthesia care increases PTH levels. In hyperparathyroid patients, hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase levels are elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in blood in many other conditions that cause hypercalcemia, but not usually in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower serum calcium levels through an effect on GI absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of decreased nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, and this causes the fraction of phosphate excreted by each nephron to increase. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands—one of the entities termed secondary hyperparathyroidism.

Symptomatic primary hyperparathyroidism in patients younger than 50 years or with serum calcium levels more than 1 mg/dL higher than the upper limit of normal, a greater than 30% or greater reduction in the glomerular filtration rate (GFR), or severe bone demineralization is usually treated surgically. If the patient refuses surgery or if other illnesses render surgery inadvisable, medical management with the calcimimetic cinacalcet makes management much more feasible. The difficulty with such management is that the hyperfunctioning parathyroid glands secrete more hormone as the serum calcium concentration is lowered—as though the calcium set point for feedback regulation of PTH secretion had been raised. Blanchard and colleagues demonstrated that patients with “asymptomatic” primary hyperparathyroidism have clinical improvement of their symptoms postoperatively even after 1 year. Younger patients and those with higher preoperative calcium levels show the best improvement.

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative and preprocedure problems. The ECG can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 39-3). Because severe hypercalcemia can result in hypovolemia, normal intravascular volume and electrolyte status should be restored before commencement of anesthesia and surgery.

Management of hypercalcemia preoperatively should include (even in urgent or emergency situations) treatment of the underlying cause—a frequent strategy in surgical patients with malignancy-associated hypercalcemia. Antitumor therapy preoperatively for both malignant and nonmalignant causes of hypercalcemia can include hydration and diuresis to increase urinary calcium excretion. Restoration of intravascular volume, augmentation and excretion of urinary sodium (with saline infusion), and administration of diuretics (furosemide is commonly used) generally increase urinary calcium excretion substantially. Infusion rates of 200 to 400 mL/hour preoperatively are commonly used, but monitoring is needed to avoid administration of an excessive amount of intravenous fluids, especially because many patients have compromised cardiac pumping ability. Other complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL); administration of furosemide is also often helpful in these situations. Phosphate should be given to correct hypophosphatemia because it decreases calcium uptake into bone, increases calcium excretion, and stimulates breakdown of bone. Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcemic patients. Other
measures to decrease reabsorption of bone include the bisphosphonates pamidronate sodium (90 mg intravenously) and zoledronate (4 mg intravenously), salmon calcitonin (100 to 400 units every 12 hours).

Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after intravenous administration. Side effects include urticaria and nausea. It is so rapid acting that it can be used to reduce calcium levels while waiting for hydration and a bisphosphate to take effect. Dialysis can also be used when appropriate.

It is especially important to know whether the hypocalcemia has been chronic because serious cardiac, renal, or CNS abnormalities may have resulted.

**Hypocalcemia**

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, hypovitaminosis D, hungry bones after correction of hyperparathyroidism, anticonvulsant therapy, citrate infusion, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. The most common cause of hypocalcemia is hypoalbuminemia. In true hypocalcemia (i.e., when the free calcium concentration is low), myocardial contractility varies directly with levels of blood ionized calcium, although contractility decreased only 20% when ionized calcium levels changed from 1.68 to 1.34 mmol/L. The clinical signs of hypocalcemia are as follows: clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesia (oral and perioral); parkinsonism; tetany; Chvostek sign; dry and scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trousseau sign.

Hypocalcemia delays ventricular repolarization, hence increasing the QTc interval (normal, 0.35 to 0.44 second). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, and a second-degree heart block results. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient.95 Thus, monitoring the QT interval as corrected for the heart rate is a useful, but not always accurate means of monitoring hypocalcemia in any individual patient (see Fig. 39-3). CHF may also occur with hypocalcemia, but this is rare. Because CHF in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels may be normalized preoperatively in a patient with impaired exercise tolerance. Normalization can be achieved intravenously over a 15-minute period if absolutely necessary. Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.

Patients with hypocalcemia may have seizures. They may be focal, Jacksonian, petit mal, or grand mal in appearance, indistinguishable from such seizures in the absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti–vitamin D effect).

In long-standing hypoparathyroidism, calcifications may appear above the sella; these calcifications represent deposits of calcium in and around small blood vessels of the basal ganglia. They may be associated with a variety of extrapyramidal syndromes.

The most common cause of acquired hypoparathyroidism is surgery of the thyroid or parathyroid glands. Other causes include autoimmune disorders, therapy with iodine-131, hemosiderosis or hemochromatosis, neoplasia, and granulomatous disease. Idiopathic hypoparathyroidism has been divided into three categories: an isolated persistent neonatal form, branchial dysgenesis, and autoimmune candidiasis related to multiple endocrine deficiencies.

Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH as a result of abnormalities in G-protein function.

Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for unrelated conditions. Their calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia may be treated with intravenous calcium gluconate preoperatively. Initially, 10 to 20 mL of 10% calcium gluconate may be given at a rate of 5 mL/minute. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/minute of 10% calcium gluconate in 500 mL of solution over a period of 6 hours helps keep serum calcium at adequate levels. Magnesium and phosphate levels may also require normalization to normalize cardiovascular and nervous system function.

The objective of therapy is to bring the symptoms under control before the surgical procedure and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative and preprocedure ECG is useful for maintaining the QTc interval. The preoperative and preprocedure QTc value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible. Changes in the calcium level may alter the duration of muscle relaxation, so such alterations may be monitored by using a twitch monitor in these (as well as all other) patients.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial in patients with advanced osteitis. Internal redistribution of magnesium, calcium, or both ions may occur (into “hungry bones”) after parathyroidectomy and may cause hypomagnesemia, hypocalcemia, or both conditions. Because the tendency to tetany increases with alkalosis, hyperventilation is usually...
assiduously avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for the Chvostek and Trousseau signs. (Serum calcium, not ionized calcium, depends on the albumin level, with a decline of approximately 0.8 mg/dL for each 1 g/dL drop in serum albumin level.) Because the Chvostek sign can be elicited in 10% to 15% of patients who are not hypocalcemic, an attempt should be made to elicit this sign preoperatively to ensure that its appearance is meaningful. The Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerve at the angle of the jaw. The Trousseau sign is elicited by applying a blood pressure cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contraction of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the blood pressure cuff.

**Osteoporosis**

Fifty percent of women who are older than 65 years sustain an osteoporotic fracture. (Because men are living longer, osteoporosis has become an increasing problem for them, too, and reports indicate a 15% per decade hip fracture rate for men >65 years old.95 Men with COPD (even without steroid treatment) are at high risk for vertebral fractures and thus may be allowed to position and move themselves onto and off surgical tables. Furthermore, in either gender, each vertebral fracture is associated with a 10% decrease in lung capacity. Diagnosis and treatment of these conditions have increased with routine use of dual-energy x-ray absorptiometry or quantitative ultrasonography. Because T-scores and Z-scores were developed to relate changes in white postmenopausal women to those at age 21 years, care must be used in interpreting the results. Known risk factors include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco use, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing exercise by itself, use of soft drinks, and Asian or white ancestry. Although therapy for osteoporosis (use of bisphosphates, bone mineral depositories, weight-bearing exercises, calcium, vitamin D, estrogen, and now designer estrogens that may be useful for men, such as raloxifene [Evista]) does not have major known implications for anesthesia care,96-98 bone fractures in such patients have occurred on movement to and from an operating table. Recombinant PTH and calcitonin are also used, but again, no reports of perioperative interactions have been prominent. Thus, the precautions mentioned earlier for hyperparathyroid patients relative to self-positioning and careful positioning may be useful.

**PITUITARY ABNORMALITIES**

**Anterior Pituitary Hypersecretion**

The anterior pituitary gland (or master endocrine gland) consists of five identifiable types of secretory cells (and the hormones that they secrete): somatotrophs (GH), corticotrophs (ACTH), lactotrophs (prolactin), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and thyrotrophs (TSH). Secretion of these pituitary hormones is largely regulated by a negative-feedback loop by hypothalamic regulatory hormones and by signals that originate from the target site of pituitary action. Six hypothalamic hormones have been characterized: dopamine, the prolactin-inhibiting hormone; somatostatin, the GH release-inhibiting hormone; GH-releasing hormone (GHRH); corticotropin-releasing hormone (CRH); gonadotropin-releasing hormone (GnRH or LHRH); and TRH. Most pituitary tumors (>60%) are hypersecretory and are classified according to the excess production of a specific anterior pituitary hormone.

The most common disorders of pituitary hypersecretion are those related to excesses of prolactin (amenorrhea, galactorrhea, and infertility), ACTH (Cushing syndrome), and GH (acromegaly). In addition to knowing the pathophysiologic processes of the disease involved, the anesthesiologist must determine whether the patient recently underwent air pneumoencephalography (almost obsolete, but still used rarely). If so, nitrous oxide should not be used to lessen the risk of intracranial hypertension from gas collection. CT or MRI of the sella has largely replaced neuroencephalography.

More than 99% of cases of acromegaly are attributable to pituitary adenoma (or use of recombinant GH for unapproved aging prevention, for which this substance is not effective, as of current data). Thus, the primary treatment of acromegaly is transsphenoidal surgery (or withdrawal of drug) and symptomatic treatment of the carpal tunnel or other syndromes provoked. If the pituitary tumor is not totally removed, patients are often offered external pituitary irradiation. In the case of suprasellar extension, conventional transfrontal hypophysectomy is often performed. The dopaminergic agonist bromocriptine can lower GH levels, but the long-term follow-up with this drug is not favorable. Octreotide, a long-acting analogue of somatostatin, now given in depot form approximately once a month, produces effective palliation in 50% of patients. Other medical therapies such as pegvisomant or somatostatin analogues are also medications that have been tried before surgical intervention. In 2011, new guidelines were published with few changes to the available recommendations.99 However, the new guidelines reported some evidence that medication taken preoperatively may result in a better postoperative outcome.

Difficulty with endotracheal intubation should be anticipated in a patient with acromegaly; lateral neck radiographs or CT scans of the neck and direct or indirect visualization can identify patients with subglottic stenosis or an enlarged tongue, mandible, epiglottis, or vocal cords. If placement of an arterial line is necessary, a brachial or femoral site may be preferable to a radial site.100
Anterior Pituitary Hypofunction

Anterior pituitary hypofunction results in deficiency of one or more of the following hormones: GH, TSH, ACTH, prolactin, or gonadotropin. No special preoperative and preprocedure preparation is required for a patient deficient in prolactin or gonadotropin; deficiency in GH, however, can result in atrophy of cardiac muscle, a condition that may necessitate preoperative and preprocedure cardiac evaluation. Nonetheless, anesthetic problems have not been documented in patients with isolated GH deficiency. Acute deficiencies are another matter.

Acute pituitary deficiency is often caused by bleeding into a pituitary tumor. In surgical specimens of resected adenomas, as many as 25% show evidence of hemorrhage. These patients often have acute headache, visual loss, nausea or vomiting, ocular palsy, disturbances of consciousness, fever, vertigo, or hemiparesis. In such patients, rapid transsphenoidal decompression should be accompanied by consideration of replacement therapy, including glucocorticoids, and treatment of increased intracranial pressure.

Obstetric anesthesiologists are often aware of these pituitary failure problems (see also Chapter 77); Sheehan syndrome is the clinical manifestation of pituitary infarction associated with hypotension after or during obstetric hemorrhage. Conditions that strongly suggest this diagnosis are failure to start postpartum lactation, increasing fatigue, cold intolerance, and especially hypotension unresponsive to volume replacement and pressors.

Posterior Pituitary Hormone Excess and Deficiency

Secretion of vasopressin or antidiuretic hormone (ADH) is enhanced by increased serum osmolality or the presence of hypotension. Inappropriate secretion of vasopressin, without relation to serum osmolality, results in hyponatremia and fluid retention. This inappropriate secretion can result from the following: a variety of CNS lesions; drugs such as nicotine, narcotics, chlorpropamide, clofibrate, vincristine, vinblastine, and cyclophosphamide; and pulmonary infections, hypothyroidism, adrenal insufficiency, and ectopic production from tumors. Preoperative and preprocedure management of a surgical patient with inappropriate secretion of vasopressin includes appropriate treatment of the causative disorders and restriction of water. Occasionally, drugs that inhibit the renal response to ADH (e.g., lithium or demeclocycline) should be administered preoperatively to restore normal intravascular volume and electrolyte status.

Most of the clinical features associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are related to hyponatremia and the resulting brain edema; such features include weight gain, weakness, lethargy, mental confusion, obtundation, and disordered reflexes and may culminate in convulsions and coma. This form of edema rarely leads to hypertension.

Investigators have recognized that 10% to 20% of long-distance and marathon runners have SIADH with increased vasopressin secretion. Because such people not infrequently undergo surgical treatment of injuries, SIADH symptoms and laboratory evaluation may be routine for that group as well.

SIADH should be suspected in any patient with hyponatremia who excretes urine that is hypertonic relative to plasma. The following laboratory findings further support the diagnosis:

1. Urinary sodium greater than 20 mEq/L
2. Low serum levels of BUN, creatinine, uric acid, and albumin
3. Serum sodium lower than 130 mEq/L
4. Plasma osmolality lower than 270 mOsm/L
5. Urine hypertonic relative to plasma

Noting the response to water loading is a useful way of evaluating patients with hyponatremia. Patients with SIADH are unable to excrete dilute urine even after water loading. Assay of ADH in blood can confirm the diagnosis. Too vigorous treatment of chronic hyponatremia can result in disabling demyelination.

Patients with mild to moderate symptoms of water intoxication can be treated with restriction of fluid intake to approximately 500 to 1000 mL/day. Patients with severe water intoxication and CNS symptoms may need vigorous treatment consisting of intravenous administration of 200 to 300 mL of a 5% saline solution over a period of several hours, followed by fluid restriction.

Treatment should be directed at the underlying problem. If SIADH is drug induced, use of the drug should be withdrawn. Inflammation should be treated with appropriate measures, and neoplasms should be managed by surgical resection, irradiation, or chemotherapy, whichever is indicated.

No drugs are available that can suppress release of ADH from the neurohypophysis or from a tumor. Phenytoin (Dilantin) and narcotic antagonists such as naloxone and butorphanol have some inhibiting effect on physiologic ADH release but are clinically ineffective in patients with SIADH. Drugs that block the effect of ADH on renal tubules include lithium, which is rarely used because of its toxicity often outweighs its benefits, and demethylchlorotetracycline in doses of 900 to 1200 mg/day. Demethylchlorotetracycline interferes with the ability of the renal tubules to concentrate urine, thereby causing excretion of isotonic or hypotonic urine and lessening the hyponatremia. This drug can be used in ambulatory patients with SIADH when it is difficult to restrict fluids.

When a patient with SIADH comes to the operating room for any surgical procedure, fluids are managed by measuring central volume status by CVP, pulmonary artery lines, or the cross-sectional left ventricular area at end-diastole on transesophageal echocardiography and by frequent assays of urine osmolality, plasma osmolality, and serum sodium, including the period immediately after the surgical procedure. Despite the common impression that SIADH is frequently seen in older patients in the postoperative period, studies have shown that the patient’s age and the type of anesthetic used have no bearing on the postoperative development of SIADH. It
is not unusual to see several patients in the neurosurgical ICU suffering from this syndrome. The diagnosis is usually one of exclusion. Patients with SIADH generally require only restriction of intravenous fluids; very rarely is hypertonic saline needed.

Lack of ADH, which results in diabetes insipidus, is caused by pituitary disease, brain tumors, infiltrative diseases such as sarcoidosis, head trauma (including trauma after neurosurgery), or lack of a renal response to ADH. The last can result from such diverse conditions as hypokalemia, hypercalcemia, sickle cell anemia, obstructive uropathy, and renal insufficiency. Preoperative or preprocedure treatment of diabetes insipidus consists of restoring normal intravascular volume by replacing urinary losses, administering desmopressin acetate (DDAVP) nasally, and giving daily fluid requirements intravenously.

Perioperative management of patients with diabetes insipidus is based on the extent of the ADH deficiency. Management of a patient with complete diabetes insipidus and a total lack of ADH does not usually present any major problem as long as the side effects of the drug are avoided and the presence of the condition is known preoperatively. Just before the surgical procedure, the patient is given the usual dose of DDAVP intranasally or an intravenous bolus of 100 milliunits of aqueous vasopressin, followed by a constant infusion of 100 to 200 milliunits/hour. The dose is usually adjusted to permit the daily breakthrough polyuria that prevents the iatrogenic syndrome of SIADH. All the intravenous fluids given intraoperatively should be isotonic to reduce the risk of water depletion and hyponatremia. Plasma osmolality should be measured every hour, both intraoperatively and immediately postoperatively. If plasma osmolality rises much higher than 290 mOsm/L, hypotonic fluids can be administered; the rate of the intraoperative vasopressin infusion can be increased to greater than 200 milliunits/hour.

For patients who have a partial deficiency of ADH, it is not necessary to use aqueous vasopressin perioperatively unless plasma osmolality rises to more than 290 mOsm/L. Nonosmotic stimuli (e.g., volume depletion) and the stress of surgery usually cause the release of large quantities of ADH perioperatively. Consequently, these patients require only frequent monitoring of plasma osmolality during this period.

Because of side effects, the dose of vasopressin should be limited to that necessary for control of diuresis. The oxytocic and coronary artery-constricting properties of vasopressin make this limit especially applicable to patients who are pregnant or have CAD.

### Diseases Involving the Cardiovascular System

#### Hypertension

Analysis of the perioperative treatment of hypertension is important because of the prevalence of the condition (30% of the general population in the United States), the great risk in perioperative care of a hypertensive patient, and the high cost of unnecessary delays in surgical treatment. Numerous studies over the years have evaluated the impact of hypertension as one of the risk factors for cardiac morbidity. More recently, the need to delay surgery because of poorly controlled hypertension has been questioned. Weksler and colleagues studied 989 hypertensive patients who were treated on a long-term basis and who underwent noncardiac surgery with diastolic blood pressure between 110 and 130 mm Hg and no previous myocardial infarction (MI), unstable or severe angina pectoris, renal failure, pregnancy-induced hypertension, left ventricular hypertrophy, previous coronary revascularization, aortic stenosis, preoperative dysrhythmias, conduction defects, or stroke. The control group had their surgical procedures postponed and remained in the hospital for control of blood pressure, and the study patients received 10 mg of nifedipine intranasally. No statistically significant differences in postoperative complications were observed, thus suggesting that this subset of patients without significant cardiovascular comorbid conditions can proceed with surgery despite elevated blood pressure on the day of the operation.

Several studies have assessed the relationship between cardiovascular disease and preoperative hypertension. In a multicenter study of patients undergoing coronary artery bypass graft (CABG), the presence of isolated systolic hypertension was associated with a 30% increased incidence of perioperative cardiovascular complications when compared with normotensive individuals. Kheterpal and colleagues integrated data from their anesthesia information system (AIMS) and the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) and found hypertension to be one of the independent predictors of events. Wax and colleagues used their AIMS to identify independent predictors of troponin elevation or death, and independent predictors of adverse outcome included increased baseline systolic blood pressure, intraoperative diastolic blood pressure lower than 85 mm Hg, increased intraoperative heart rate, blood transfusion, and anesthetic technique, controlling for standard risk factors. A delay of surgery did not result in interval normalization of blood pressure.

Although preoperative blood pressure (both systolic and diastolic) is a significant predictor of postoperative morbidity, no data definitively establish whether preoperative treatment of hypertension reduces perioperative risk. Until a definitive study is performed, we recommend letting the weight of evidence guide preoperative treatment of a patient with hypertension. Such treatment would be based on three general beliefs: (1) the patient should be educated regarding the importance of lifelong treatment of hypertension, even isolated systolic hypertension; (2) perioperative hemodynamic fluctuations occur less frequently in treated than in untreated hypertensive patients (as demonstrated by Prys-Roberts and colleagues and confirmed by Goldman and Caldera and Mangano and associates); and (3) hemodynamic fluctuations have some relation to morbidity. Kheterpal and colleagues demonstrated that patients who sustained a cardiac adverse event were more likely to experience an episode of mean arterial pressure lower than 50 mm Hg,
an episode of 40% decrease in mean arterial pressure, and an episode of heart rate higher than 100 beats/minute.105 The data of Pasternack and colleagues and Weksler and associates imply that rapid correction of blood pressure or prevention of increases in heart rate may be all that is needed.105,110 Taken together, these data suggest that maintenance of normal blood pressure is critical in patients with hypertension.

Preoperative data should be used to determine the individualized range of suitable arterial blood pressure values that are tolerable by a particular patient during and after a surgical procedure. That is, if blood pressure is 180/100 mm Hg and the heart rate is 96 beats/minute on admission with no signs or symptoms of myocardial ischemia, these levels can likely be tolerated during a surgical procedure. Conversely, if during the night blood pressure decreases to 80/50 mm Hg and the heart rate to 48 beats/minute and a new cerebral deficit does not occur, the patient can probably safely tolerate such levels during anesthesia. Therefore, on the basis of preoperative data, we derive an individualized set of values for each patient. However, hypotension in patients at risk for a cerebrovascular event should be avoided. For example, the POISE (Perioperative Ischemic Evaluation) study demonstrated that short-term β-blocker administration resulted in an increased incidence of stroke and death that was associated with an increased rate of hypotension.111

Preoperative Administration of All Antihypertensive Drugs

Continuation of all antihypertensive drugs preoperatively should be considered, except ACE inhibitors or angiotensin II antagonists, for which no clear consensus exists. Coriat and colleagues found that ACE inhibitors were associated with hypotension in 100% of patients during induction versus approximately 20% in whom ACE inhibitors were withheld on the morning of the surgical procedure.112 Bertrand and co-workers performed a prospective randomized study that demonstrated that more severe hypotensive episodes requiring vasoconstrictor treatment occurred after induction of general anesthesia in patients treated on a long-term basis with an angiotensin II antagonist and receiving the drug on the morning before the operation than in those in whom angiotensin II antagonists were discontinued on the day before the surgical procedure.113 Khetarpal and colleagues performed a propensity-matched analysis of 12,381 noncardiac surgical cases.114 Patients with long-term ACE inhibitor or angiotensin receptor blocker and diuretic therapy showed more periods with a mean arterial blood pressure lower than 70 mm Hg, periods with a 40% decrease in systolic blood pressure, periods with a 50% decrease in systolic blood pressure, and vasopressor boluses than did patients receiving diuretic therapy alone. If these drugs are continued, vasopressin is the drug of choice for refractory hypotension. Investigators at the Cleveland Clinic evaluated 79,228 patients (9905 ACE inhibitor users [13%] and 66,620 [87%] non–ACE inhibitor users) who had noncardiac surgery between 2005 and 2009.115 These investigators did not find any association between use of ACE inhibitors and intraoperative or postoperative upper airway complications. ACE inhibitor use was not associated with in-hospital complications or increased 30-day mortality.

ISCHEMIC HEART DISEASE

Preoperative evaluation of a patient with ischemic heart disease (see also Chapter 67) and a discussion of the AHA/ACC guidelines can be found in Chapter 38.116 New guidelines were published in 2014 by both the AHA/ACC and the European Society of Cardiology.116a,166b

Role of Coronary Artery Bypass Graft or Percutaneous Coronary Interventions Before Noncardiac Surgical Procedures

Coronary revascularization may reduce the perioperative risk before noncardiac surgery (see also Chapter 67). Earlier successful preoperative revascularization may decrease postoperative cardiac risk twofold to fourfold in patients undergoing elective vascular surgery.117,118 The strongest retrospective evidence comes from the Coronary Artery Surgery Study (CASS) registry, which enrolled patients from 1978 to 1981. Operative mortality in patients with CABG performed before noncardiac surgery was 0.9% but was significantly higher at 2.4% in patients without previous CABG. However, a 1.4% mortality rate was associated with the CABG procedure itself.

Eagle and colleagues reported on a long-term analysis of patients entered into the CASS.119 These investigators studied patients assigned to medical or surgical therapy for CAD for more than 10 years who subsequently underwent 3368 noncardiac operations in the years after assignment of coronary treatment. Intermediate-risk surgery such as abdominal, thoracic, or carotid endarterectomy were associated with a combined morbidity and mortality rate of 1% to 5% and a small but significant improvement in outcome in patients who had previously undergone revascularization. The most significant improvement in outcome occurred in patients who underwent major vascular surgery such as abdominal or lower extremity revascularization. However, this observational study did not randomize patients and was undertaken in the 1970s and 1980s, before significant advances in medical, surgical, and percutaneous coronary strategies.119

Landesberg and coauthors retrospectively reviewed long-term outcomes in 578 major vascular procedures.120 By multivariate analysis, age, type of vascular surgery, presence of diabetes, previous MI, and moderate to severe ischemia on preoperative thallium scanning independently predicted mortality, and preoperative coronary revascularization predicted improved survival. Long-term survival after major vascular surgery was significantly improved if patients with moderate to severe ischemia on preoperative thallium scanning underwent selective coronary revascularization.

The benefit of percutaneous coronary intervention (PCI) before noncardiac surgery has also been examined in several cohort studies. Posner and colleagues used an administrative data set of patients who underwent PCI and noncardiac surgery in Washington State.121 These
investigators matched patients with coronary disease who were undergoing noncardiac surgery with and without previous PCI and looked at cardiac complications. In this nonrandomized design, Posner and colleagues noted a significantly lower rate of 30-day cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. However, PCI within 90 days of noncardiac surgery did not improve outcome. Although the explanation for these results is unknown, they may support the notion that PCI performed “to get the patient through surgery” may not improve perioperative outcome because cardiac complications may not occur in patients with stable or asymptomatic coronary stenosis. PCI may actually destabilize coronary plaque, which becomes manifest in the days or weeks after noncardiac surgery.

Godet and associates studied a cohort of 1152 patients after abdominal aortic surgery in which 78 patients underwent PCI. In the PCI group, the observed percentages of patients with a severe postoperative coronary event (9.0%; 95% confidence interval [CI], 4.4 to 17.4) or death (5.1% [95% CI, 2.0 to 12.5]) were not significantly different from the expected percentages (8.2% and 6.9%, respectively), which was confirmed by propensity analysis. PCI did not seem to significantly limit cardiac risk or death after aortic surgery.

Several randomized trials have addressed the value of testing and CABG or PCI, or both, in a subset of patients. McFalls and colleagues reported the results of a multicenter randomized trial in the VA Health System in which patients with documented CAD on coronary angiography, excluding those with left main CAD or a severely depressed ejection fraction (<20%), were ran- 

prior (CABG >1 year and ≤5 years; PTCA >6 months and ≤2 years) in 45 cases (9%), and remote (CABG ≥5 years; PTCA ≥2 years) in 48 cases (10%). Outcomes in patients with previous PTCA were similar to those after CABG (P = .7). Significant differences in adverse cardiac events and mortality were found among patients with CABG performed within 5 years or PTCA within 2 years (6.3%, 1.3%, respectively), individuals with remote revascularization (10.4%, 6.3%), and nonrevascularized patients stratified at high risk (13.3%, 3.3%) or intermediate/low risk (2.8%, 0.9%). The authors concluded that previous coronary revascularization (CABG <5 years; PTCA <2 years) may provide only modest protection against adverse cardiac events and mortality after major arterial reconstruction.

PCI using coronary stenting poses several special issues. Kaluza and associates reported on the outcome of 40 patients who underwent prophylactic coronary stent placement less than 6 weeks before major noncardiac surgery requiring general anesthesia. Among these patients, 7 MIs, 11 major bleeding episodes, and 8 deaths were noted. All deaths and MIs, as well as 8 of the 11 bleeding episodes, occurred in patients subjected to surgical procedures less than 14 days after stenting. Four patients died after undergoing surgical procedures 1 day after stenting. Wilson and colleagues reported on 207 patients who underwent noncardiac surgery within 2 months of stent placement. Eight patients died or suffered an MI, all of whom were among the 168 patients who had surgical procedures 6 weeks after stent placement. Vicenzi and co-workers studied 103 patients and reported that the risk of suffering a perioperative cardiac event was 2.11-fold greater in patients with recent stents (<35 days before surgery) than in those who underwent PCI more than 90 days before surgical procedures. Leibowitz and associates studied a total of 216 consecutive patients who underwent PCI within 3 months of noncardiac surgery (PTCA, 122; stent, 94). A total of 26 patients (12%) died, 13 in the stent group (14%) and 13 in the PTCA group (11%), a nonsignificant difference. The incidence of acute MI and death within 6 months was not significantly different (7% and 14% in the stent group and 6% and 11% in the PTCA group, respectively). Significantly more events occurred in the 2 groups when noncardiac surgery was performed within 2 weeks of PCI. Based on the accumulating data, elective noncardiac surgery after PCI, with or without stent placement, should be delayed for 4 to 6 weeks.

Drug-eluting stents may represent an even greater problem during the perioperative period based on case reports. Nasser and coauthors described two patients with in-stent thrombosis occurring 4 and 21 months after the implantation of sirolimus-eluting stents. Drug-eluting stents may represent an additional risk over a prolonged period (≤12 months), particularly if antiplatelet drugs are discontinued. One study demonstrated that although the frequency of major noncardiac surgery in the year after drug-eluting stent placement was more than 4%, the overall risk of adverse outcomes was less than previously reported when surgical procedures were performed months after drug-eluting stent placement. However, the risk was significantly increased in the week after major noncardiac surgery. A population-based study in Canada using administrative health care databases demonstrated that the earliest optimal time for elective surgery is 46 to 180 days after bare metal stent implantation or more than 180 days after drug-eluting stent implantation. Hawn and colleagues used a national, retrospective cohort study of 41,989 VA and non-VA operations occurring in the 24 months after coronary stent implantation between 2000 and 2010. Among patients undergoing noncardiac surgery within 2 years of coronary stent placement, major adverse cardiac events were associated with emergency surgery and advanced cardiac disease but not stent type or timing of surgery beyond 6 months after stent implantation (Fig. 39-5).

**Perioperative Risk Factors for Cardiac Morbidity and Mortality**

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states, such as myocardial ischemia with minimal exertion, active CHF, symptomatic valvular heart disease, and significant cardiac arrhythmias. The presence of unstable angina is associated with a 28% incidence of perioperative MI. Such patients would benefit from delaying elective surgery to address their CAD. For those patients with chronic stable angina, exercise tolerance appears to be a good method of assessing perioperative risk.

In virtually all studies, the presence of active CHF has been associated with increased perioperative cardiac morbidity. In addition, multiple studies have demonstrated that reduced ejection fraction is associated with an increased incidence of perioperative cardiac events. Flu and colleagues performed echocardiography in patients undergoing vascular surgery and found that for open surgical procedures, asymptomatic systolic left ventricular dysfunction and asymptomatic diastolic left ventricular dysfunction were both associated with increased 30-day cardiovascular event rates (OR, 2.3; 95% CI, 1.4 to 3.6; and OR, 1.8; 95% CI 1.1 to 2.9, respectively) and long-term cardiovascular mortality (hazard ratio, 4.6; 95% CI 2.4 to 8.5; and hazard ratio, 3.0; 95% CI 1.5 to 6.0, respectively). In patients undergoing endovascular surgery (n = 356), only symptomatic heart failure was associated with an increase in 30-day cardiovascular events and long-term cardiovascular mortality. These results suggest that stabilization of ventricular function and treatment of pulmonary congestion is prudent before elective surgery.

A recent MI has traditionally been an important predictor of perioperative risk. The more recent the MI, particularly within 3 to 6 months, the greater is the perioperative risk. However, like the Goldman Cardiac Risk Index, medicine has changed and outcomes are improved. The classic article by Rao and associates that was published in 1983 cited a reinfarction rate of nearly 30% if noncardiac surgery occurred within 3 months of a prior infarction. These reinfarctions had a very high mortality rate. With the advent of dedicated postoperative ICUs, more vigilant monitoring, and early intervention, the postoperative reinfarction rate has decreased by almost an order of magnitude. The 2014 AHA/ACC Foundation (AHA/ACCF) guidelines advocate the use of 60 days as being high risk. After that time, further risk stratification depends on clinical symptoms.
For those patients without overt symptoms or a history of CAD, the probability of CAD varies with the type and number of atherosclerotic risk factors present. Diabetes accelerates the progression of atherosclerosis, which can frequently be silent, leading many clinicians to assume that diabetes is a CAD equivalent and treating patients as such. Diabetes is an independent risk factor for perioperative cardiac morbidity, and the preoperative treatment with insulin has been included in the Revised Cardiac Risk Index (RCRI). In attempting to determine the degree of the increased risk associated with diabetes, the treatment modality, duration of the disease, and other associated end-organ dysfunction should be taken into account.

Significant intraoperative factors that correlate with perioperative risk and that may be avoided or altered are (1) unnecessary use of vasopressors, (2) unintentional hypotension (this point is controversial, however, because some investigators have found that unintentional hypotension does not correlate with perioperative morbidity), (3) hypothermia, (4) too low or too high a hematocrit, and (5) lengthy operations.

Significant intraoperative factors that correlate with perioperative morbidity and probably cannot be avoided are (1) emergency surgery and (2) thoracic or intraperitoneal surgery or above-the-knee amputations.

Several risk indices were developed in a prospective cohort study by Lee and associates. They studied 4315 patients 50 years old or older who were undergoing elective major noncardiac procedures in a tertiary care teaching hospital. The 6 independent predictors of complications included in a RCRI were high-risk type of surgery, history of ischemic heart disease, history of CHF, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine greater than 2.0 mg/dL; increasing cardiac complication rates were noted with an increasing number of risk factors. The RCRI has become the standard tool in the literature for assessing perioperative cardiac risk in a given individual and has been used to direct the decision to perform cardiovascular testing and implement perioperative management protocols. It has been validated for both short-term and long-term cardiovascular outcomes. It has also been shown to predict long-term quality of life. Therefore, the RCRI can be used to help define both the short-term and long-term risks of cardiovascular disease in the surgical patient.

The American College of Surgeons NSQIP created a Surgical Risk Calculator from 525 participating hospitals.

and more than 1 million operations.\textsuperscript{167} This risk calculator uses the specific current procedural terminology code of the procedure being performed to enable procedure-specific risk assessment and includes 21 patient-specific variables (e.g., age, sex, body mass index, dyspnea, previous MI). From this input, it calculates the percentage of risk of a major adverse cardiac event, death, and 8 other outcomes. Use of this risk calculator may offer the best estimation for surgery-specific risk of a major adverse cardiac event and death.

The American College of Surgeons NSQIP Myocardial Infarction and Cardiac Arrest (MICA) risk prediction rule is more specific for cardiac complications.\textsuperscript{168} Using these definitions of outcome and chart-based data collection methods, the authors derived a risk index that was robust in the derivation and validation stages and appeared to outperform the RCRI (which was tested in the same data set) in terms of discriminative power, particularly among patients undergoing vascular surgery.

A primary issue with all these indices is that a simple estimate of risk does not help in refining perioperative management for an individual patient. Therefore, the consultant must communicate the extent and stability of the patient’s CAD, rather than make a simple statement of risk classification.

The goal in providing anesthesia to patients with ischemic heart disease is to achieve the best preoperative condition obtainable by treating conditions that correlate with perioperative risk. The next step is to intraoperatively monitor for conditions that correlate with perioperative risk and avoid circumstances that lead to perioperative risk.

### Preoperative and Preprocedure Therapy

The only way known to increase oxygen supply to the myocardium of patients with coronary artery stenosis is to maintain adequate diastolic blood pressure, hemoglobin concentration, and oxygen saturation (see also Chapter 38). The main goals of anesthesia practice for these patients have been to decrease the determinants of myocardial oxygen demand, heart rate, ventricular wall tension, and contractile performance and to improve plaque stabilization. Thus, medical management designed to preserve all viable myocardial tissue may include the following:

1. Continuation of β-adrenergic receptor blocking drugs (propranolol, atenolol, esmolol, or metoprolol) to avoid β-blocker withdrawal leading to increased contractility and heart rate. Multiple studies have demonstrated improved outcome in patients given perioperative β-adrenergic blockers, especially if the heart rate is controlled.\textsuperscript{169,170} However, newer studies have demonstrated that β-adrenergic blockers may not be effective if the heart rate is not well controlled or in lower-risk patients.\textsuperscript{171-173} The POISE trial enrolled 8351 high-risk β-blocker–naïve patients who were randomized to high-dose continuous-release metoprolol versus placebo.\textsuperscript{111} A significant reduction in the primary outcome of cardiovascular events was reported, along with a 30% reduction in the MI rate, but with a significantly increased rate of 30-day all-cause mortality and stroke. The current ACC/AHA guidelines on perioperative β-blockade advocate that perioperative β-blockade is a class I indication and should be used in patients previously taking β-blockers and those with a positive stress test who are undergoing major vascular surgery, although short-term administration without titration may be associated with harm (Box 39-3).

2. Vasodilation (with nitroglycerin or its “long-acting” analogues nitroprusside, hydralazine, or prazosin) to decrease ventricular wall tension may be beneficial, although currently no randomized trials support the prophylactic use of these agents.\textsuperscript{109,110,174} The use of Swan-Ganz catheters and transesophageal echocardiography for this type of patient is described in Chapter 45.\textsuperscript{159,175} and the intraoperative management of patients with ischemic heart disease is discussed in further detail in Chapter 67 and in published guidelines.\textsuperscript{116}

3. Aspirin, statins, exercise, and diet. These choices seem to be indicated in many patients. Briefly, we believe that drugs given on a long-term basis (e.g., antihypertensive medications and some ACE inhibitors) should be continued through the morning of the surgical procedure (see earlier). The topic of long-term drug

---

**BOX 39-3** 2014 ACC/AHA Recommendations for Perioperative β-Blockade

<table>
<thead>
<tr>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>- β-Blockers should be continued in patients undergoing surgery who have been on β-blockers chronically.\textsuperscript{111-117} (Level of Evidence: B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>- It is reasonable for the management of β-blockers after surgery to be guided by clinical circumstances, independent of when the agent was started.\textsuperscript{110,117,118} (Level of Evidence: B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>- In patients with three or more RCRI risk factors (e.g., diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, cerebrovascular accident), it may be reasonable to begin β-blockers before surgery.\textsuperscript{117} (Level of Evidence: B)</td>
</tr>
<tr>
<td>- In patients with a compelling long-term indication for β-blocker therapy but no other RCRI risk factors, initiating beta blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit.\textsuperscript{111,117,120} (Level of Evidence: B)</td>
</tr>
<tr>
<td>- In patients in whom β-blocker therapy is initiated, it may be reasonable to begin perioperative β-blockers long enough in advance to assess safety and tolerability, preferably more than 1 day before surgery.\textsuperscript{116,121-123} (Level of Evidence: B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class III: Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>- β-Blocker therapy should not be started on the day of surgery.\textsuperscript{118} (Level of Evidence: B)</td>
</tr>
</tbody>
</table>

therapy is discussed in more detail in the last section of this chapter, on drug therapy.

4. Perioperative transfusion therapy is discussed in more detail in Chapter 61. The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Repair of Hip Fracture) trial was unable to demonstrate benefit in high-risk patients with hip fracture between a high and low transfusion trigger.176

**VALVULAR HEART DISEASE**

Major alterations in the preoperative management of patients with valvular heart disease have been made regarding the use of anticoagulant therapy and are now based on the causes of the disease. Preoperative and intraoperative management of patients with valvular heart disease is discussed in Chapters 38 and 67.

The prognosis and, presumably, the perioperative risk for patients with valvular heart disease depend on the stage of the disease. Although stenotic lesions progress faster than do regurgitant lesions, regurgitant lesions secondary to infective endocarditis, rupture of the chordae tendineae, or ischemic heart disease can be rapidly fatal. Left ventricular dysfunction is common in the late stage of valvular heart disease.

Preoperative maintenance of drug therapy can be crucial; for example, the condition of a patient with aortic stenosis can deteriorate rapidly with the onset of atrial fibrillation or flutter because the atrial contribution to left ventricular filling can be critical in maintaining cardiac output. One of the most serious complications of valvular heart surgery and of preoperative valvular heart disease is cardiac arrhythmia. Conduction disorders and long-term therapy with antiarrhythmic and inotropic drugs are discussed elsewhere in this chapter.

The reader is referred to Chapter 94 and to other sources for discussion of the management of a child with congenital heart disease who is undergoing noncardiac surgery.177

**Preoperative Antibiotic Prophylaxis for Endocarditis**

Patients who have any form of valvular heart disease, as well as those with intracardiac (ventricular septal or atrial septal defects) or intravascular shunts, should be protected against endocarditis at the time of a known bacteremic event. Endocarditis has occurred in a sufficiently significant number of patients with hypertrophic cardiomyopathy (subvalvular aortic stenosis, asymmetric septal hypertrophy) and mitral valve prolapse to warrant the inclusion of these two conditions in the prophylaxis regimen.

Bacteremia occurs after the following events: dental extraction, 30% to 80%; brushing of teeth, 20% to 24%; use of oral irrigation devices, 20% to 24%; barium enema, 11%; transurethral resection of the prostate (TURP), 10% to 57%; upper GI endoscopy, 8%; nasotracheal intubation, 16% (4 of 25 patients); and orotracheal intubation, 0% (0 of 25 patients). The most recent guidelines from the AHA consisted of an update in 2008 from the AHA/ACC on endocarditis in patients with valvular heart disease, with changes from the 2006 document shown in Table 39-7.178

**Cardiac Valve Prostheses and Anticoagulant Therapy and Prophylaxis for Deep Vein Thrombosis**

In patients with prosthetic valves, the risk of increased bleeding during a procedure in a patient receiving antithrombotic therapy must be weighed against the increased risk of thromboembolism caused by stopping the therapy. Common practice in patients undergoing noncardiac surgery with a mechanical prosthetic valve in place is cessation of anticoagulant therapy 3 days preoperatively. This time frame allows the international normalized ratio to fall to less than 1.5 times normal. The oral anticoagulants can then be resumed on postoperative day 1. Using a similar protocol, Katholi and colleagues found no perioperative episodes of thromboembolism or hemorrhage in 25 patients.179 An alternative approach in patients at high risk for thromboembolism is conversion to heparin during the perioperative period. The heparin can then be discontinued 4 to 6 hours preoperatively and resumed shortly thereafter. Current prosthetic valves may have a lower incidence of this complication, and the risk associated with heparin may outweigh its benefit in the perioperative setting. According to the AHA/ACC guidelines, heparin can usually be reserved for patients who have had a recent thrombus or embolus (arbitrarily within 1 year), those with demonstrated thrombotic problems when previously off therapy, those with a Björk-Shiley valve, and those with more than three risk factors (atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis).180 A lower threshold for recommending heparin should be considered in patients with mechanical valves in the mitral position, in whom a single risk factor would be sufficient evidence of high risk. Subcutaneous low-molecular-weight heparin offers an alternative outpatient approach.181 It is appropriate for the surgeon and cardiologist to discuss the optimal perioperative management for such a patient, including a review of the most recent guidelines.182 A new guideline publication was published in 2014.182a

Regional anesthetic techniques may be avoided, although this issue is controversial.183 Many practitioners do not hesitate to use regional anesthesia in patients who are receiving prophylaxis for deep vein thrombosis.184-186 However, epidural hematoma has been associated with anticoagulant therapy in many reports. Large retrospective reviews of outcome after epidural or spinal anesthesia, or both, during or shortly before initiation of anticoagulant therapy with heparin have not reported neurologic dysfunction related to hematoma formation in any patient.187,188 This paucity of damaging epidemiologic evidence, although reassuring, does not reduce the need for frequent evaluation of neurologic function and a search for back pain in the perioperative period after regional anesthesia in any patient receiving any clotting function inhibitor, including aspirin.183,189-191 The risk of regional anesthesia concurrent with prophylaxis for deep vein thrombosis with heparin is greater with the use of low-molecular-weight heparin. (Heparin-induced thrombocytopenia has been treated successfully with intravenous immunoglobulin.)185 The American Society of Regional Anesthesia and Pain Management has issued a consensus statement on the use of regional anesthesia in anticoagulated patients.192 They
suggest that the decision to perform spinal or epidural anesthesia or analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, with the small but definite risk of spinal hematoma weighed against the benefits of regional anesthesia for a specific patient.

Deep vein thrombosis is so common in postoperative patients that almost 1% of postsurgical patients die of fatal pulmonary embolism (Table 39-8).193 Because of this high mortality risk, prophylaxis against deep vein thrombosis has attained widespread acceptance; thus, prophylaxis often begins with 5000 units of heparin given subcutaneously 2 hours preoperatively.193-195 Other trials have shown equal effect with external pneumatic compression.194,196 Persuading surgeons to use this technique may provide greater assurance in using regional anesthesia. Such an option, however, is not available for patients with a prosthetic valve. Newer recommendations are available from the American College of Chest Physicians for prophylaxis against venous thromboembolism.197

Another problem that can arise is managing a pregnant patient with a prosthetic valve during delivery. It is recommended that warfarin be replaced by subcutaneous heparin during the peripartum period. During labor and delivery, elective induction of labor is advocated with discontinuation of all anticoagulant therapy, as indicated for the particular valve prosthesis (discussed earlier).198

Auscultation of the prosthetic valve should be performed preoperatively to verify normal functioning. Abnormalities in such sounds warrant preoperative consultation and verification of functioning.

**CARDIAC CONDUCTION DISTURBANCES: CARDIAC ARRHYTHMIAS**

Bradyarrhythmias, especially if profound or associated with dizziness or syncope, are generally managed with pacemakers (see also Chapters 45 to 47). However, chronic bifascicular block (right bundle branch block with a left anterior or posterior hemiblock or left bundle...
patients rarely have complete heart block perioperatively. Therefore, prophylactic preoperative insertion of temporary pacing wires for bifascicular block does not seem warranted. However, a central route can be established in advance in the event that a temporary pacemaker needs to be inserted (most operating rooms do not rely on transthoracic pacing, although it may be attempted if available).\textsuperscript{201} The actual pacemaker equipment and appropriate personnel should be immediately available, and the equipment should be tested regularly, because symptomatic heart block does occur perioperatively in more than 1% of patients. One study appears to have confirmed this rate of at least 1% for patients undergoing cardiac surgery.\textsuperscript{202} One percent of patients in whom a pacing pulmonary artery catheter was not inserted preoperatively subsequently required pacing before cardiopulmonary bypass. By contrast, 19% of patients who had such a catheter in place underwent cardiac pacing before cardiopulmonary bypass. Predictors of the need for pacing included previous symptomatic bradyarrhythmia, a history of transient complete AV block, and aortic valve disease.

Older studies demonstrated that a rate of more than five PVCs per minute on preoperative examination correlates with perioperative cardiac morbidity.\textsuperscript{146,153-155} To the classic criteria for treating PVCs (the presence of R-on-T couplets, the occurrence of more than three PVCs per minute, and multifocality of PVCs) must be added frequent (>10/hour over a 24-hour period) and repetitive ventricular beats. Electrophysiologic and programmed ventricular stimulation studies are being used to indicate and guide treatment of patients with ischemic heart disease or recurrent arrhythmias and survivors of out-of-hospital cardiac arrest. Although such patients are often treated with antiarrhythmic therapy, attention to their underlying condition should be a focus of our preoperative management. Long-term antiarrhythmic therapy is discussed in the last section of this chapter, on drug therapy. Torsades de pointes is an arrhythmia characterized by episodes of alternating electrical polarity such that the major vector of the QRS complex seems to alternate around an isoelectric line. The hallmark enabling differential diagnosis from ventricular tachycardia is the unusual response of this arrhythmia to commonly used antiarrhythmic drugs. In other words, the use of drugs that prolong the QT interval (e.g., quinidine, procainamide, disopyramide, some of the antihistamines, and the antipsychotic phenothiazines) may well make the arrhythmia more frequent or of longer duration. Reports of the sudden occurrence of torsades de pointes during surgical procedures have been rare in the anesthesia literature. Immediate therapy consists of the administration of magnesium or electrical cardioversion, followed by overdrive cardiac pacing or the administration of \(\beta\)-adrenergic agonists and discontinuation of drugs that prolong the QT interval.

Premature atrial contractions and cardiac rhythm other than sinus also correlate with perioperative cardiac morbidity.\textsuperscript{146,154} These arrhythmias may be more a marker of poor cardiovascular reserve than a specific cause of perioperative cardiac complications.

Preexcitation syndrome is the name for supraventricular tachycardias associated with AV bypass tracts.\textsuperscript{203}

---

**TABLE 39-8 INCIDENCE OF DEEP VEIN THROMBOSIS AND FATAL PULMONARY EMBOLISM**

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Incidence of</th>
<th>Proximal Deep Vein Thrombosis</th>
<th>Fatal Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;40 yr</td>
<td>10</td>
<td>&lt;1</td>
<td>0.1</td>
</tr>
<tr>
<td>Age &gt;60 yr</td>
<td>10-40</td>
<td>3-15</td>
<td>0.8</td>
</tr>
<tr>
<td>Malignancy</td>
<td>50-60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic repair</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open prostatectomy</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other urologic</td>
<td>30-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Gynecologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With malignancy</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without malignancy</td>
<td>10-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniotomy</td>
<td>20-80</td>
<td>1.5-3.0</td>
<td></td>
</tr>
<tr>
<td>Laminectomy</td>
<td>4-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>40-80</td>
<td>10-20</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>48-75</td>
<td>1.0-5.0</td>
<td></td>
</tr>
<tr>
<td>Tibial fracture</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>60-70</td>
<td>20</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td>Head, neck, chest wall</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>60-75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute spine injury</td>
<td>60-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bed bound</td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TURP, Transurethral resection of the prostate.
Successful treatment, which is predicated on an understanding of the clinical and electrophysiologic manifestations of the syndrome, consists of either catheter ablation techniques or surgery using preoperative and intraoperative techniques that avoid release of sympathetic and other vasoactive substances and therefore tachyarrhythmias. Anesthesia for electrophysiologic procedures is discussed in Chapter 68.

### DISORDERS OF THE RESPIRATORY AND IMMUNE SYSTEMS

#### GENERAL PREOPERATIVE AND PREPROCEDURE CONSIDERATIONS

Pulmonary complications after procedures requiring anesthesia are as common as cardiovascular complications—even more common if deep vein thrombosis is included. Moreover, pulmonary complications are equally important or more important to the patient and the health system in terms of morbidity, mortality, length-of-stay extension, and cost.

Although little may seem to have changed in the preoperative preparation of patients with respiratory disease, this impression is not true. Major changes in drug therapy have occurred, and appreciation of the effects of smoking and sleep apnea on perioperative and long-term care has increased. (Preoperative and preprocedure identification and perioperative care of patients with sleep apnea are discussed in the earlier section on obesity and in Chapter 71.)

The main purpose of preoperative testing is to identify patients at risk for perioperative complications so that appropriate perioperative therapy can be instituted to foster return to functional status. Preoperative assessment can also establish baseline function and the feasibility of surgical intervention. Whereas numerous investigators have used pulmonary function tests to define inoperability or high-risk versus low-risk groups for pulmonary complications, few have been able to demonstrate that the performance of any specific preoperative or intraoperative measure, except perhaps smoking cessation and physical activity such as a walking program, reliably decreases perioperative pulmonary morbidity or mortality. Because routine preoperative pulmonary testing and care are discussed extensively in Chapter 51, the current discussion is limited to an assessment of the effectiveness of this type of care.

In fact, few randomized prospective studies indicate an outcome benefit of preoperative preparation. Stein and Cas-sara randomly allocated 48 patients to undergo preoperative therapy (cessation of smoking, administration of antibiotics for purulent sputum, and use of bronchodilating drugs, postural drainage, chest physiotherapy, and ultrasonic nebulizer) or no preoperative therapy. The no-treatment group had a mortality of 16% and morbidity of 60%, as opposed to 0% and 20%, respectively, for the treatment group. In addition, the treatment group spent an average of 12 postoperative days in the hospital as compared with 24 days for the 21 survivors in the no-treatment group.

Collins and colleagues prospectively examined the benefits of preoperative antibiotics, perioperative chest physiotherapy and therapy with bronchodilating drugs, and routine postoperative analgesia (morphine) on postoperative respiratory complications in patients with COPD. Of these therapies, only preoperative treatment with antibiotics had a beneficial effect.

Hulzebos and colleagues performed a single-center randomized trial of intensive inspiratory muscle training. Preoperative inspiratory muscle training reduced the incidence of postoperative pulmonary complications and the duration of postoperative hospitalization in patients at high risk of developing a pulmonary complication who were undergoing CABG surgery.

Warner and co-workers collected data retrospectively about smoking history and prospectively (concurrently) about pulmonary complications for 200 patients undergoing CABG. These investigators documented that 8 weeks or more of smoking cessation was associated with a 66% reduction in postoperative pulmonary complications. Smokers who stopped for less than 8 weeks actually had an increase (from 33% for current smokers to 57.1% for recent quitters) in the rate of 1 or more of the 6 complications surveyed: purulent sputum with pyrexia; need for respiratory therapy care; bronchospasm requiring therapy; pleural effusion or pneumothorax (or both) necessitating drainage; segmental pulmonary collapse, as confirmed by radiography; or pneumonia necessitating antibiotic therapy. Other investigators have found that both shorter and longer periods of cessation of smoking were needed before achieving cardiovascular and hematologic benefit. Bluman and associates performed a retrospective chart review of 410 patients undergoing noncardiac surgery at a VA hospital. Current smoking was associated with a nearly 6-fold increase in the risk of a postoperative pulmonary complication. Reduction in smoking within 1 month of surgery was not associated with a decreased risk for postoperative pulmonary complications. Nakagawa and coauthors also reported higher pulmonary complication rates in patients undergoing pulmonary surgery who quit within 4 weeks of surgery than in current smokers or those who had stopped smoking for more than 4 weeks. Wong and colleagues performed a systematic review of 25 studies of smoking cessation. At least 4 weeks of abstinence from smoking reduced respiratory complications, and abstinence of at least 3 to 4 weeks reduced wound healing complications. Short-term (<4 weeks) smoking cessation did not appear to increase or reduce the risk of postoperative respiratory complications.

Two randomized trials focused on smoking cessation. Wong and colleagues performed a prospective, multicenter, double-blind, placebo-controlled trial, in which 286 patients were randomized to receive varenicline or placebo. A perioperative smoking cessation intervention with varenicline increased abstinence from smoking 3, 6, and 12 months after elective noncardiac surgery with no increase in serious adverse events. Lee and colleagues randomized patients to a group receiving no specific smoking cessation intervention or to an intervention group that received (1) brief counseling by the preadmis-sion nurse, (2) brochures on smoking cessation, (3) referral to the Canadian Cancer Society’s Smokers’ Helpline, and (4) a free 6-week supply of transdermal nicotine replacement therapy. All outcome assessors and caregivers...
on the operative day were blinded to group assignment. Smoking cessation occurred in 12 patients (14.3%) in the intervention group as compared with 3 patients (3.6%) in the control group (relative risk, 4.0; 95% CI, 1.2 to 13.7; \( P = .03 \)). The overall rate of combined intraoperative and immediate postoperative complications was not significantly different between intervention and control groups. At follow-up 30 days postoperatively, smoking cessation was reported in 22 patients (28.6%) in the intervention group compared with 8 patients (11%) in controls (relative risk, 2.6; 95% CI, 1.2 to 5.5; \( P = .008 \)).

When Skolnick and co-workers studied 602 children prospectively, exposure to passive smoking (as measured by urinary cotinine, the major metabolite of nicotine) correlated directly with airway complications. Children with the least exposure to passive smoke had the fewest complications. Second-hand smoke may be a model for particulate air pollution with PM 2.5 particles, which have immediate and long-term effects in increasing lung dysfunction and inflammatory stimuli throughout the body. In this sense, reducing particulate and diesel exhaust exposure in the 2 weeks before surgical procedures may make sense, but such a hypothesis has not been tested (and outpatient surgery centers located next to busy freeways may prove to be appropriate sites for studying such subtle inhibition of healing secondary to diesel particles).

Celli and associates performed a randomized prospective controlled trial of intermittent positive-pressure breathing (IPPB) versus incentive spirometry and deep-breathing exercises in 81 patients undergoing abdominal surgery. The groups exposed to a respiratory therapist (regardless of the treatment given) had more than a 50% lower incidence of clinical complications (30% to 33% versus 88%) and shorter hospital stays than did the control group. Thus, this third prospective study indicates that outcome improves when any concern about lung function is shown by someone knowledgeable in maneuvers designed to clear lung secretions.

Bartlett and co-workers randomly assigned 150 patients undergoing extensive laparotomy to 1 of 2 groups. One group received preoperative instruction in and postoperative use of incentive spirometry (10 times/hour). The other group received similar medical care but no incentive spirometry. Only 7 of 75 patients using incentive spirometry had postoperative pulmonary complications, as opposed to 19 of 75 in the control group. However, other studies have not shown a benefit for specific treatments or have been too contaminated with bias to have a clear result emerge. Lyager and colleagues randomly assigned 103 patients undergoing biliary or gastric surgery to receive either incentive spirometry with preoperative and postoperative chest physiotherapy or only preoperative and postoperative chest physiotherapy. No difference in the postoperative course or pulmonary function was found between the groups. Other studies have shown a specific benefit (i.e., greater than that provided by routine care) for chest physiotherapy and IPPB. These studies are usually poorly controlled, not randomized, or retrospective in design (or any combination); these deficiencies probably substantially bias the results toward finding a benefit in reducing postoperative pulmonary complications. Although randomized prospective studies showed no benefit or actual harm from chest physiotherapy and IPPB on the resolution of pneumonia or postoperative pulmonary complications, the studies cited earlier and numerous retrospective studies strongly suggest that preoperative evaluation and treatment of patients with pulmonary disease actually decrease perioperative respiratory complications, even if only by causing a change in anesthetic techniques.

Meta-analyses have suggested a benefit of anesthetic and pain management with respect to respiratory outcomes. Rodgers and associates reviewed 141 trials involving 9559 patients who had been randomized to receive neuraxial blockade or general anesthesia. Overall mortality was significantly less frequent in the neuraxial blockade group (2.1% versus 3.1%) (see also Chapter 56). The relative risk of pneumonia in the neuraxial blockade group was 0.61 (CI, 0.48 to 0.81), and the relative risk of respiratory depression was 0.41 (CI, 0.23 to 0.73). Neuman and colleagues examined a retrospective cohort of 18,158 patients undergoing surgery for hip fracture in 126 hospitals in New York in 2007 and 2008. Patients receiving regional anesthesia experienced fewer pulmonary complications (359 [6.8%] versus 1040 [8.1%]; \( P < .005 \)). Regional anesthesia was associated with a lower adjusted odds of mortality (OR, 0.710; 95% CI, 0.541, 0.932; \( P = .014 \)) and pulmonary complications (OR, 0.752; 95% CI, 0.637, 0.887; \( P < .0001 \)) relative to general anesthesia. In subgroup analyses, regional anesthesia was associated with improved survival and fewer pulmonary complications among patients with intertrochanteric fractures but not among patients with femoral neck fractures (see also Chapter 56).

Not all studies demonstrate beneficial effects of pharmacologic pretreatment. In afebrile outpatient American Society of Anesthesiologists (ASA) class I and II children with no lung disease or findings who underwent noncavitary, nonairway surgery lasting less than 3 hours, neither albuterol nor ipratropium premedication decreased adverse events (see also Chapter 94).

Evaluation of dyspnea is especially useful (see also Chapter 96). Boushy and co-workers found that grades of preoperative dyspnea correlated with postoperative survival. (Grades of respiratory dyspnea are provided in Table 39-9.) Mittman demonstrated an increased risk of

| TABLE 39-9 GRADE OF DYSPNEA CAUSED BY RESPIRATORY PROBLEMS (ASSESSMENT IN TERMS OF WALKING ON A LEVEL SURFACE AT A NORMAL PACE) |
|---|---|
| Category | Description |
| 0 | No dyspnea while walking on a level surface at a normal pace |
| I | “I am able to walk as far as I like, provided I take my time” |
| II | Specific (street) block limitation (“I have to stop for a while after one or two blocks”) |
| III | Dyspnea on mild exertion (“I have to stop and rest while going from the kitchen to the bathroom”) |
| IV | Dyspnea at rest |

death after thoracic surgery, from 8% in patients without dyspnea to 56% in patients who were dyspneic. Similarly, Reichel found that no patients died after pneumonectomy if they were able to complete a preoperative treadmill test for 4 minutes at the rate of 2 mph on level ground. Other studies have found that the history and examination of an asthmatic subject can also predict the need for hospitalization. Wong and colleagues found that the risk index correlated with postoperative pulmonary complications (Table 39-10).

Arozullah and associates developed the first validated multifactorial risk index for postoperative respiratory failure, defined as mechanical ventilation for more than 48 hours after surgical procedures or reintubation and mechanical ventilation after postoperative extubation. In a prospective cohort study of 181,000 male veterans as part of the National Veterans Administration Surgical Quality Improvement Program, 7 factors independently predicted risk (Table 39-11). With increasing numbers of risk factors present, the rate of complications increased from 0.5% (class 1) to 26.6% (class 4). Arozullah and colleagues subsequently developed a risk index for postoperative pulmonary failure by using data on 160,805 patients undergoing major noncardiac surgery and validated the

<table>
<thead>
<tr>
<th>Category</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Expiratory Spirogram</td>
<td></td>
</tr>
<tr>
<td>A. Normal (% FVC + [% FEV1/FVC] &gt; 150)</td>
<td>0</td>
</tr>
<tr>
<td>B. % FVC + (% FEV1/FVC) = 100-150</td>
<td>1</td>
</tr>
<tr>
<td>C. % FVC + (% FEV1/FVC) &lt;100</td>
<td>2</td>
</tr>
<tr>
<td>D. Preoperative FVC &lt;20 mL/kg</td>
<td>3</td>
</tr>
<tr>
<td>E. Postbronchodilator FEV1/FVC &lt;50%</td>
<td>3</td>
</tr>
<tr>
<td>II. Cardiovascular System</td>
<td></td>
</tr>
<tr>
<td>A. Normal</td>
<td>0</td>
</tr>
<tr>
<td>B. Controlled hypertension, myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>without sequelae for &gt;2 yr</td>
<td></td>
</tr>
<tr>
<td>C. Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, congestive heart failure, angina</td>
<td>1</td>
</tr>
<tr>
<td>III. Nervous System</td>
<td></td>
</tr>
<tr>
<td>A. Normal</td>
<td>0</td>
</tr>
<tr>
<td>B. Confusion, obtundation, agitation, spasticity, discoordination, bulbar malfunction</td>
<td>1</td>
</tr>
<tr>
<td>C. Significant muscular weakness</td>
<td>1</td>
</tr>
<tr>
<td>IV. Arterial Blood Gases</td>
<td></td>
</tr>
<tr>
<td>A. Acceptable</td>
<td>0</td>
</tr>
<tr>
<td>B. PaCO2 &gt;50 mm Hg or PaO2 &lt;60 mm Hg on room air</td>
<td>1</td>
</tr>
<tr>
<td>C. Metabolic pH abnormality &gt;7.50 or &lt;7.30</td>
<td>1</td>
</tr>
<tr>
<td>V. Postoperative Ambulation</td>
<td></td>
</tr>
<tr>
<td>A. Expected ambulation (minimum, sitting at bedside) within 36 hr</td>
<td>0</td>
</tr>
<tr>
<td>B. Expected complete bed confinement for ≥36 hr</td>
<td>1</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Surgery</td>
<td></td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>14.3 (12.0-16.9)</td>
</tr>
<tr>
<td>Neurosurgery, upper</td>
<td>4.21 (3.80-4.67)</td>
</tr>
<tr>
<td>abdominal, or peripheral</td>
<td></td>
</tr>
<tr>
<td>vascular</td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>3.10 (2.40-4.01)</td>
</tr>
<tr>
<td>Other surgery*</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>3.12 (2.83-3.43)</td>
</tr>
<tr>
<td>Albumin &lt;30 g/L</td>
<td>2.53 (2.28-2.80)</td>
</tr>
<tr>
<td>Blood Urea Nitrogen &lt;30 mg/dL</td>
<td>2.29 (2.04-2.56)</td>
</tr>
<tr>
<td>Partially or Fully Dependent</td>
<td>1.92 (1.74-2.11)</td>
</tr>
<tr>
<td>Status</td>
<td></td>
</tr>
<tr>
<td>History of COPD</td>
<td>1.81 (1.66-1.98)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>1.91 (1.71-2.13)</td>
</tr>
<tr>
<td>0-69</td>
<td>1.51 (1.36-1.69)</td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>


COPD, Chronic obstructive pulmonary disease.

*Other surgery includes ophthalmologic, ear, nose, mouth, lower abdominal, extremity, dermatologic, spine, and back surgery.

index by using data on an additional 155,266 patients. Patients were divided into 5 risk classes by using risk index scores (Table 39-12). Pneumonia rates were 0.2% in patients with 0 to 15 risk points, 1.2% in those with 16 to 25 risk points, 4.0% in those with 26 to 40 risk points, 9.4% in those with 41 to 55 risk points, and 15.3% in those with more than 55 risk points.

Gupta and colleagues used the American College of Surgeons NSQIP to develop a risk model for postoperative respiratory failure. On multivariate logistic regression analysis, five preoperative predictors of postoperative respiratory failure were identified: type of surgery, emergency case, dependent functional status, preoperative sepsis, and higher ASA class (Table 39-13).

### SPECIFIC DISEASES

#### Pulmonary Vascular Diseases

Pulmonary vascular diseases include pulmonary hypertension secondary to heart disease (postcapillary disorders), parenchymal lung disease (pulmonary precapillary disorders), pulmonary embolism, and cor pulmonale from COPD. Optimal preoperative management of these conditions requires treatment of the underlying disease. Because pulmonary embolism can be particularly difficult to diagnose, it is crucial to be especially alert to the possibility of this disease. The clinical findings of pulmonary emboli are not always present or specific for the diagnosis. The history may include tachypnea, dyspnea, palpitations,
Chapter 39: Anesthetic Implications of Concurrent Diseases

TABLE 39-12 POSTOPERATIVE PNEUMONIA RISK INDEX

<table>
<thead>
<tr>
<th>Preoperative Risk Factor</th>
<th>Point Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal aortic aneurysm repair</td>
<td>15</td>
</tr>
<tr>
<td>Thoracic</td>
<td>14</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td>10</td>
</tr>
<tr>
<td>Neck</td>
<td>8</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>8</td>
</tr>
<tr>
<td>Vascular</td>
<td>3</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>80 yr</td>
<td>17</td>
</tr>
<tr>
<td>70-79 yr</td>
<td>13</td>
</tr>
<tr>
<td>60-69 yr</td>
<td>9</td>
</tr>
<tr>
<td>50-59 yr</td>
<td>4</td>
</tr>
<tr>
<td><strong>Functional Status</strong></td>
<td></td>
</tr>
<tr>
<td>Totally dependent</td>
<td>10</td>
</tr>
<tr>
<td>Partially dependent</td>
<td>6</td>
</tr>
<tr>
<td>Weight loss &gt;10% in past 6 mo</td>
<td>7</td>
</tr>
<tr>
<td>History of COPD</td>
<td>5</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>4</td>
</tr>
<tr>
<td>Impaired sensorium</td>
<td>4</td>
</tr>
<tr>
<td>History of cerebrovascular accident</td>
<td>4</td>
</tr>
<tr>
<td><strong>Blood Urea Nitrogen Level</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;2.86 mmol/L (0.8 mg/dL)</td>
<td>4</td>
</tr>
<tr>
<td>7.85-10.7 mmol/L (22-30 mg/dL)</td>
<td>2</td>
</tr>
<tr>
<td>≥10.7 mmol/L (≥30 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Transfusion &gt;4 Units</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Emergency Surgery</strong></td>
<td>3</td>
</tr>
<tr>
<td>Steroid Use for Chronic Condition</td>
<td>3</td>
</tr>
<tr>
<td>Current Smoker Within 1 Yr</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol Intake &gt;2 Drinks/Day in Past 2 Wk</td>
<td>2</td>
</tr>
</tbody>
</table>

From Arozullah AM, Khuri SF, Henderson WG, et al: Development and valida-

TABLE 39-13 PREOPERATIVE VARIABLES SIGNIFICANTLY ASSOCIATED WITH AN INCREASED RISK FOR POSTOPERATIVE RESPIRATORY FAILURE IN 2007 MODEL FROM THE AMERICAN COLLEGE OF SURGEONS NATIONAL SURGICAL QUALITY IMPROVEMENT PROJECT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR</th>
<th>95% Wald CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally dependent functional status†</td>
<td>4.07</td>
<td>3.68-4.51</td>
</tr>
<tr>
<td>Partially dependent functional status‡</td>
<td>2.16</td>
<td>1.98-2.34</td>
</tr>
<tr>
<td>ASA class 1‡</td>
<td>0.03</td>
<td>0.02-0.05</td>
</tr>
<tr>
<td>ASA class 2‡</td>
<td>0.14</td>
<td>0.11-0.17</td>
</tr>
<tr>
<td>ASA class 3‡</td>
<td>0.54</td>
<td>0.44-0.67</td>
</tr>
<tr>
<td>ASA class 4‡</td>
<td>1.28</td>
<td>1.04-1.57</td>
</tr>
<tr>
<td>Preoperative sepsis (none)§</td>
<td>0.46</td>
<td>0.42-0.50</td>
</tr>
<tr>
<td>Preoperative sepsis§</td>
<td>1.32</td>
<td>1.16-1.49</td>
</tr>
<tr>
<td>Preoperative septic shock§</td>
<td>2.47</td>
<td>2.16-2.82</td>
</tr>
<tr>
<td>Emergency case (absence versus presence)</td>
<td>0.56</td>
<td>0.52-0.61</td>
</tr>
<tr>
<td>Anorectal‡</td>
<td>0.26</td>
<td>0.15-0.44</td>
</tr>
<tr>
<td>Aortic†</td>
<td>2.94</td>
<td>2.35-3.68</td>
</tr>
<tr>
<td>Bariatric†</td>
<td>0.36</td>
<td>0.27-0.49</td>
</tr>
<tr>
<td>Brain†</td>
<td>2.08</td>
<td>1.15-3.78</td>
</tr>
<tr>
<td>Breast†</td>
<td>0.07</td>
<td>0.04-0.12</td>
</tr>
<tr>
<td>Cardiac†</td>
<td>1.32</td>
<td>0.92-1.88</td>
</tr>
<tr>
<td>Ear, nose, and throat‡</td>
<td>1.11</td>
<td>0.26-4.71</td>
</tr>
<tr>
<td>Foregut†</td>
<td>2.64</td>
<td>2.13-3.27</td>
</tr>
<tr>
<td>Hepatopancreatobiliary‡</td>
<td>0.57</td>
<td>0.45-0.71</td>
</tr>
<tr>
<td>Gallbladder, appendix, adrenals, and spleen‡</td>
<td>1.78</td>
<td>1.44-2.18</td>
</tr>
<tr>
<td>Intestinal‡</td>
<td>0.59</td>
<td>0.33-1.07</td>
</tr>
<tr>
<td>Neck‡</td>
<td>0.29</td>
<td>0.09-0.94</td>
</tr>
<tr>
<td>Obstetrics and gynecology‡</td>
<td>0.42</td>
<td>0.33-0.55</td>
</tr>
<tr>
<td>Other abdominal‡</td>
<td>1.27</td>
<td>1.001-1.62</td>
</tr>
<tr>
<td>Peripheral vascular‡</td>
<td>0.79</td>
<td>0.63-0.98</td>
</tr>
<tr>
<td>Skin‡</td>
<td>0.73</td>
<td>0.55-0.95</td>
</tr>
<tr>
<td>Spine‡</td>
<td>0.593</td>
<td>0.25-1.39</td>
</tr>
<tr>
<td>Thoracic‡</td>
<td>1.96</td>
<td>1.43-2.68</td>
</tr>
<tr>
<td>Venous‡</td>
<td>0.134</td>
<td>0.05-0.37</td>
</tr>
<tr>
<td>Urologic‡</td>
<td>1.36</td>
<td>0.82-2.28</td>
</tr>
</tbody>
</table>


*The estimate and the standard error (SE) refer to the estimate of the logistic regression coefficient for the specific variable and its associated SE. C-statistic, 0.894.

†Reference group, independent functional status.
‡Reference group, ASA class 5.
§Reference group, preoperative systemic inflammatory response syndrome.
¶Reference group, hernia surgery.

syncope, chest pain, or hemoptysis. Physical examination can reveal a pleural rub, wheezing, rales, a fixed and split second heart sound, right ventricular lift, or evidence of venous thrombosis, none of which are present in most patients. If the ECG shows an S1Q3 pattern, spiral CT or lung perfusion scans can be obtained to rule out the diagnosis of pulmonary emboli. A high degree of suspicion is necessary to warrant angiography and anticoagulation or fibrinolytic therapy. If possible, the reactivity of the pulmonary vasculature should be determined because it may be enhanced or decreased by such drugs as nifedipine, hydralazine, nitroglycerin, prazosin, tolazoline, phentolamine, sildenafil citrate, and nitric oxide. Monitoring of pulmonary artery pressure is often required. Preoperative measures should be undertaken to ensure that the patient is not exposed to conditions that elevate pulmonary vascular resistance (e.g., hypoxia, hypercapnia, acidosis, lung hyperinflation, hypothermia)250 or that decrease blood volume (prolonged restriction of fluid intake) or systemic vascular resistance.

**Infectious Diseases of the Lung**

Preoperative evaluation and treatment should follow the basic guidelines outlined in the introduction to this section and in Chapter 38. Treatment of the underlying disease should be completed before all but emergency surgery is performed.

Even though elective surgery should be postponed whenever infectious diseases of the lung are present, patients undergoing emergency surgery often have nosocomial infections and immunocompromised systems. The predominant pathogens for nosocomial pneumonia are gram-negative bacilli, *Staphylococcus aureus*, *Haemophilus influenzae*, anaerobes, and pneumococci. Furthermore,
part iv: anesthesia management

the incidence of tuberculosis increased rapidly in the late 1980s and in the 1990s, probably because of reactivation in patients infected with HIV. increased funding and directly observed antituberculosis therapy have more than offset immigrant and travel risk to cause the incidence of tuberculosis to decrease. tuberculosis leads to chronic pulmonary and systemic symptoms. affected patients may have malaise, headache, fever, hemoptysis, and extrapulmonary diseases affecting the skin, cerebral lymph nodes, kidneys, pericardium, and meninges. active disease is treated with four-drug therapy: isoniazid, pyrazinamide, ethambutol or streptomycin, and rifampin for 9 months. therapy should probably be started preoperatively. management of these emergency patients (many of whom have adult respiratory distress syndrome [ARDS]) before they are brought to the operating room may include initiation of antiinfective therapy, optimization of fluid status and gas exchange, and therapy for the underlying pathophysiologic process.

chronic diseases of the lung

treatment of COPD (reactive airways) may include the use of β-adrenergic drugs, parasympatholytic agents (especially for exercise-induced asthma), systemic or inhaled corticosteroids, and leukotriene antagonists. an estimated 5% of the population has bronchospasm. some investigators recommend using inhaled bronchodilators as first-line drugs and reducing the dose of inhaled steroids, such as beclomethasone dipropionate, budesonide, mometasone, and fluticasone, which are inactivated after absorption. however, in large doses, these “inhaled” steroids can suppress adrenal function, and supplemental systemic corticosteroids may be needed at times of stress (see the earlier discussion in the section on adrenocortical malfunction). preoperative assessment must include gaining knowledge of drug regimens and their effects and education of the patient regarding proper use of an inhaler (Box 39-4), given that these drugs can interact dangerously with anesthetics (see the last section of this chapter) or can be used inappropriately and therefore produce side effects without maximum benefit.206-216

No known interaction between the inhaled anticholinergic ipratropium bromide and muscle relaxants has been reported. patients can feel fine at rest but must be tested by exercise or spirometry to document the degree of current bronchospasm. furthermore, a symptomatic response to bronchodilators in an asymptomatic patient may not predict whether the patient will respond to bronchodilator therapy. an estimated 10% of asthmatic patients exhibit sensitivity to aspirin and may react not only to compounds containing aspirin but also to tartrazine, yellow dye number 5, indomethacin, other nonsteroidal antiinflammatory drugs, and aminophylline.251

cystic fibrosis is characterized by dilatation and hypertrophy of the bronchial glands, mucous plugging of the peripheral airways, and frequently, bronchitis, bronchiectasis, and bronchiolitis. for all these conditions, the measures recommended earlier in this section, as well as appropriate hydration to allow mobilization of secretions, constitute optimal preprocedure therapy.

Surgical resection is the primary therapy for non–small cell carcinomas (e.g., adenocarcinoma, squamous cell carcinoma, and large cell carcinoma). these carcinomas account for 75% of all lung carcinomas, 12% of all malignant tumors, and 20% of all cancer deaths in the United States.252 success of surgery can be predicted by the stage of the tumor.

the combination of chemotherapy and radiation therapy is the current treatment of choice for small cell carcinomas of the lung.253 oat cell (small cell) carcinoma of the lung and bronchial adenomas are known for their secretion of endocrinologically active substances, such as ACTH-like hormones. squamous cell cancers in the superior pulmonary sulcus produce Horner syndrome, as well as characteristic pain in areas served by the eighth cervical nerves and first and second thoracic nerves. these tumors are now treated with preoperative radiation; surgical resection leads to an almost 30% “cure” rate.

anaphylaxis, anaphylactoid responses, and allergic disorders other than those related to lung diseases and asthma

anaphylactic and anaphylactoid reactions. Anaphylaxis is a severe life-threatening allergic reaction. allergic applies to immunologically mediated reactions, as opposed to those caused by pharmacologic idiosyncrasy, by direct toxicity or drug overdosage, or by drug interaction.254-256 Anaphylaxis is the typical immediate hypersensitivity reaction (type I). Such reactions are produced by immunoglobulin E (IgE)–mediated release of pharmacologically active substances. These mediators in turn produce specific end-organ responses in the skin (urticaria), the respiratory system (bronchospasm and upper airway edema), and the cardiovascular system (vasodilation, changes in inotropy, and increased capillary permeability). Vasodilation occurs at the level of the capillary and postcapillary venule and leads to erythema, edema, and smooth muscle contraction. This clinical syndrome is called anaphylaxis. By contrast, an anaphylactoid reaction denotes an identical or very similar clinical response that is not mediated by IgE or (usually) an antigen-antibody process.255,256

In anaphylactic reactions, an injected or inhaled (or ingested) substance—usually drugs, food, or insect venom—can serve as the allergen itself. Low-molecular-weight agents are believed to act as haptenes that form

---

**Box 39-4 Procedures for Correct Use of a Metered-Dose Inhaler**

- Remove the cap and hold the inhaler upright.
- Shake the inhaler.
- Tilt the head back slightly and exhale steadily to functional residual capacity.
- Position the inhaler by using a spacer between the actuator and the mouth.
- Press down on the inhaler while taking a slow, deep breath (3 to 5 seconds).
- Hold the full inspiration for at least 5 and up to 10 seconds, if possible, to allow the medication to reach deeply into the lungs.
- Repeat inhalations as directed. Waiting 1 minute after inhalation of the bronchodilator may permit subsequent inhalations to penetrate more deeply into the lungs and is necessary to ensure proper delivery of the dose. Rinse your mouth and expectorate after using the inhaler.
Chapter 39: Anesthetic Implications of Concurrent Diseases

immunologic conjugates with host proteins. The offending substance, regardless of whether it is a hapten, may be the parent compound, a nonenzymatically generated product, or a metabolic product formed in the patient’s body. When an allergen binds immunospecific IgE antibodies on the surface of mast cells and basophils, histamine and eosinophilic chemotactic factors of anaphylaxis are released from storage granules in a calcium- and energy-dependent process. Other chemical mediators are rapidly synthesized and are subsequently released in response to cellular activation. These mediators include the following: slow-reacting substance of anaphylaxis, which is a combination of three leukotrienes; other leukotrienes; kinins; platelet-activating factors; adenosine; chemotactic factors; heparin; tryptase; chymase; and prostaglandins, including the potent bronchoconstrictor prostaglandin D₂. eosinophil growth and activating factors; mast cell growth factors; and proinflammatory and other factors that contribute to the IgE isotype switch.

The end-organ effects of the mediators produce the clinical syndrome of anaphylaxis. Usually, a first wave of symptoms, including those caused by vasodilation and a feeling of impending doom, is quickly followed by a second wave as the cascade of mediators amplifies the reactions. In a sensitized patient, onset of the signs and symptoms caused by these mediators is usually immediate but may be delayed 2 to 15 minutes or, in rare instances, as long as 2.5 hours after the parenteral injection of antigen. After oral administration, manifestations may occur at unpredictable times.

Mast cell proliferation, together with severe progressive inflammation, contributes to the worsening of symptoms that occurs even after an allergen load is no longer present. The antigen present in cells and lymphocytes, as well as activated mast cells, starts to induce the production of cytokines. These proinflammatory cytokines recruit more inflammatory cells, a process that leads to tissue edema and mediates a second wave of mast cell degranulation. This second wave can promote the recurrence of severe symptoms 6 to 8 hours later and necessitates, some believe, at least 8 hours of continued ICU-like observation.

In addition, biologically active mediators can be generated by multiple effector processes to produce an anaphylactoid reaction. Activation of the blood coagulation and fibrinolytic systems, the kinin-generating sequence, or the complement cascade can produce the same inflammatory substances that result in an anaphylactoid reaction. The two mechanisms known to activate the complement system are called classical and alternative. The classical pathway can be initiated through IgG or IgM (transfusion reactions) or plasmin. The alternative pathway can be activated by lipopolysaccharides (endotoxin), drugs (Althesin), radiographic contrast media, melanocytes (noryn tricot membranes for bubble oxygenators), cellophane membranes of dialyzers, vascular graft material, latex or latex-containing products, and perflurocarbon artificial blood. The most common drugs responsible for intraoperative anaphylaxis are muscle relaxants (see also Chapters 34 and 35). In addition, one of the primary concerns regarding the delayed approval of sugammadex in the United States has been “hypersensitivity reactions,” which includes anaphylaxis. However, latex accounts for a significant number of these reactions, and the incidence of intraoperative anaphylaxis caused by latex is increasing. It is now probably the second most important cause of intraoperative anaphylaxis. In addition, histamine can be liberated independent of immunologic reactions.

Mast cells and basophils release histamine in response to chemicals or drugs. Most narcotics can release histamine, and they can produce an anaphylactoid reaction, as can radiographic contrast media, 4-tubocurarine, and thiopental. What makes some patients susceptible to release of histamine in response to drugs is unknown, but hereditary and environmental factors may play a role.

Intravenous contrast material is probably the most frequently used agent that causes anaphylactoid reactions. Because diagnostic (skin and other) tests are helpful only in IgE-mediated reactions, pretesting is not useful for contrast reactions. Pretreatment with diphenhydramine, cimetidine (or ranitidine), and corticosteroids has been reported to be useful in preventing or ameliorating anaphylactoid reactions to intravenous contrast material, as well as perhaps to narcotics. Unfortunately, very large doses of steroids (1 g of methylprednisolone intravenously) may be necessary to obtain a beneficial effect. The efficacy of large-dose steroid therapy has not been confirmed. Other common substances associated with anaphylactic or anaphylactoid reactions that may merit preoperative therapy include antibiotics, intravascular volume expanders, and blood products (see also Chapters 61 and 62). The anesthesiologist should always be prepared perioperatively to treat an anaphylactoid or anaphylactoid response.

In some cases, a patient with a history of an anaphylactic or anaphylactoid reaction must receive a substance suspected of producing such a reaction (e.g., iodinated contrast material). In addition, some patients have a higher than average likelihood of having a reaction, thus warranting well-planned pretreatment and therapy for possible anaphylactic and anaphylactoid reactions.

**Minimizing Risks Preoperatively.** Although virtually all evidence on this subject is merely anecdotal, enough consistent thought recurs through the literature to justify proposing an optimal approach to these problems. First, predisposing factors should be sought; patients with a history of atopy or allergic rhinitis should be suspected of being at risk. Because anaphylactic and anaphylactoid reactions to contrast media occur 5 to 10 times more frequently in patients with a previously suspected reaction, consideration should be given to the administration of low-osmotic agents and both H₁- and H₂-receptor antagonists for 16 to 24 hours before exposing these patients to a suspected allergen. H₁-receptor antagonists appear to require this much time to act on the receptor. Volume status can be optimized, and perhaps large doses of steroids (1 g of hydrocortisone) should also be administered before exposing patients to agents associated with a high incidence of anaphylactic or anaphylactoid reactions. Older patients and patients taking β-adrenergic blocking drugs present special problems; they are at higher risk of having complications from both pretreatment (especially vigorous hydration) and therapy for anaphylactic reactions.
Primary Immunodeficiency Diseases

Primary immunodeficiency diseases usually manifest early in life as recurrent infections. Along with survival achieved with antibiotic and antibody treatment these infections have new prominent features: cancer and allergic and autoimmunity disorders. Hereditary angioneurotic edema is an autosomal dominant genetic disease characterized by episodes of angioneurotic edema involving the subcutaneous tissues and submucosa of the GI tract and airway and often manifested as abdominal pain. These patients have a functionally impotent inhibitor or deficiency of an inhibitor to complement component C1. Treatment of an acute attack is supportive because epinephrine, antihistamines, and corticosteroids often fail to work. Plasma transfusions have been reported to resolve attacks or make them worse (theoretically by supplying either C1 esterase inhibitor or previously depleted complement components). The severity of attacks can be prevented or decreased by drugs that are either plasmin inhibitors (e.g., ε-aminocaproic acid [EACA] and tranexamic acid) or androgens (e.g., danazol). Because trauma can precipitate acute attacks, prophylactic therapy with danazol, intravenous EACA, plasma, or all three is recommended before elective surgery. A partially purified C1 esterase inhibitor has been used in two patients.

Most of the 1 in 700 persons who have selective IgA deficiency (i.e., <5 mg/dL) have repeated serious infections or connective tissue disorders. These infections commonly involve the respiratory tract (e.g., sinusitis, otitis) or GI tract (manifested as diarrhea, malabsorption, or both). If the patient has rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus, the anesthetist should consider the possibility of isolated IgA deficiency. However, patients with this disorder can be otherwise healthy. Because antibodies to IgA may develop in these patients if they were previously exposed to IgA (as could occur from a previous blood transfusion), subsequent blood transfusions may cause anaphylaxis even when they contain washed erythrocytes. Transfusions should therefore consist of blood donated by another IgA-deficient patient.

Many immunomodulators are now being given to augment cancer treatments; no interactions among these modulators, no effects on the incidence of immune reactions during anesthesia, and no interactions with anesthetic effects have been reported except those regarding immunosuppressant drugs (see the last section of this chapter).

Immunonutrition is increasingly being used preoperatively by patients and prescribed by providers to decrease inflammatory responses. Whereas excellent data on the benefits of probiotics in changing the intestinal milieu to decrease inflammation can be found, limited data are available on their effects on peri-procedural recovery or outcomes.

DISEASES OF THE CENTRAL NERVOUS SYSTEM, NEUROMUSCULAR DISEASES, AND PSYCHIATRIC DISORDERS

Evaluation of a patient with neurologic or psychiatric disease can be found in Chapter 38. Information gathered from the history that warrants further investigation includes a previous need for postoperative ventilation in a patient without inordinate lung disease, which indicates the possibility of metabolic neurologic disorders such as porphyria, alcoholic myopathy, other myopathies, neuropathies, and neuromuscular disorders such as myasthenia gravis. Other historical information warranting further investigation includes the use of drugs such as the following: steroids; guanidine; anticonvulsants, anticoagulant, and antiplatelet drugs; lithium; tricyclic antidepressants; phenothiazines; and butyrophenones.

Although preoperative treatment of most neurologic disorders may not lessen perioperative morbidity, knowledge of the pathophysiologic characteristics of these disorders is important in planning intraoperative and postoperative management. Thus, preoperative knowledge about these disorders and their associated conditions (e.g., cardiac arrhythmias with Duchenne muscular dystrophy or respiratory and cardiac muscle weakness with dermatomyositis) may reduce perioperative morbidity. A primary goal of neurologic evaluation is to determine the site of the lesion in the nervous system. Such localization to one of four levels (supratentorial compartment, posterior fossa, spinal cord, peripheral nervous system) is essential for accurate diagnosis and appropriate management. (Disorders accompanied by increased intracranial pressure and cerebrovascular disorders are discussed in Chapters 17 and 70.)

COMA

Little is known about specific anesthetic or perioperative or periprocedural choices that alter outcome for a comatose patient, but as for all other conditions, the cause of the coma should be known so that drugs can be avoided that may worsen the condition or that may not be metabolized because of organ dysfunction (see also Chapters 96 and 101). First, the patient should be observed. Yawning, swallowing, or licking of the lips implies a “light” coma with major brainstem function intact. If consciousness is depressed but respiration, pupillary reactivity to light, and eye movements are normal and no focal motor signs are present, metabolic depression is likely. Abnormal pupillary responses may indicate hypoxia, hypothermia, local eye disease, or drug intoxication with belladonna alkaloids, narcotics, benzodiazepines, or glutethimide; pupillary responses may also be abnormal, however, after the
use of eye drops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or a perforated viscus, care should be taken to render the patient as metabolically normal as possible before the surgical procedure. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain as a result of a reverse osmotic effect caused by dysequilibrium of the urea concentration.

The physical examination can be extremely helpful preoperatively in assessing the prognosis. Arms flexed at the elbow (i.e., decorticate posture) imply bilateral hemisphere dysfunction but an intact brainstem, whereas extension of the legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brainstem or deep hemisphere level. Seizures are often seen in patients with uremia and other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate the absence of a structural CNS lesion.

**EPILEPTIC SEIZURES**

Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Six percent to 10% of individuals younger than 70 years old will experience a seizure at some time during their lifetime. Fifty percent to 70% of patients with one seizure will never have another. However, 70% of people with two seizures will have an epileptic focus, be candidates for antiseizure medications, and be subject to withdrawal seizures after anesthesia if such medications are not continued. A *seizure* is the term for the clinical event defined as a synchronous, rhythmic depolarization of brain cortical neurons. *Epilepsy* is the condition manifested by recurrent, unprovoked seizures. Sometimes syncopal episodes can be mistaken for seizures, especially when interviews are compressed in the short time frame of a preoperative visit. Twenty-five percent of patients with a seizure have a normal electroencephalogram (EEG) when they are interictal. Thus, a negative EEG result does not indicate that someone with a seizure will not have a withdrawal seizure when emerging from anesthesia. Seizures can be generalized (arising from deep midline structures in the brainstem or thalamus, usually without an aura or focal features during the seizure), partial focal motor, or sensory (the initial discharge comes from a focal unilateral area of the brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the patient’s intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative-hypnotic drugs or alcohol, use of narcotics, use of eye drops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or a perforated viscus, care should be taken to render the patient as metabolically normal as possible before the surgical procedure. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain as a result of a reverse osmotic effect caused by dysequilibrium of the urea concentration.

The physical examination can be extremely helpful preoperatively in assessing the prognosis. Arms flexed at the elbow (i.e., decorticate posture) imply bilateral hemisphere dysfunction but an intact brainstem, whereas extension of the legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brainstem or deep hemisphere level. Seizures are often seen in patients with uremia and other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate the absence of a structural CNS lesion.

**EPILEPTIC SEIZURES**

Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Six percent to 10% of individuals younger than 70 years old will experience a seizure at some time during their lifetime. Fifty percent to 70% of patients with one seizure will never have another. However, 70% of people with two seizures will have an epileptic focus, be candidates for antiseizure medications, and be subject to withdrawal seizures after anesthesia if such medications are not continued. A *seizure* is the term for the clinical event defined as a synchronous, rhythmic depolarization of brain cortical neurons. *Epilepsy* is the condition manifested by recurrent, unprovoked seizures. Sometimes syncopal episodes can be mistaken for seizures, especially when interviews are compressed in the short time frame of a preoperative visit. Twenty-five percent of patients with a seizure have a normal electroencephalogram (EEG) when they are interictal. Thus, a negative EEG result does not indicate that someone with a seizure will not have a withdrawal seizure when emerging from anesthesia. Seizures can be generalized (arising from deep midline structures in the brainstem or thalamus, usually without an aura or focal features during the seizure), partial focal motor, or sensory (the initial discharge comes from a focal unilateral area of the brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the patient’s intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative-hypnotic drugs or alcohol, use of narcotics,
or the receptor’s response to dopamine, (2) stimulating the receptor directly with bromocriptine and lergotrile, (3) implanting dopaminergic tissue, or (4) decreasing cholinergic activity. Newer therapies using the monoamine oxidase inhibitor (MAOI) deprenyl or adrenal medullary transplants to slow the progression of disease appear promising, and even treatment with high-dose coenzyme Q10 seems to be strikingly beneficial. Experiences with deprenyl in the perioperative milieu is insufficient to make proscriptions about its use. Anticholinergic agents have been the initial drugs of choice because they decrease tremor more than muscle rigidity. Dopamine does not pass the blood-brain barrier, so its precursor L-dopa (levodopa) is used. Unfortunately, L-dopa is decarboxylated to dopamine in the periphery and can cause nausea, vomiting, and arrhythmia. These side effects are diminished by the administration of α-methylidihydrazine (carbidopa), a decarboxylase inhibitor that does not pass the blood-brain barrier. Refractoriness to L-dopa develops, and it is now debated whether the drug should be used only when symptoms cannot be controlled with other anticholinergic medications. “Drug holidays” have been suggested as one means of restoring the effectiveness of these compounds, but cessation of such therapy may result in marked deterioration of function and need for hospitalization. Therapy for Parkinson disease should be initiated preoperatively and be continued through the morning of the surgical procedure; such treatment seems to decrease drooling, the potential for aspiration, and ventilatory weakness. Reinstating therapy promptly after surgery is crucial as avoiding drugs such as the phenothiazines and butyrophenones (droperidol, and perhaps alfentanil), which inhibit the release of dopamine (and perhaps alfentanil) or compete with dopamine at the receptor. Carbidopa or levodopa in low doses (20 to 200 mg nightly versus the usual 60 to 600 mg/day for Parkinson disease) is commonly used in the nonparkinsonian restless leg syndrome of older adults (present in 2% to 5% of individuals >60 years old). This drug also should be given the night before and the night immediately after the surgical procedure. Clozapine (a benzodiazepine) does not appear to worsen the movement disorders of Parkinson disease and has been used postoperatively to stop levodopa-induced hallucinations. Patients with Parkinson disease may also undergo deep brain stimulation under monitored anesthesia care.

Dementia, a progressive decline in intellectual function, can be caused by treatable infections (e.g., syphilis, cryptococcosis, coccidioidomycosis, Lyme disease, tuberculosis), depression (a trial of antidepressants is indicated in most patients), side effects of medications (digitalis has slowed brain function more than the heart rate), myxedema, vitamin B₁₂ deficiency, chronic drug or alcohol intoxication, metabolic causes (liver and renal failure), neoplasms, partially treatable infections (HIV), untreatable infections (Creutzfeldt-Jakob syndrome), or decreased acetylcholine in the cerebral cortex (Alzheimer disease). This last condition occurs in more than 0.5% of Americans. Although these patients are often given cholinergic agonists, controlled trials of these drugs have not as yet shown major significant benefit. Gingko has improved subjective symptoms in 37% of patients versus 23% of those given placebo. Although later controlled trials failed to confirm its benefit in early Alzheimer disease or in healthy older individuals, gingko is still popular. However, the prevalence of Alzheimer disease and the desperation of the patients and their families have now widened such therapies. Cholinergic medications improve functioning in patients with Alzheimer disease. These families often desire surgery, but the interactions of these drugs and therapies with perioperative analgesic and anesthetic drug therapies are not well established. One case report noted intraoperative bradycardia in such patients with two cholinergic drugs. A link may exist among Alzheimer disease, postoperative cognitive dysfunction, and inhaled anesthetics. Deposition of β-amyloid can occur in animals exposed to inhaled anesthetics. Whether this link is clinically relevant in humans remains to be determined. Most reversible dementias represent either drug-induced delirium or depression. At present, early results with stimulation at “threshold testing” are promising and seem to stimulate dendritic regrowth and may reverse some or much of the cognitive decline. Creutzfeldt-Jakob disease has been transmitted inadvertently by surgical instruments and corneal transplants; the causative virus or protein particle is not inactivated by heat, disinfectants, or formaldehyde.

More than 90% of patients with chronic recurring headaches are categorized as having migraine, tension, or cluster headaches. The mechanism of tension or cluster headaches may not differ qualitatively from that of migraine headaches; all may be manifestations of labile vasomotor regulation. A headache is said to be migraine if it is characterized by four of the following five “POUNDbing” conditions: if it is Pulsating, if it lasts One day or more, if it is Unilateral, if Nausea occurs, and if it Disturbs daily activities.

Treatment of cluster and migraine headaches centers on the use of serotonin drugs such as sumatriptan or ergotamine and its derivatives. Other drugs that may be effective are propranolol, calcium channel inhibitors, cyproheptadine, prednisone, antihistamines, tricyclic antidepressants, phenoxyt, and diuretic drugs, as well as biofeedback. Giant cell arteritis, glaucoma, and all the meningitides, including Lyme disease, are other causes of headache that may benefit from preoperative treatment. No other special treatment is indicated preoperatively for a patient who has a well-delineated cause for the headaches. Acute migraine attacks can sometimes be terminated by ergotamine tartrate aerosol or by injection of sumatriptan or dihydroergotamine mesylate intravenously; general anesthesia has also been used. We normally continue all prophylactic headache medicine, although the decision to continue aspirin through the morning of the surgical procedure is usually left to the surgeon.

BACK PAIN, NECK PAIN, AND SPINAL CANAL SYNDROMES

Acute spinal cord injury is discussed earlier in the section on autonomic dysfunction. Although it is a common problem, little is written about the anesthetic
management of syndromes related to herniated disks, spondylosis (usually of advancing age), and the congenital narrowing of the cervical and lumbar spinal canal that gives rise to symptoms of nerve root compression. One report stresses the importance of the vascular component in the mechanism of damage to the spinal cord and hence the theoretic desirability of slight hypertension perioperatively.\textsuperscript{294} Another report suggests the use of awake intubation, a fiberoptic bronchoscope, and monitoring of evoked potentials.\textsuperscript{295} Other than the common-sense approach of seeking neurologic consultation or, if necessary, using awake positioning of patients in a comfortable position before emergency root decompression procedures, no special procedures appear to be necessary. Patients with back pain may be receiving large doses of narcotics that may influence the anesthetic plan.

**DEMYELINATING DISEASES**

Demyelinating diseases constitute a diffuse group of diseases ranging from those with uncertain cause (e.g., multiple sclerosis, in which genetic, epidemiologic, and immunologic factors are probably all involved and interferon-β appears to be a promising treatment\textsuperscript{296}) to those that follow infection, vaccination (e.g., Guillain-Barré syndrome), or antimitobolite treatment of cancer. Therefore, demyelinating diseases can have very diverse symptoms. Apparently, a risk of relapse of these diseases exists immediately after surgery. Because relapse may occur as a result of rapid electrolyte changes in the perioperative period, such changes may be avoided. In addition, perioperative administration of steroids may be a protective measure.\textsuperscript{100} Both spinal anesthesia and epidural anesthesia have been administered without problems.\textsuperscript{297,298} Multiple sclerosis and demyelinating diseases in general are the most common causes of nontraumatic disability in young adults. The age-adjusted survival rate is 80% of that of unaffected individuals, or put another way, the average patient with multiple sclerosis ages 1.2 years for every year with the disease. However, the variability of the disease makes this average rate of aging almost meaningless. No treatment alters most of these disease processes, although ACTH, steroids, interferon-β, glatiramer acetate (Copaxone), and plasmapheresis may ameliorate or abbreviate a relapse, or even alter disease progression, especially progression of multiple sclerosis and (if started within 2 weeks of onset) Guillain-Barré syndrome.\textsuperscript{299} Such an effect is consonant with the hypothesis of an immunologic disorder as the cause of these diseases. Care should be taken to avoid succinylcholine in these patients because of the risk of hyperkalemia.

**METABOLIC DISEASES**

Included in the category of metabolic diseases is nervous system dysfunction secondary to porphyrias, alcoholism, uremia, hepatic failure, and vitamin B\textsubscript{12} deficiency. The periodic paralysis that can accompany thyroid disease is discussed in the later section on neuromuscular disorders.

Alcoholism or heavy alcohol intake is associated with the following: acute alcoholic hepatitis (see also Chapter 73), the activity of which declines as alcohol is withdrawn; myopathy and cardiomyopathy, which can be severe; and withdrawal syndromes. Within 6 to 8 hours of withdrawal, the patient may become tremulous, a state that usually subsides within days or weeks. Alcoholic hallucinosis and withdrawal seizures generally occur within 24 to 36 hours. These seizures are generalized grand mal attacks; when focal seizures occur, other causes should be sought. Delirium tremens usually appears within 72 hours of withdrawal and is often preceded by tremulousness, hallucinations, or seizures. These three symptoms, combined with perceptual distortions, insomnia, psychomotor disturbances, autonomic hyperactivity, and, in a large percentage of cases, another potentially fatal illness (e.g., bowel infarction or subdural hematoma), are components of delirium tremens. This syndrome is now treated with benzodiazeines. Nutritional disorders of alcoholism include alcoholic hypoglycemia and hypothermia, alcoholic polyneuropathy, Wernicke-Korsakoff syndrome, and cerebellar degeneration. In patients with alcoholism (i.e., those who drink at least two six packs of beer or 1 pint of whiskey/day or the equivalent), emergency surgery and anesthesia (despite alcoholic hepatitis) are not associated with worsening abnormalities in liver enzymes. In addition, approximately 20% of patients with alcoholism also have COPD. A patient who has a history of alcohol abuse therefore warrants careful examination of many systems for quantification of preoperative physical status.

Although hepatic failure can lead to coma with high-output cardiac failure, unlike uremia, it does not lead to chronic polyneuropathy. Uremic polyneuropathy is a distal symmetric sensorimotor polyneuropathy that may be improved by dialysis. The use of depolarizing muscle relaxants in patients with polyneuropathies has been questioned (see also Chapter 34). We believe that patients who have neuropathy associated with uremia should not be given succinylcholine because of a possible exaggerated hyperkalemic response.

Pernicious anemia caused by vitamin B\textsubscript{12} deficiency may result in subacute combined degeneration of the spinal cord; the signs are similar to those of chronic nitrous oxide toxicity. Both pernicious anemia and nitrous oxide toxicity are associated with peripheral neuropathy and disorders of the pyramidal tract and posterior column (which governs fine motor skills and the sense of body position). Combined-system disease can also occur without anemia, as can nitrous oxide toxicity in dentists and nitrous oxide abusers. Patients with vitamin B\textsubscript{12} deficiency and anemia, if treated with folate, improve hematologically but progress to dementia and severe neuropathy. It may thus be prudent to give an intramuscular injection of 100 μg of vitamin B\textsubscript{12} or 800 μg orally before giving folate to a patient who has signs of combined-system degeneration.\textsuperscript{300}

The porphyrias are a constellation of metabolic diseases that result from an autosomally inherited lack of functional enzymes active in the synthesis of hemoglobin. Figure 39-6 schematically depicts the abnormalities that result from these enzyme deficits. Type 1, 3, and 4 porphyrias can cause life-threatening neurologic abnormalities. These conditions are characterized by the presence of aminolevulinic acid (ALA) or porphobilinogen,
or both, in urine; these substances do not occur in porphria cutanea tarda, a disease that does not incur neurologic sequelae. In acute intermittent porphyria, the typical pattern consists of acute attacks of colicky pain, nausea, vomiting, severe constipation, psychiatric disorders, and lesions of the lower motoneuron that can progress to bulbar paralysis. Certain drugs can induce the enzyme ALA synthetase and thereby exacerbate the disease process. Such sensitizing drugs include barbiturates, meprobamate, chlordiazepoxide, glutethimide, diazepam, hydroxydione, phenytoin, imipramine, pentazocine, birth control pills, ethyl alcohol, sulfonamides, griseofulvin, and ergotamine preparations. Patients often have attacks during infection, fasting, or menstruation. Administration of glucose suppresses ALA synthetase activity and prevents or ablates acute attacks. Drugs used in anesthetic management that are reported to be safe for patients with porphyria include neostigmine (Prostigmin), atropine, gallamine, succinylcholine, 6-tubocurarine, pancuronium, nitrous oxide, procaine, propofol, propanidid, etomidate, meperidine, fentanyl, morphine, droperidol, promazine, promethazine, and chlorpromazine. Although ketamine has been used, postoperative psychoses attributable to the disease may be difficult to distinguish from those possibly caused by ketamine. In addition, although ketamine and etomidate are reported to be safe in humans, they seem to be porphyrinogenic in rats. Propofol has been used without provoking porphyria in at least two susceptible patients.

**Figure 39-6.** Schematic depiction of the functional enzyme deficits that occur in some of the porphyrias. ALA, Aminolevulinic acid; PBG, porphobilinogen.

**NEUROMUSCULAR DISORDERS**

Neuromuscular disorders consist of conditions affecting any major component of the motor unit: motoneuron, peripheral nerve, neuromuscular junction, and muscle. Neuropathies may involve all components of the nerve, thereby producing sensory, motor, and autonomic dysfunction, or only one component. Myopathies may involve the proximal muscles, the distal muscles, or both.

Myasthenia gravis is a disorder of the muscular system caused by partial blockade or destruction of nicotinic acetylcholine receptors by IgG antibodies (see also Chapters 34, 38, and 80). The severity of the disease correlates with the ability of antibodies to decrease the number of available acetylcholine receptors. Treatment of myasthenia is usually begun with anticholinesterase drugs, but in moderate and severe disease, treatment progresses to steroids and thymectomy. Immunosuppressive drugs and plasmapheresis are initiated if the more conservative measures fail, and intravenous immunoglobulin, a rapid-onset therapy, is reserved for acute exacerbations and myasthenic crises.

One major problem for the anesthesiologist involves the use of muscle relaxants and their reversal (see also Chapter 35). Because much of the care of patients with myasthenia gravis involves tailoring the amount of anticholinesterase medication to the maximal muscle strength of the patient, derangement of the course of the patient during the surgical procedure could necessitate
reassessment of the drug dosage. For that reason, all anticholinergic drugs may be withheld for 6 hours preoperatively, and medication should be reinstituted postoperatively with extreme caution because the sensitivity of these patients to such drugs may have changed. Small doses of succinylcholine can be used to facilitate endotracheal intubation; extremely small doses of nondepolarizing drugs can be used for intraoperative relaxation not achieved by regional anesthesia or volatile anesthetics. Of prime importance is monitoring neuromuscular blockade as the guide for muscle relaxant administration and their reversal (see Chapter 53). Although controlled ventilation was frequently required for at least 24 to 48 hours postoperatively, immediate extubation has become more common. Postoperative ventilation is especially important in patients with myasthenia gravis of more than 6 years’ duration, COPD, a daily pyridostigmine requirement of 750 mg in association with significant bulbar weakness, and vital capacity of less than 40 mL/kg. One study in myasthenic patients found rapid recovery of neuromuscular function in patients receiving rocuronium when sugammadex was used for reversal. The authors suggest that the combination could be a rational alternative for myasthenic patients for whom neuromuscular blockade is mandatory during surgical procedures.

Lambert-Eaton syndrome (myasthenic syndrome) is characterized by proximal limb muscle weakness and is associated with antibodies directed against the voltage-gated calcium channels in presynaptic nerve terminals. Strength or reflexes may increase with repetitive effort. Affected patients exhibit decreased release of acetylcholine at the neuromuscular junction. Guanidine therapy enhances the release of acetylcholine from nerve terminals and improves strength. Men with this syndrome generally have small cell carcinoma of the lung or other malignant disease, whereas women often have malignant disease, sarcoidosis, thyroiditis, or a collagen-related vascular disease. In addition, these patients have increased sensitivity to both depolarizing and nondepolarizing muscle relaxants. Lambert-Eaton syndrome is also associated with an autonomic nervous system defect manifested by gastroparesis, orthostatic hypotension, and urinary retention.

Dermatomyositis and polymyositis are characterized by proximal limb muscle weakness with dysphagia. These conditions are associated with malignant disease or collagen-related vascular disease and often involve respiratory and cardiac muscle.

Periodic paralysis is another disease in which sensitivity to muscle relaxants increases. Periodic weakness starts in childhood or adolescence and is precipitated by rest after exercise, sleep, cold, surgery, or pregnancy. Hypokalemic and hyperkalemic forms exist and are associated with cardiac arrhythmias. Like thyrotropic periodic paralysis, these hypokalemic and hyperkalemic forms usually spare the respiratory muscles. Anesthetic management consists of minimizing stress and maintaining normal fluid and electrolyte status and body temperature.

Patients with muscular dystrophy now survive into their late 20s or early 30s. Because the disease involves the muscles themselves and not their innervation, conduction anesthesia cannot produce adequate relaxation of tonic muscles. Gastric dilation is also a problem, as is malignant hyperthermia. As with the other forms of muscular dystrophy, most problems in myotonic dystrophy arise from cardiac arrhythmias and inadequacy of the respiratory muscles. For all the forms of muscular dystrophy, as for all the neuropathies (discussed earlier), problems have been related to exaggerated release of serum potassium after the administration of depolarizing muscle relaxants.

Malignant hyperthermia in the patient or in a relative of the patient merits careful history taking and at least consideration of performing a test for susceptibility to the condition (see also Chapter 43). Prophylaxis with intravenous dantrolene sodium (Dantrium) may also be warranted. In some cases, malignant hyperthermia has been associated with recognizable musculoskeletal abnormalities such as strabismus, ptosis, myotonic dystrophy, hernias, kyphoscoliosis, muscular dystrophy, central core disease, and marfanoid syndrome. Appropriate preparation for a patient with previous masester spasm, or trismus, is a matter of considerable debate. Malignant hyperthermia occurs most frequently in children and adolescents; the incidence is 1 in 14,000 administrations of anesthesia. The incidence increases to 1 in 2500 patients requiring strabismus (squint) surgery.

DOWN SYNDROME

Down syndrome (trisomy 21) occurs once in 1000 births. It is associated with congenital cardiac lesions such as endocardial cushion defects (40%), ventricular septal defects (27%), patent ductus arteriosus (12%), and tetralogy of Fallot (8%). Prophylactic antibiotics should be used before predictable bacteremic events. Down syndrome is also associated with upper respiratory infections, with atlanto-occipital instability (in =15% of patients in whom it is asymptomatic in most cases, but all patients should be treated as though they have atlanto-occipital instability) and laxity of other joints, with thyroid hypofunction (50%), with an increased incidence of subglottic stenosis, and with enlargement of the tongue (or a decreased oral cavity size for a normal-sized tongue). No abnormal responses to anesthetic agents or anesthetic adjuvants have been substantiated. A reported sensitivity to atropine has been disproved, although administration of atropine to any patient receiving digoxin for atrial fibrillation should be done with care. Examination for the conditions associated with Down syndrome should precede surgery.

PREOPERATIVE PREDICTION OF INCREASED INTRACRANIAL PRESSURE DURING NEUROSURGERY

Symptoms and signs of increased intracranial pressure include morning headache or headache made worse by coughing, nausea, vomiting, disturbances in consciousness, history of large tumors, tumors involving the brainstem, neck rigidity, and papilledema. Patients with these signs, large ventricles (as seen on radiography or images of the brain), or edema surrounding supratentorial
tumors should be considered at risk for intraoperative intracranial hypertension. These patients may benefit from preoperative treatment or anesthetic management that assumes this possibility (see also Chapter 70).

Other preoperative considerations for patients with neurologic disease that can cause intracranial hypertension are the associated hyperventilation and hypoxia in patients who have severe hemiplegia and the presence of subarachnoid bleeding or other forms of intracranial hemorrhage (especially likely in women given heparin who have two or more cerebral infarcts noted on CT). Many strokes or transient ischemic attacks have a possible cardiac origin.

MENTAL DISORDERS

Perhaps the most important preoperative consideration for patients with mental disorders, in addition to developing rapport, is understanding their specific drug therapy and its effects and side effects. Lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), other antidepressants that defy classification (e.g., bupropion), phenothiazines, butyrophenones, and MAOIs are used in these patients. These drugs have potent effects and side effects that are discussed in the last section of this chapter, on drug therapy.

RENAI DISEASE AND ELECTROLYTE DISORDERS

The anesthesiologist has an important role to play in preventing the onset and consequences of renal failure and its initiators. The linking of renal failure to electrolyte disorders is more obvious: the kidney is the primary organ for regulating body osmolality and fluid volume and has a major role in excretion of the end products of metabolism. In performing these functions, the kidney becomes intimately involved in the excretion of electrolytes.

A patient with renal insufficiency whose own kidneys are still functioning is distinct not only from a patient with end-stage renal disease whose renal functions are provided by dialysis but also from a patient who has a transplanted kidney. These three groups of patients require very different preoperative preparation. In addition, acute changes in renal function present quite a different problem than do chronic alterations in function. Certain renal diseases require different preoperative preparation than others, but generally, renal disease of any origin presents the same preoperative problems (see also Chapters 23, 38, and 52).

RENAI DISEASE

Causes and Systemic Effects of Renal Disorders

Nephrotic syndrome may develop in patients with glomerular diseases without disturbing tubular function. The soundness of tubular function is an important consideration because tubular dysfunction with attendant uremia presents problems quite different from those presented by glomerular disease with only nephrotic syndrome. This is not to minimize the adverse effects of glomerular disease; nephrotic syndrome consists of massive proteinuria and consequent hypoalbuminemia. The resulting reduction in plasma oncotic pressure diminishes plasma volume and calls forth compensatory mechanisms that result in retention of sodium and water. As a result, a common clinical finding in nephrotic syndrome is edema. Thus, patients with nephrotic syndrome may have excess total-body water and decreased intravascular volume. In addition, diuretics are often given in an attempt to decrease edema. Although serum creatinine and creatinine clearance estimations have limitations as indices of the GFR (inulin clearance is still the gold standard), these measurements are, for now, the most readily available to the anesthesiologist. Plasma creatinine levels reflect endogenous muscle catabolism and dietary intake, as well as urinary excretion. Urinary excretion depends on both filtration and secretion by the kidney. Drugs that are commonly used in the preoperative and perioperative periods can distort this measure of glomerular filtration. Moreover, the commonly used methods for measuring creatinine have a 95% confidence limit of greater than 20% for a GFR higher than 30 mL/minute. Thus, a normal creatinine level of 1.3 mg/dL may give a measured value ranging from 1.0 to 1.5 mg/dL.

Furthermore, in patients with nephrotic syndrome in whom renal tubular function has been preserved, hypovolemia appears to be a significant cause of deteriorating tubular renal function. No randomized study has shown that close control of intravascular volume status in these groups of patients preserves renal tubular function (or any other measure of perioperative morbidity) to a greater degree than does less rigid control.

Uremia, the end result of renal tubular failure (i.e., failure of the concentrating, diluting, acidifying, and filtering functions) manifests in many ways. Changes occur in the cardiovascular, immunologic, hematologic, neuromuscular, pulmonary, and endocrine systems, as well as in bone. These alterations are ascribed either to the toxic end products of protein metabolism or to an imbalance in functioning of the kidney. As the number of functioning nephrons diminishes, the still-functioning nephrons attempt to increase some solute and body composition preservation functions at the expense of other functions, such as excretion of phosphate. The accumulation of phosphate increases PTH levels, which in turn produce osteodystrophy. Osteodystrophy can be managed by (1) restriction of dietary phosphate, (2) the use of gels (e.g., aluminum hydroxide or carbonate) that bind with intestinal phosphate, (3) calcium supplementation, or (4) parathyroidectomy.

Certain alterations in patients with uremia, such as neuropathy, are most logically attributed to an accumulation of toxic metabolites. Peripheral neuropathy is most often sensory and involves the lower extremities, but it may also be motor; peripheral neuropathies are frequently improved with hemodialysis and can be dramatically reversed with renal transplantation. The use of depolarizing muscle relaxants in patients with peripheral neuropathy is controversial and is discussed in the section on neuropathies. Tubular function is commonly
assessed by acidifying and concentrating capabilities. Although such tests are crude, these capabilities are usually readily evaluated by measuring urine pH and specific gravity. Better assessment of renal blood flow, for the purpose of improving renal blood flow and its distribution, is promised by the use of contrast-enhanced ultrasound in the operating room. Along with the altered volume status and cardiac complications in uremic patients, autonomic neuropathy may contribute to hypotension during anesthesia. Atherosclerosis is often accelerated in uremic patients; hypertension, with its attendant consequences, is very common.

Cardiac failure (especially episodic failure) frequently occurs in uremic patients because of the presence of many adverse conditions: anemia with increasing myocardial work, hypertension, atherosclerosis, and altered volume status. Pericarditis can manifest by pericardial rub alone or by pain (with or without hemorrhage). Cardiac tamponade should be ruled out on the basis of clinical features and by echocardiography if this diagnosis is seriously suspected preoperatively. In addition, cardiac tamponade should be treated or planned for preoperatively.

If anemia is present, its severity generally parallels the degree of uremia; chronically uremic patients seem to adapt well to anemia. No hard data have substantiated the need to give a preoperative blood transfusion to a chronically uremic patient, even when the preoperative hematocrit is as low as 16% to 18%. Even in nonuremic patients in an ICU, a randomized trial was unable to demonstrate improved outcome with a liberal transfusion strategy, and transfusions increase the risk for immune system compromise (see also Chapter 61). Thus, one of the major historical reasons for not transfusing blood in patients with end-stage renal disease has been disproved by this finding; data show that the more blood transfusions a transplant recipient receives before transplantation, the greater is the chance that the transplant will function successfully. In uremic patients, coagulation and platelet adhesiveness may be abnormal and factor III activity may be decreased. Even uremic patients who are not given corticosteroids or immunosuppressive drugs may demonstrate abnormal immunity, perhaps warranting increased attention regarding procedures that lessen patient cross-contamination.

Uremic patients exhibit a wide variety of metabolic and endocrinologic disorders in addition to hyperparathyroidism, including impaired carbohydrate tolerance, insulin resistance, type IV hyperlipoproteinemia, autonomic insufficiency, hyperkalemia, and anion-gap acidosis (caused by an inability of the kidneys to reabsorb filtered bicarbonate and excrete sufficient ammonium into urine). Furthermore, the excretion and pharmacokinetics of drugs are different in uremic patients than in normal patients. In addition, complications of hemodialysis include nutritional deficiencies, electrolyte and fluid imbalances, and mental disorders. Because these conditions can lead to serious perioperative morbidity, they should be evaluated preoperatively. No data, however, have substantiated the hypothesis that preoperative optimization of these metabolic and endocrinologic disorders reduces perioperative risk in uremic patients.

As with uremic patients, preoperative optimization of volume status is paramount in patients with kidney stones, and both are affected by carbohydrate intolerance. Seventy-five percent of all kidney stones are composed of calcium oxalate. Patients with these stones frequently take diuretic drugs, consume calcium- and citrate-rich foods, and restrict salt intake. Prevention of dehydration by institution of intravenous fluid therapy along with restricted oral intake of protein may be as important for these patients as it is for patients with struvite or uric acid stones. Struvite stones often result from urinary infection. Uric acid stones can be prevented by treatment with allopurinol, by preoperative hydration, or by alkalization of urine. Acidosis may contribute to stone formation. Again, optimal intravascular volume status is important in preventing stones and preserving renal function. More thorough discussion of renal function and physiology is provided in Chapter 23. Chapter 72 deals with the complexities of managing patients for renal surgery and other urologic procedures.

Creatinine clearance in conjunction with free water clearance appears to be the most accurate way of quantifying, for pharmacokinetic purposes, the degree of decreased renal function (see also Chapter 23). For a patient with stable renal function, creatinine clearance, which is a rough estimate of GFR, can be approximated by noting the serum creatinine level: a doubling of the creatinine level represents a halving of the GFR. Thus, a patient with a stable serum creatinine level of 2 mg/dL would have a GFR of approximately 60 mL/minute. A stable serum creatinine level of 4 mg/dL would accompany a GFR of approximately 30 mL/minute, and a stable serum creatinine level of 8 mg/dL would accompany a GFR of 15 mL/minute or less. When pregnancy and considerable edema are not present and the serum creatinine level is stable, the following formulas can be used to estimate creatinine clearance and free water clearance.

\[
\text{Creatinine clearance} = \frac{(140 - \text{Age [yr]}) \times \text{Body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}
\]

\[
\text{Free water clearance} = \text{Urine flow (mL/hour)} \times \frac{\text{Urine osmolality (mOsm/L)}}{\text{Plasma osmolality (mOsm/L)}}
\]

Note that renal function must be stable. Unstable renal function is often associated with changes in serum creatinine levels that lag by several days. Although knowing the serum creatinine level is more useful than knowing the BUN level, the BUN value provides some information, as discussed in the next section.

Free water clearance is a measure of renal concentrating ability, and it is normally ~25 to +100 mL/hour; it becomes more positive in renal insufficiency states. It may also become more positive in patients who have a head injury or high blood alcohol levels or in those undergoing aggressive fluid infusion or administration of diuretics.
Patients With Insufficient but Functioning Kidneys

One of the greatest challenges for the anesthesiologist is presented by patients with insufficient renal function whose renal function must be preserved during surgical procedures. Additionally, the presence of chronic renal failure is associated with higher rates of perioperative cardiac morbidity, which may warrant further evaluation for the presence of occult CAD. The many uremic symptoms and great perioperative morbidity associated with uremia can probably be avoided by attention to detail in the preoperative and perioperative management of patients with insufficient, but still functioning kidneys.

First, studies demonstrate that acute postoperative renal failure is associated with an extremely high mortality rate. The development of perioperative renal dysfunction has multiple risk factors, the most important of which include preexisting renal disease, heart surgery involving cardiopulmonary bypass or aortic surgery involving cross-clamping of the thoracic or abdominal aorta, and ongoing sepsis. Moreover, acute perioperative renal failure is most likely to occur in patients who have renal insufficiency before the surgical procedure, are older than 60 years, and have preoperative left ventricular dysfunction. Proper preoperative hydration probably decreases mortality after acute renal failure induced by radiocontrast agents. Clues to the presence of hypovolemia or hypercalcemia should be sought from the history and physical examination (e.g., weight loss or gain, thirst, edema, orthostatic hypotension and tachycardia, flat neck veins, dry mucous membranes, decreased skin turgor). In seriously ill patients, insertion of a pulmonary artery catheter permits more precise monitoring of intravascular fluid volume. Other causes of deterioration in function in chronic renal insufficiency are low cardiac output or low renal blood flow (in prerenal azotemia, whether because of cardiac failure or fluid depletion from diuretic drugs, BUN often increases disproportionately to increases in creatinine), urinary tract infection, use of nephrotoxic drugs, hyperkalemia, hypercalcemia, and hyperuricemia. These conditions and drugs should be avoided; if any of these conditions exist, they should be treated preoperatively.

Management of patients with renal disease is discussed in Chapter 72.

Patients Undergoing Dialysis

Patients with chronic (and at times acute) renal failure require renal replacement therapy, including conventional intermittent hemodialysis, peritoneal dialysis, and continuous renal replacement therapy (CRRT). CRRT includes a wide variety of techniques whose periperaoperative management has been reviewed (Table 39-14). Although the primary indication for CRRT is acute renal failure, it can also be used for fluid clearance, correction of electrolyte abnormalities, and management of metabolic acidosis. It can be used in surgical patients without significant hemodynamic abnormalities. These patients may return to the operating room, and their assessment and management may be complicated by the underlying disease and the use of systemic anticoagulation to prevent filter and circuit clotting. In patients undergoing intermittent treatment with hemodialysis or peritoneal dialysis, the procedure is discontinued before entering the operating room. For CRRT, the anesthesiologist must determine the appropriateness of discontinuing the therapy. With short procedures, the therapy can almost always be stopped and the arterial and venous ends of the circuit connected and run in the bypass mode. CRRT can also be used to manage fluids during the surgical procedure by changing the dialysate. If CRRT is continued, its effect on drug dosing must be recognized. In addition to effects on renal elimination of drugs, CRRT has effects resulting from changes in protein binding and volume of distribution, as well as drug removal effects from membrane permeability, membrane surface area, the ultrafiltration rate, and the dialysate flow rate.

Because a patient undergoing dialysis has already lost natural renal functioning, the emphasis in preoperative assessment shifts toward protecting other organ systems and optimally maintaining vascular access sites for cannulation. Usually, this does not require invasive monitoring. Emphasis is placed on intravascular fluid volume and electrolyte status, which can be ascertained by knowing when the patient last underwent dialysis, how much weight was normally gained or lost with dialysis, whether the fluid loss was peritoneal or intravascular, and what electrolyte composition the blood was dialyzed against. Although preoperative dialysis may benefit patients who have hyperkalemia, hypercalcemia, acidosis, neuropathy, and fluid overload, the resulting dysequeilibrium between fluid and electrolytes can cause problems. Because hypervolemia induced by dialysis can lead to intraoperative hypotension, we try to avoid weight and fluid reduction in patients undergoing preoperative dialysis. In addition, hypopnea

![Table 39-14 Characteristics of Renal Replacement Therapy](https://www.elsevier.com/books/clinical-anesthesia/978-0-323-38850-6)
has been found to occur during and after dialysis when the dialysate contained acetate. Avoiding an acetate bathing solution may prevent this cause of hypoventilation.

When renal transplant recipients have subsequent surgical procedures, the status of their renal function must be determined (i.e., whether they have normal renal function, insufficient but still functioning kidneys, or end-stage renal disease requiring hemodialysis) (see also Chapter 74). Descriptions of side effects of immunosuppressive drugs should also be sought. The drugs used preoperatively and intraoperatively to prevent acute rejection themselves have serious side effects that encourage close monitoring of blood glucose and cardiovascular function. Because renal transplantation greatly increases the risk of infection, it is very important to avoid invasive monitoring and prevent patient cross-contamination.

**Drugs in Patients With Renal Failure**

Patients with renal azotemia have a threefold or higher risk of having an adverse drug reaction than do patients with normal renal function. The risk is increased by two conditions. First, excessive pharmacologic effects result from high levels of a drug or its metabolite (e.g., the metabolite of meperidine) in blood because of physiologic changes in target tissues induced by the uremic state. An example is excessive sedation in a uremic patient with standard blood levels of sedative-hypnotic drugs. Second, excessive administration of electrolytes with drugs also increases the risk of having an adverse drug reaction. Administration of standard doses of drugs that depend on renal excretion for their elimination can result in drug accumulation and enhanced pharmacologic effect. In one report, patients with end-stage renal disease required significantly higher propofol doses to achieve the clinical endpoint of hypnosis than did patients with normal renal function.

**INFECTIOUS DISEASE**

Sepsis is a leading cause of postoperative morbidity, probably through a decrease in systemic vascular resistance related to activation of the complement system and other mediators. Thus, attention to the effects of antibiotic drugs must be supplemented by attention to intravascular volume status. The degree of impairment of the infected organ and its effect on anesthesia should be assessed. For instance, endocarditis merits examination of the following: intravascular volume status; antibiotic and other drug therapy and side effects; myocardial function; and renal, pulmonary, neurologic, and hepatic function—organ systems that can be affected by endocarditis.

Although all surgery except emergency or essential operations is proscribed when an acute infectious disease is present, many such diseases (e.g., influenza and pneumococcal pneumonia) and even inflammatory conditions are becoming less frequent because of successful immunization recommendations and programs. Furthermore, even though acute infections are less common, surgery in patients with chronic viral diseases such as hepatitis and HIV infection is more frequent. Many of these patients may also harbor opportunistic infections such as tuberculosis or may have other systemic problems. Whether anesthesia or surgery, or both, exacerbates these infections or their systemic manifestations is not clear.

**ELECTROLYTE DISORDERS**

Disorders of calcium, magnesium, and phosphate balance are discussed in the earlier section on diseases involving the endocrine system and disorders of nutrition (see also Chapters 38 and 60).

**Hyponatremia and Hypernatremia**

Electrolyte disorders are usually detected by determining the levels of electrolytes in serum. These concentrations reflect the balance between water and electrolytes. The osmolality of all body fluids is normally maintained within the narrow physiologic range of 285 to 290 mOsm/kg H2O by integration of three key processes: thirst, release of ADH, and responsiveness of the medullary collecting ducts to ADH. Because of the permeability of biologic membranes, intracellular osmolality and extracellular osmolality are almost always equal and can be estimated by the following formula:

$$2 \left[ \text{Na}^{+} \right] (\text{mEq/L}) + \frac{[\text{Glucose}] (\text{mg/dL})}{18} + \frac{[\text{BUN}] (\text{mg/dL})}{2.8} = \text{mOsm/kg}$$

This formula will become easier to calculate when we convert fully to the International System of Units (SI units; metric system) because millimoles (mmol) can be substituted for mg/(factor) in the foregoing formula to read

$$2 \left[ \text{Na}^{+} \right] + [\text{Glucose}] + [\text{BUN}] = \text{mOsm/kg}$$

with concentrations expressed in millimoles per liter (mmol/L). Although secretion of ADH is tightly controlled by osmotic stimuli at 285 to 290 mOsm/kg, the osmotic threshold for thirst is high (300 mOsm/kg), thus making this sign an important guide to volume deficiency.

Hyponatremia is perhaps the third most common fluid electrolyte abnormality in hospitalized patients. (Magnesium deficiency occurs in as many as 25% [see Chapter 59], and potassium deficiency, discussed later in this section, occurs in as many as 10%). Hyponatremia can occur in isotonic, hypertonic, or hypotonic forms. For example, isotonic hyponatremia can develop in protein or liquid accumulation states such as myeloma. Hypertonic hyponatremia can be present with hyperglycemia or with infusions of glycine (as in the TURP syndrome). Hypotonic hyponatremia is the largest classification and is subdivided according to the status of the extracellular fluid into hypovolemic, isovolumic, or hypervolemic hypotonic hyponatremia. All three types require that excretion of renal water be impaired despite continued intake of dilute fluid. Common causes of hypovolemic hypotonic hyponatremia are GI losses (vomiting, diarrhea), third-space losses (diuretics or salt-wasting nephropathy), and
adrenal insufficiency (Box 39-6). Hypervolemic hypotonic hyponatremic states complicate severe cardiac failure, cirrhosis, nephrotic syndrome, and renal failure and are characterized by retention of sodium with disproportionately larger amounts of water.

The more common isovolumic hypotonic hyponatremia is caused by retention of water without sodium. Because edema is not usually clinically apparent, such patients appear isovolumic. Edema is most often caused by SIADH, which in turn may be caused by CNS or pulmonary tumors or dysfunction. Secretion of ADH increases with age, thus rendering older adults more prone to hyponatremia. Drugs that potentiate the secretion of ADH (tricyclic antidepressants and vincristine) or its effects on the medullary collecting duct system in the kidney (nonsteroidal antiinflammatory drugs and chlorpropamide) or that have similar effects (oxytocin) may be more likely to cause hyponatremia in older adults. To establish the diagnosis of SIADH, the physician should determine that the patient is free of renal and cardiac dysfunction, has normal adrenal and thyroid function, and is normovolemic. Urine osmolality would then be found to exceed 100 mOsm/kg, serum osmolality would be low, and urine sodium excretion would be higher than 20 mEq/L (20 mOsm/L).

Disturbances in serum sodium therefore reflect alterations in glucose metabolism, renal function, or accumulation of body water. The last can be affected by disturbances in thirst, release of ADH, and renal function. Thus, hyponatremia reflects a relative excess of free water and can occur when total-body sodium increases (as in edematous disorders), when total-body sodium is normal (as in excess of free water because of SIADH), or when total-body sodium decreases (as occurs with too aggressive use of diuretic drugs). Definition of the cause defines the treatment. For instance, water restriction is the mainstay of therapy for SIADH. Administration of demeclocycline is another option that corrects SIADH by inducing a reversible nephrogenic diabetes insipidus. The anesthesiologist is faced with the question of what levels of electrolytes require treatment before anesthesia. Although slowly developing hyponatremia usually produces few symptoms, the patient may be lethargic and apathetic. Chronic hyponatremia is better tolerated than acute hyponatremia because of mechanisms regulating intracellular fluid volume that alleviate brain edema; the loss of other solutes from cells decreases the osmotic movement of water into cells. Nonetheless, severe chronic hyponatremia (i.e., serum sodium levels <123 mEq/L) can cause brain edema.

By contrast, acute hyponatremia may be manifested by severe symptoms requiring emergency treatment: profound cerebral edema with obtundation, coma, convulsions, and disordered reflexes and thermoregulatory control. Depending on the cause and relative total sodium and water content, treatment can range from the administration of hypertonic saline or mannitol (with or without diuretic drugs) to restriction of fluids or administration of other drugs. Because neurologic damage may develop if the serum sodium concentration is increased too rapidly, the rate of increase should not exceed 1 mEq/L/hour. After the serum sodium concentration has reached 125 mEq/L, therapy may consist of water restriction; more rapid correction may result in CNS demyelination. In hyponatremic patients who have excess total-body water secondary to SIADH, serum levels can be corrected by giving furosemide, 1 mg/kg, and hypertonic saline to replace the loss of electrolytes in urine. The diagnosis of SIADH is discussed earlier in this chapter (see the section on pituitary abnormalities).

Neither acute nor chronic hyponatremia necessitates restoration of serum sodium to normal levels; brain swelling usually disappears at a serum sodium level of 130 mEq/L.

Hyponatremia occurs much less commonly than hyponatremia. It is often iatrogenic (e.g., it can be caused by failure to provide sufficient free water to a patient who is unconscious or who has had a recent stroke-induced deficit of the thirst mechanism) and can occur in the presence of low, normal, or excess total-body sodium. The primary symptoms of hyponatremia relate to brain cell shrinkage. Because too rapid correction of hyponatremia can lead to cerebral edema and convulsions, correction should be made gradually. Again, with no data to support this stance, we believe that all patients undergoing surgical procedures should have serum sodium concentrations of less than 150 mEq/L before anesthesia.

**Hypokalemia and Hyperkalemia**

Hypokalemia and hyperkalemia are also discussed in Chapters 38 and 59. The relationship between the measured potassium concentration in serum and total-body potassium stores can best be described with a scattergram. Only 2% of total-body potassium is stored in plasma (4200 mEq in cells and 60 mEq in extracellular fluid). In

---

**Box 39-6 Types and Causes of Hypotonic Hyponatremia**

**Hypovolemic**
- Gastrointestinal losses
- Vomiting
- Diarrhea
- Skin losses
- Third-space losses
- Lung losses
- Renal losses
- Diuretics
- Renal damage
- Urinary tract obstruction
- Adrenal insufficiency

**Isovolemic**
- Syndrome of inappropriate secretion of antidiuretic hormone
- Renal failure
- Water intoxication
- Hypokalemia
- Dysfunctional osmostat

**Hypervolemic**
- Congestive heart failure
- Nephrosis
- Liver dysfunction

*Serum osmolality less than 280 mOsm/L.
normal persons, 75% of the 50 to 60 mEq/L of total-body potassium is stored in skeletal muscle, 6% in red blood cells, and 5% in the liver. Thus, a 20% to 25% change in potassium levels in plasma could represent a change in total-body potassium of 1000 mEq or more if the change were chronic or as little as 10 to 20 mEq if the change were acute.

As with serum sodium levels, acute changes in serum potassium levels are less well tolerated than chronic changes. Chronic changes are relatively well tolerated because of the equilibration of serum and intracellular stores that takes place over time to return the resting membrane potential of excitable cells to nearly normal levels.

Hyperkalemia can result from the following: factitious increase of potassium administration (as in red blood cell hemolysis); excessive exogenous potassium from sources such as salt substitutes or, in large amounts, bananas; cellular shifts in potassium (as a result of metabolic acidosis, tissue and muscle damage after burns, use of depolarizing muscle relaxants, or intense catabolism of protein); and decreased renal excretion (as occurs in renal failure, renal insufficiency with trauma, and therapy with potassium-sparing diuretic drugs, especially when combined with ACE inhibitors or mineralocorticoid deficiency).346-348 Factitious hyperkalemia can occur when a tourniquet is left on too long or even by simple fist clenching.349

The major danger in anesthetizing patients who have disorders of potassium balance appears to be abnormal cardiac function (i.e., both electrical disturbance346 and poor cardiac contractility). Hyperkalemia lowers the resting membrane potential of excitable cardiac cells and decreases the duration of the myocardial action potential and upstroke velocity. This decreased rate of ventricular depolarization, in addition to the beginning of repolarization in some areas of the myocardium while other areas are still undergoing depolarization, produces a progressively widening QRS complex that merges with the T wave into a sine wave on the ECG. At a potassium level greater than 6.7 mEq/L, the degree of hyperkalemia and the duration of the QRS complex correlate well.346 This correlation is even better than the correlation between the serum potassium level and T-wave changes. Nevertheless, the earliest manifestations of hyperkalemia are narrowing and peaking of the T wave. Although not diagnostic of hyperkalemia, T waves are almost invariably peaked and narrow when serum potassium levels are 7 to 9 mEq/L. When serum potassium levels exceed 7 mEq/L, atrial conduction disturbances appear, as manifested by a decrease in P-wave amplitude and an increase in the PR interval. Supraventricular tachycardia, atrial fibrillation, PVCs, ventricular tachycardia, ventricular fibrillation, or sinus arrest may all occur.

The ECG and cardiac alterations associated with hyperkalemia are potentiated by low serum levels of calcium and sodium. Intravenous administration of saline, bicarbonate, glucose with insulin (1 unit/2 g glucose), and calcium can reverse these changes by shifting some extracellular potassium into the cell.

β-Adrenergic stimuli also cause redistribution of potassium into the cell. Indeed, the plasma potassium concentration measured in samples immediately before surgical procedures is usually 0.2 to 0.8 mEq/L lower than that measured during the less stressful period 1 to 3 days before surgery.350 β-Adrenergic receptor blocking drugs can be used to prevent such an effect preoperatively. A β-adrenergic receptor stimulating agent (20 mg of nebulized albuterol for a 70-kg patient) can be used to treat hyperkalemia when it occurs; it decreases potassium levels 1.0 mEq/L within 30 minutes, and its effect lasts 2 hours.351 Although nebulized β2-agonists effectively lower plasma potassium concentrations by stimulating sodium- and potassium-dependent adenosine triphosphatase, this therapy should be used as an adjunct to rather than a substitute for more established measures. Kayexalate (sodium polystyrene sulfonate) enemas can be given to bind potassium in the gut in exchange for sodium. Dialysis against a hypokalemic solution also decreases serum potassium levels. However, in a hyperkalemic patient, hypoventilation can be dangerous during anesthesia because each 0.1 change in pH can produce a 0.4 to 1.5 mEq/L change in serum potassium levels in the opposite direction. For example, if pH decreases from 7.4 to 7.3, serum potassium levels could increase from 5.5 to 6.5 mEq/L.

Hypokalemia can be caused by inadequate intake of potassium, excessive GI loss (through diarrhea, vomiting, nasopharyngeal suctioning, long-term use of laxatives, or ingestion of cation exchange resins, as in certain wines), excessive renal loss (because of the use of diuretic drugs, renal tubular acidosis, chronic chloride deficiency, metabolic alkalosis, mineralocorticoid excess, excessive ingestion of licorice, use of antibiotics, ureterosigmoidostomy, and diabetic ketoacidosis), and shifts of potassium from extracellular to intracellular compartments (as occurs in alkalosis, insulin administration, administration of a β-adrenergic agonist or stress, barium poisoning, and periodic paralysis). As with hyperkalemia, knowledge of the cause of the potassium deficiency and appropriate preoperative evaluation and treatment of that cause may be as important as treatment of the deficiency itself. Also like hyperkalemia, hypokalemia may reflect small or vast changes in total-body potassium. Acute hypokalemia may be much less well tolerated than chronic hypokalemia. The major worrisome manifestations of hypokalemia pertain to the circulatory system, both the cardiac and peripheral components. In addition, chronic hypokalemia results in muscle weakness, hypoperistalsis, and nephropathy.

Cardiovascular manifestations of hypokalemia include the following: autonomic neuropathy, which results in orthostatic hypotension and decreased sympathetic reserve; impaired myocardial contractility; and electrical conduction abnormalities, which can result in sinus tachycardia, atrial and ventricular arrhythmias, and disturbances in intraventricular conduction that can progress to ventricular fibrillation. In addition to arrhythmias, the ECG shows widening of the QRS complex, ST-segment abnormalities, progressive diminution of the T-wave amplitude, and a progressive increase in the U-wave amplitude. Surawicz found these changes to be invariably present when serum potassium levels decreased to less than 2.3 mEq/L.346 Although U waves are not specific for
hypokalemia, they are sensitive indicators of the condition. Replenishing the total-body potassium deficit for a depletion reflected by a serum deficit of 1 mEq/L (e.g., from 3.3 to 4.3 mEq/L) may require 1000 mEq of potassium. Even if this amount could be given instantaneously (and it should not be replenished at a rate exceeding 250 mEq/day), it would take 24 to 48 hours to equilibrate in all tissues. Potassium-depleted myocardium is unusually sensitive to digoxin, calcium, and most important, potassium. Rapid potassium infusion in a hypokalemic patient can produce arrhythmias as severe as those produced by hypokalemia itself.352 One potential strategy to prevent hypokalemia from anxiety and stress includes premedication with clonidine.353

Thus, the decision to proceed with surgery and anesthesia in the presence of acute or chronic depletions or excesses of potassium depends on many factors.354-359 The cause and treatment of the underlying condition creating the electrolyte imbalance and the effect of that imbalance on perioperative risk and physiologic processes must be known. The urgency of the operation, the degree of electrolyte abnormality, the medications given, the acid-base balance, and the suddenness or persistence of the electrolyte disturbance are all considerations. For example, a small study of patients undergoing vascular access procedures with preoperative potassium levels of higher than 6 mmol/L demonstrated no adverse outcomes.357 Similarly, in a cohort study in which 38 patients had a preoperative potassium level higher than 5.5 mEq/L, no dysrhythmias or major morbidity were associated with the use of succinyllcholine.358

Retrospective epidemiologic studies attribute significant risk to the administration of potassium (even long-term oral administration).354 In one study, 1910 of 16,048 consecutive hospitalized patients were given oral potassium supplements. Of these 1910 patients, hyperkalemia contributed to death in 7, and the incidence of complications of potassium therapy was 1 in 250. Armed with such data, many internists do not prescribe oral potassium therapy for patients given diuretic drugs. Yet these patients frequently become moderately hypokalemic.360 Modest hypokalemia occurs in 10% to 50% of patients given diuretic drugs. Should surgery be delayed to subject such patients to the risks of potassium therapy?

Three studies investigated whether modest hypokalemia was a problem by prospectively seeking arrhythmias on the ECGs of patients who had various preoperative levels of potassium.355,356,359 No difference in the incidence of arrhythmias occurred in 25 normokalemic (K+ > 3.4 mEq/L) patients, 25 moderately hypokalemic (K+ = 3 to 3.4 mEq/L) patients, and 10 severely hypokalemic (K+ < 2.9 mEq/L) patients.355 Wahr and coauthors studied 2402 patients undergoing elective CABG and concluded that a serum potassium level less than 3.5 mmol/L was a predictor of serious perioperative arrhythmia (OR, 2.2; 95% CI, 1.2 to 4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0 to 3.6), and postoperative atrial fibrillation/flutter (OR, 1.7; 95% CI, 1.0 to 2.7).359 The inability of the eye to pick up these changes—or even the inability of Holter recordings for short periods (which seem not to have been used in this study)—points to the need for confirming studies.

Modest hypokalemia can have severe consequences.360,361 Holland and co-workers treated 21 patients with 50 mg of hydrochlorothiazide twice a day for 4 weeks.361 These patients had a history of becoming hypokalemic during diuretic therapy; no patients had cardiac disease or were taking other medications. Before and after diuretic therapy, 24-hour ambulatory ECGs were recorded. This study is also subject to the limitations of Holter monitoring. Ventricular ectopy, including complex ventricular ectopy (multifocal PVCs, ventricular couplets, ventricular tachycardia), developed in 7 of the 21 patients (33%). Potassium repletion decreased the number of ectopic ventricular beats per patient from 71.2 to 5.4/hour. Apparently, some patients are sensitive to even minor potassium depletion. In the Multiple Risk Factor Intervention Trial involving 361,662 patients, more than 2000 of whom were treated for hypertension with diuretics, the reduction in serum potassium after diuretic therapy was greater in patients with PVCs.360

### Gastrointestinal and Liver Diseases

#### Gastrointestinal Disease

**Preoperative Search for Diverse Associated Disorders in Gastrointestinal Disease**

Although preoperative preparation of the GI tract is usually the responsibility of the surgeon, GI disease can and often does cause derangements in many or all other systems (see also Chapter 38). Such disturbances can affect the safety of anesthesia for the patient. Preoperative preparation should include knowledge of disease processes and their effects to guide the patient smoothly through the perioperative period. The major advances of correcting fluid and electrolyte disorders and optimizing nutritional status preoperatively allow surgical procedures to be performed in patients with GI disease previously deemed to be too great a risk and may have lessened the risk for others.44-47,362 Nonetheless, in patients with GI disease, thorough assessment of intravascular fluid volume, electrolyte concentrations, and nutrition is essential, including an evaluation of the supervening side effects of these therapies (e.g., hypophosphatemia from parenteral nutrition, hyperkalemia or cardiac arrhythmias from too vigorous treatment of hypokalemia, and CHF from too rapid or too vigorous treatment of hypovolemia).

In addition to the vast alterations in fluids, electrolytes, and nutrition that can occur with such diverse GI diseases as neoplasms and pancreatitis, patients with GI disorders can have gastrosophageal reflux disease, bowel obstruction, vomiting, or hypersecretion of acid. These effects may merit rapid induction of anesthesia with the application of cricoid pressure or endotracheal intubation with the patient unanesthetized (awake), preoperative nasogastric suctioning, or preoperative use of histamine receptor blocking drugs. Clotting abnormalities may need to be corrected because fat-soluble vitamin K (often malabsorbed) is necessary for the synthesis of factors II, VII, IX, and X in the liver (see also Chapter 62). Liver disease is often associated with GI disease and, if
severe enough, can also result in a deficiency of clotting factors synthesized by the liver. Not all patients with carcinoid tumors have symptoms attributable to secretion of hormone by the tumor. Some do, however, and unexpected carcinoid can manifest intraoperatively by hypersecretion of gastric fluid. The most comprehensive series in the literature indicates that only 7% of patients have carcinoid syndrome, which typically consists of flushing, diarrhea, and valvular heart disease. Of those patients with the syndrome, approximately 74% have cutaneous flushing, 68% have intestinal hypermotility, 41% have cardiac symptoms, and 18% have wheezing. Factors influencing symptoms include the location of the tumor and the specific hormones produced and secreted. Although it is generally believed that if patients do not exhibit carcinoid syndrome, the tumors are not producing serotonin (5-hydroxytryptamine [5-HT]), such may not be the case. Approximately 50% of patients with carcinoid tumors of the GI tract demonstrate evidence of 5-HT production as manifested by elevated urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of 5-HT. Carcinoid syndrome is usually associated with ileal carcinoid tumors that have metastasized to the liver. Presumably, the liver clears mediators released from the tumor. Impairment of this clearing ability by the metastatic tumor results in carcinoid syndrome.

Most patients with carcinoid tumors and increased urinary 5-HIAA levels have typical carcinoid tumors originating from the midgut (ileum or jejunum). These patients excrete only small amounts of 5-hydroxytryptophan (5-HTP). Patients with atypical carcinoid tumors that originate in the foregut (bronchus, stomach, and pancreas) excrete large amounts of 5-HT and 5-HTP, as well as moderately higher amounts of 5-HIAA. Although it is generally agreed that 5-HT is responsible for the diarrhea experienced by patients with carcinoid tumors, other neurohumoral agents may contribute to the flushing and hypotension, including dopamine, histamine, and some of the neuropeptides such as substance P, neurotensin, vasoactive intestinal peptide, and somatostatin.

The net physiologic effect of circulating 5-HT represents a composite of both direct action (mediated by 5-HT receptors) and indirect action (mediated through modulation of adrenergic neurotransmission). The existence of several subtypes of 5-HT receptors may account for the different effects of 5-HT on various serotonin-sensitive tissue beds. Indirect actions are effected through alterations in catecholamine release and depend on the level of circulating 5-HT. 5-HT has little if any direct effect on the heart. With increased levels, however, positive chronotropic and inotropie myocardial effects may occur, mediated by the release of noradrenaline (norepinephrine). Effects of serotonin on the vasculature include both vasoconstriction and vasodilation.

Alterations in GI function attributed to 5-HT include increased motility and net intestinal secretion of water, sodium chloride, and potassium. 5-HT reportedly causes bronchoconstriction in many animals, but rarely in humans. Patients with asthma are a possible exception. Carcinoid tumors frequently manifest as diarrhea with fluid and electrolyte abnormalities. Because these tumors secrete vasoactive substances, patients can exhibit...
hypotension or hypertension along with the flush associated with release of vasoactive substances. Vasoactive substances can be released from the tumor by any number of substances, including catecholamines. Until the 1990s, management of patients with this tumor was a real challenge for the anesthesiologist. Thus, anesthesiologists of that era had to tread a fine line between avoiding substances known to release 5-HT (e.g., d-tubocurarine and morphine) and inducing anesthesia so light that painful stimuli activated a sympathetic stress response. The anesthesiologist also needed to be ready and able to treat hypotension, decreased peripheral vascular resistance, bronchospasm, and hypertension. α-Adrenergic receptor blockade with the phenothiazines, butyrophenones, or phenoxybenzamine and β-adrenergic receptor blockade with propranolol have been advocated to prevent catecholamine-mediated release of vasoactive substances. These practices, however, can lead to hypotension. Nevertheless, the difficulty in managing carcinoid syndrome seemed to change with the availability of a somatostatin analogue. In fact, somatostatin is now such a powerful inhibitor of the release of peptides from carcinoid tumors and an inhibitor of the peptic effects on receptor cells that it is the therapy of choice for preoperative, intraoperative, and postoperative management of carcinoid symptoms and crises. In cardiac surgical patients, mortality has declined over time, and vasopressors have been shown to be safe in conjunction with octreotide. However, the ease of management of most patients should not lull the anesthesiologist into being unprepared—in fact, somatostatin has caused problems of its own and has failed to prevent severe hypotension and bronchospasm.

In patients with severe hypotension that is not treatable with somatostatin, the drug of choice is either angiotensin or vasopressin. (Angiotensin is not commercially available in the United States.) However, the vasoactive substances released by carcinoid tumors cause fibrosis of the heart valves that often results in pulmonic stenosis or tricuspid insufficiency. To increase cardiac output in a patient with tricuspid insufficiency, the anesthesiologist should avoid drugs or situations that increase pulmonary vascular resistance (e.g., angiotensin, vasopressin, acidosis, hypercapnia, hypothermia). In addition, the production of large amounts of 5-HT (equal to 200 mg/day of 5-HIAA) can lead to the development of niacin deficiency with pellagra (as occurs with diarrhea, dermatitis, and dementia).

Acute increase of plasma kinin activity in patients with carcinoid tumors has been the explanation for the symptoms of carcinoid syndrome. The physiologic effects of kinins are known to include vasodilation of smaller resistance vessels and stimulation of the release of histamine from mast cells. The latter action potentiates their own vasodilating properties and further reduces systolic and diastolic blood pressure. In addition, increases in vascular permeability may lead to edema. Kinins do not affect the myocardium directly.

Steroids have been effective in treating the symptoms of bronchial carcinoid tumors. Although prophylactic preoperative administration and intraoperative therapeutic use have been described, controlled studies of beneficial effects are lacking. Aprotinin, like steroids, inhibits the kallikrein cascade. This drug is capable of blocking the proteinase activity of kallikrein, and some reports have described a dramatic clinical response.

A subset of patients with symptoms of carcinoid syndrome excretes histamine at increased levels in their urine. Histamine causes vasodilation of small blood vessels, which leads to flushing and decreased total peripheral resistance. Histamine is known to cause bronchoconstriction, particularly in patients with bronchial asthma and other pulmonary diseases. Its role in carcinoid bronchospasm, if any, is uncertain. Histamine receptor blocking drugs have been used with some success in alleviating the flushing associated with carcinoid syndrome. H2 antagonism alone was found to be just as effective as combination therapy in preventing symptoms; pure H1 antagonism, however, was ineffective. These therapies have been relegated to a second-line defense since the use of somatostatin.

Catecholamines aggravate the symptoms of carcinoid syndrome, presumably by stimulating release of hormone by the tumor. The mechanism by which this release occurs remains obscure. Adrenergic receptors have not been demonstrated in carcinoid tumors, nor do these tumors usually have neural innervation. Perhaps adrenergic stimuli work through their mechanical effects on the gut and vessels to stimulate the release of tumor products. Treatment of patients with carcinoid tumors by means of α- and β-adrenergic antagonists has been beneficial in ameliorating flushing in some instances but ineffective in others.

The results of prospective studies on somatostatin to ameliorate the symptoms of carcinoid syndrome have been dramatic. Somatostatin appears to be a major advance in the treatment of carcinoid syndrome.

Bronchospasm with or without flushing also develops in many patients when vasoactive substances are released. Thus, a patient with carcinoid tumor may be well or may be severely incapacitated by pulmonary, neurologic, nutritional, fluid, electrolytic, or cardiovascular disturbances. Therefore, although the GI system in itself may not require extensive preoperative preparation, GI disease can cause disturbances in any or all other systems that require extensive preoperative preparation to optimize the patient’s condition in addition to preoperative knowledge of physiology and the effects of diseases to guide patients through the perioperative period smoothly. In addition, the anesthesiologist’s understanding of the nature of the surgical procedure probably aids in determining the system involvement caused by the GI disorder.

Another perioperative consideration is that patients with GI diseases (perhaps even more so than those with other diseases) have had to endure the psychosocial trauma of having to live with their disease for long periods or the necessity of facing such a prospect. They need emotional support and holistic kindnesses as much as, if not more than, other patients without sacrificing scientific rigor in the treatment of their condition. Obtaining relevant psychological data while gathering medical information, sitting (not standing) while taking the history, and empathizing with the patient about how difficult it must be to accomplish tasks with this disease (stressing
accomplishments, we have found) legitimize the physician’s interests in and support of the patient’s pain and other psychosocial issues. The time spent sitting and talking with the patient also allows the anesthesiologist to discuss options for pain therapy with the patient, why systemic morphine may be avoided in a patient with a fresh bowel anastomosis,380 and other issues that show the anesthesiologist to be both a competent physician and particularly concerned with that patient’s well-being. In addition to an appreciation of the organic effects of the disease, attention to emotional support of these patients perioperatively presents opportunities to use one’s full skills as a physician to bring about healing.

LIVER DISEASE

What are the risks of giving anesthesia to patients with acute liver disease who require emergency surgery? What are the risks of giving anesthesia to patients with chronic impairment of liver function? What can be done to minimize these risks? Although one may think that the experiences gained from providing anesthesia for liver transplantation would answer many of these questions, a substantial difference exists between optimizing cardiovascular function to meet the needs of a new liver (e.g., supply of nutrients) and maintaining liver function in a diseased liver. Hepatic physiology and pathology are discussed in Chapter 22.

HEMATOLOGIC DISORDERS AND ONCOLOGIC DISEASE

HEMATOLOGIC DISORDERS

Sickle Cell Anemia and Related Hemoglobinopathies

The sickle cell syndromes constitute a family of hemoglobinopathies caused by abnormal genetic transformation of amino acids in the heme portion of the hemoglobin molecule. The sickle cell syndromes arise from a mutation in the β-globin gene that changes the sixth amino acid from valine to glutamic acid. A major pathologic feature of sickle cell disease is the aggregation of irreversibly sickled cells in blood vessels. The molecular basis of sickling is the aggregation of deoxygenated hemoglobin B molecules along their longitudinal axis.381 This abnormal aggregation distorts the cell membrane and thereby produces a sickle shape. Irreversibly sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues.381-384 Some investigators have challenged this hypothesis, with several studies showing enhanced adhesion of sickled erythrocytes to vascular endothelium.385 Some other abnormal hemoglobins interact with hemoglobin S to various degrees and give rise to symptomatic disease in patients heterozygous for hemoglobin S and one of the other hemoglobins such as the hemoglobin of thalassemia (hemoglobin C).

Three tenths of 1% of the African American population in the United States have sickle cell–thalassemia disease (hemoglobin SC); these patients also have end-organ disease and symptoms suggestive of organ infarction. For these patients, perioperative considerations should be similar to those for patients with sickle cell disease (hemoglobin SS).

Whereas 8% to 10% of African Americans have the sickle cell trait (hemoglobin AS), 0.2% are homozygous for sickle cell hemoglobin and have sickle cell anemia. Sickle cell trait is a heterozygous condition in which the individual has one βS globin gene and one βA globin gene, which results in the production of both hemoglobin S and hemoglobin A, with a predominance of hemoglobin A. Sickle cell trait should not be considered a disease because hemoglobin AS cells begin to sickle only when the oxygen saturation of hemoglobin is less than 20%. No difference has been found between physiologically normal persons (those with hemoglobin AA) and those with hemoglobin AS regarding survival rates or the incidence of severe disease, with one exception: patients with hemoglobin AS have a 50% increase in pulmonary infarction. However, single case reports of a perioperative death and a perioperative brain infarct in two patients with hemoglobin AS disease do exist, as does a report of death believed to be caused by aorticaval compression during general anesthesia that resulted in a sickling crisis.386 The need for exchange transfusion before cardiac surgery has been debated.387,388 Frequent measurement of oxygen saturation (pulse oximetry) in multiple areas of the body is recommended, including the ear and toe in pregnant patients.386 The pathologic end-organ damage that occurs in sickle cell states is attributable to three processes: the sickling or adhesion (or both) of cells in blood vessels, which causes infarcts and subsequent tissue destruction secondary to tissue ischemia; hemolytic crisis secondary to hemolysis; and aplastic crises that occur with bone marrow exhaustion, which can rapidly result in severe anemia. Logic dictates that patients currently in crisis not undergo surgery except for extreme emergencies, and then only after an exchange transfusion.383,385-389

Because sickling is increased with lowered oxygen tensions, acidosis, hypothermia, and the presence of more desaturated hemoglobin S, current therapy includes keeping the patient warm and well hydrated, giving supplemental oxygen, maintaining high cardiac output, and not creating areas of stasis with pressure or tourniquets. Meticulous attention to these practices in periods when we do not usually pay most careful attention (i.e., waiting in the preinduction area) or when gas exchange may be most unmatched to the cardiovascular-metabolic demands (early postoperative period) may be important in lessening morbidity. Even following these measures routinely, with no special emphasis placed on the periods described, succeeded in reducing mortality to 1% in several series of patients with sickle cell syndromes.386,389,390 Retrospective review of patients’ charts led the authors of those studies to conclude that, at most, a 0.5% mortality rate could be attributed to the interaction between sickle cell anemia and anesthesia.

Several investigators have advocated using partial exchange transfusions perioperatively. In children with sickle cell anemia and acute lung syndromes, partial exchange transfusion improved clinical symptoms and blood oxygenation. In addition, serum bilirubin levels
decreased in patients with acute liver injury. Clinical improvement of pneumococcal meningitis and cessation of hematuria in papillary necrosis also accompanied exchange transfusion. The goal of exchange transfusion is to increase the concentration of hemoglobin A to 40% and the hematocrit to 35%. The 40% figure is an arbitrary one because no controlled studies have established a threshold ratio of hemoglobin A to hemoglobin S that would render blood unable to sickle in vivo. To achieve the 40% ratio in a 70-kg adult, approximately 4 units of washed erythrocytes would have to be exchanged; the system is inexpensive but efficient.

The possible decrease in perioperative morbidity after partial exchange transfusion has not been compared with the risks of exchange, except in 2 studies, in which the risks of exchange were found to exceed the benefits. In the first study, a retrospective review of 82 surgical procedures performed between 1978 and 1986 in 60 patients, no advantage was noted for preoperative exchange transfusion as measured by a decrease in postoperative complications. (However, only the sickest patients may have received exchange transfusions because patients were not randomly allocated to exchange or nonexchange groups.) A slight increase in postoperative atelectasis requiring treatment was seen in patients given preoperative transfusions. More than 50% of the patients given transfusions had a postoperative complication. Patients who began with a hematocrit higher than 36% had a lower rate of complications. In the second study, a randomized comparison of aggressive versus conservative transfusion practices in 551 patients (604 operations), perioperative sickling complications were not different between groups, and transfusion-related complications were substantially less in the conservatively treated group. A more recent retrospective review of 14 patients with sickle cell anemia who were undergoing total hip revision supports the decision to perform a simple transfusion preoperatively if the patient’s hemoglobin is significantly lower than their steady-state hemoglobin level. Transfusion can be used intraoperatively according to hemoglobin level or blood loss volume. Other conditions are common in sickle cell syndromes: pulmonary dysfunction with increased shunting, renal insufficiency, gallstones, small MIls, priapism, stroke, aseptic necrosis of bones and joints, ischemic ulcers, retinal detachment as a result of neovascularization, and complications of repeated transfusions.

In thalassemia, globin structures are normal, but because of gene deletion, the rate of synthesis of either the α or β chains of hemoglobin (αα- and β-thalassemia, respectively) decreases. Two copies of the gene that codes for the α-globin chain are located on chromosome 16. Deletion of all four of these genes causes cell death in utero, and three deletions cause severe chronic hemolysis and a shortened life span. α-Thalassemia-1 (trait) occurs when two genes have been deleted and mild anemia results; α-thalassemia-2 (silent) occurs when the two genes have been deleted but no mild anemia or microcytosis results. In α-thalassemia trait, the hemoglobin A2 level is normal. β-Thalassemia is associated with an excess of α chains, which denature developing erythrocytes, thereby leading to their premature death in marrow or to shortened survival in the circulation. An elevated hemoglobin A2 level is the hallmark of β-thalassemia trait, a common cause of mild anemia and microcytosis. Bone marrow transplantation and pharmacologic manipulation of hemoglobin F synthesis are being tried in these hemoglobinopathies, as is direct gene replacement therapy. These therapies seem to be promising in even reversing liver failure from previous iron overload. These syndromes are common in Southeast Asia, India, and the Middle East and in people of African descent.

In thalassemia, facial deformity from erythropoietin-stimulated ineffective erythrophoiesis (ineffective because of a genetic inability to produce useful hemoglobin) was reported to make endotracheal intubation difficult. This one case report has not been amplified, and no reports of this complication in patients with sickle cell anemia have been published. However, the anemia associated with these syndromes often produces compensatory hyperplasia of the erythroid marrow, which in turn is associated with severe skeletal abnormalities.

Cytoskeletal Anemias (Hereditary Spherocytosis and Elliptocytosis), Enzyme-Deficient Anemias, and Autoimmune Hemolytic Anemias

Congenital abnormalities of the erythrocyte membrane are becoming better understood. In elliptocytosis and hereditary spherocytosis, the membrane is more permeable to cations and is more susceptible to lipid loss when cell energy is depleted than is the membrane of a normal red blood cell. Both hereditary spherocytosis (present in 1 in 5000 people) and hereditary elliptocytosis are inherited as autosomal dominant traits. In both disorders, defects in the membrane are thought to result from a mutation of spectrin, a structural protein of the membrane cytoskeleton. Although the therapeutic role of splenectomy in these diseases is not fully defined, in severe disease, splenectomy is known to improve the shortened life span of the red blood cell 100% (from 20 to 30 days to 40 to 70 days). Because splenectomy predisposes the patient to gram-positive septicemia (particularly pneumococcal), perhaps patients should be given pneumococcal vaccine preoperatively before predictable bacteremic events. No specific problems related to anesthesia have been reported for these disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (a gender-linked recessive trait) is also reported to occur in approximately 8% of African American men. Young cells have normal activity, but older cells are grossly deficient when compared with normal cells. A deficiency in G6PD results in hemolysis of the erythrocyte and the formation of Heinz bodies. Red blood cell hemolysis can also occur with intercurrent infections or after the administration of drugs that produce substances requiring G6PD for detoxification (e.g., methemoglobin, glutathione, and hydrogen peroxide). Drugs to be avoided are sulfa drugs, quinidine, prilocaine, lidocaine, antimarial drugs, antipyretic drugs, nonnarcotic analgesics, vitamin K analogues, and perhaps sodium nitroprusside.

The autoimmune hemolytic anemias include cold antibody anemia, warm antibody anemia (idiopathic), and drug-induced anemia.
anemias are mediated by IgM or IgG antibodies, which at room temperature and lower temperatures cause red blood cells to clump. When these patients are given blood transfusions, the cells and all fluid infusions must be warm, and body temperature must be meticulously maintained at 37°C if hemolysis is to be prevented. Warm antibody (or idiopathic) hemolytic anemia is a difficult management problem characterized by chronic anemia, the presence of antibodies active against red blood cells, a positive Coombs test, and difficulty crossmatching blood. For patients undergoing elective surgery, autologous transfusions, predeposit of blood with or without erythropoietin stimulation, and blood from rare Rh-negative red blood cell donors or the patient’s first-degree relatives (or both) can be used. In emergency situations, the possibility of autotransfusion, splenectomy, or corticosteroid treatment should be discussed with a hematologist knowledgeable in this area.

Drug-induced anemias have three mechanisms. In receptor-type hemolysis, a drug (e.g., penicillin) binds to the membrane of the red blood cell, and the complex stimulates the formation of an antibody against the complex. In “innocent bystander” hemolysis, a drug (e.g., quinidine, sulfonamide) binds to a plasma protein, thereby stimulating an antibody (IgM) that cross-reacts with an erythrocyte. In autoimmune hemolysis, the drug stimulates the production of an antibody (IgG) that cross-reacts with the erythrocyte. Drug-induced hemolytic anemias generally cease when therapy with the drug ends. In emergency situations, the least incompatible cells available should be used for blood transfusion.

Granulocytopenia

Granulocyte mechanisms have undergone experimental elaboration since 2000, partly because of the molecular biologic revolution: in addition to erythropoietin (discussed earlier), more than 14 hemolymphopoietic growth factors or cytokines have been characterized biochemically and cloned genetically. These growth factors interact with cell-surface receptors to produce their major actions (Table 39-15). Use of the colony-stimulating factors has permitted more intense oncologic treatment. The few reports related to their perioperative effects detail the unfavorable adverse consequences that such therapies can have on gas exchange when adverse immunologic effects occur.

In patients who have fewer than 500 granulocytes/mL of blood and established sepsis, the use of growth factor and granulocyte transfusion has been shown to prolong life. Although bone marrow transplantation is being used increasingly, complications usually occur after transplantation, not on harvesting of cells (at which time the anesthesiologist who is not involved in critical care is most frequently involved). Abnormal results on pulmonary function testing before bone marrow transplantation seem to predict complications after transplantation, but not so strongly as to preclude transplantation.

Platelet Disorders

Although inherited platelet disorders are rare, acquired disorders are quite common and affect at least 20% of all patients in medical and surgical ICUs, with infections and drug therapies being the leading causes (see also Chapter 61). Both acquired and inherited platelet conditions cause skin and mucosal bleeding, whereas defects in plasma coagulation produce deep tissue bleeding or delayed bleeding. Perioperative treatment of inherited platelet disorders (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome) consists of platelet transfusions. EACA has been used successfully (experimentally, 1 g/70 kg four times daily) to decrease perioperative bleeding in thrombocytopenic patients. The much more common acquired disorders may respond to one of several therapies (see Chapter 61). Immune thrombocytopenias, such as those associated with lupus erythematosus, idiopathic thrombocytopenic purpura, uremia, hemolytic-uremic syndrome, platelet transfusions, heparin, and thrombocytosis, may respond to steroids, splenectomy, plateletpheresis, eradication of Helicobacter pylori, or alkylating agents or may require platelet transfusions, plasma exchange, whole blood exchange, or transfusion; sometimes these disorders do not respond to anything. Traditionally, splenectomy is performed when steroid therapy fails or reaches a dosage that poses unacceptable risks of toxicity. Newer agents such as anti-D immune globulin and rituximab may induce desirable remissions in idiopathic thrombocytopenic purpura without splenectomy.

Thrombotic thrombocytopenic purpura is a rare disorder of unknown cause. Despite various therapies, this disorder carries a very high mortality rate. However, the introduction of plasmapheresis has improved response rates dramatically in patients with this disease. One uncontrolled study implies that the benefit lies not only in improvement of the hematologic picture but also in prevention of ARDS, a leading cause of death in these patients. In that study, early institution of plasmapheresis improved oxygenation.

By far the largest number of platelet abnormalities consists of drug-related defects in the aggregation and release of platelets. Aspirin irreversibly acetylates platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandin endoperoxidases. Because cyclooxygenase is not regenerated in the circulation within the life span of the platelet and because this enzyme is essential for the aggregation of platelets, one aspirin tablet may affect platelet function for a week. All other drugs that inhibit platelet function (e.g., vitamin E, indomethacin, sulfipyrazone, dipyriramole, tricyclic antidepressant drugs, phenothiazines, furosemide, steroids) do not inhibit cyclooxygenase function irreversibly; these drugs disturb platelet function for only 24 to 48 hours. If emergency surgery is needed before the customary 8-day period for platelet regeneration after aspirin therapy or if the 2-day period for other drugs has not elapsed, administration of 2 to 5 units of platelet concentrate will return platelet function in a 70-kg adult to an adequate level and platelet-induced clotting dysfunction to normal. Only 30,000 to 50,000 normally functioning platelets per milliliter are needed for normal clotting. Because low-dose aspirin therapy (<650 mg/day) allows aspirin to be gone from the body 24 hours after the last dose and because the body makes 70,000 platelets/mL blood per day, a 48-hour
<table>
<thead>
<tr>
<th>Cytokine/Other Names</th>
<th>Biologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>Erythrocyte production</td>
</tr>
<tr>
<td>Interleukin-3 (IL-3)</td>
<td>Stimulates proliferation and differentiation of granulocyte, macrophage, eosinophil, mast cell, megakaryocyte, and T- and B-cell lineage and early myeloid stem cells</td>
</tr>
<tr>
<td>Interleukin-2 (IL-2)</td>
<td>Growth factor for T cells, activates cytotoxic T lymphocytes, promotes synthesis of other cytokines, enhances natural killer cell function</td>
</tr>
<tr>
<td>Interleukin-4</td>
<td>Enhances antibody production (IgG and IgE) and up-regulates class II MHC molecules and Fc receptors on B cells</td>
</tr>
<tr>
<td>Interleukin-5</td>
<td>Enhances antibody production (IgA)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>B-cell differentiation and IgG secretion</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor (G-CSF)</td>
<td>Stimulates proliferation and differentiation, early myeloid stem cells, and—in the presence of erythropoietin—erythropoiesis</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony-stimulating factor (GM-CSF)</td>
<td>Stimulates granulocyte, macrophage, and megakaryocyte proliferation and differentiation, early myeloid stem cells, as well as platelet production (may be a thrombopoietin)</td>
</tr>
<tr>
<td>Colony-stimulating factor-1</td>
<td>Stimulates predominantly macrophage-monocyte proliferation and differentiation with lesser effects on granulocytes</td>
</tr>
<tr>
<td>Colony-stimulating factor-1</td>
<td>Acts synergistically with other factors on earlier myeloid stem cells</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Induces synthesis of acute-phase proteins by hepatocytes</td>
</tr>
<tr>
<td>Interleukin-1 (α and β)</td>
<td>Activates resting T cells, cofactor for T- and B-cell proliferation</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Chemotactic for monocytes and neutrophils</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Induces production of growth factors, including G-CSF, GM-CSF, IL-6, CSF-1, IL-3, and interferon by many cells</td>
</tr>
<tr>
<td>Interleukin-1 (α and β)</td>
<td>Radioprotective in mice</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>In the presence of IL-3, enhances mast cell growth; with G-CSF, enhances granulocytes of GM colony formation; and with erythropoietin and/or IL-1, stimulates erythroid and megakaryocyte colony formation</td>
</tr>
</tbody>
</table>

Continued
Hemophilia and Related Clotting Disorders

Abnormalities in blood coagulation as a result of defects in plasma coagulation factors are either inherited or acquired. Inherited disorders include X-linked hemophilia A (a defect in factor VIII activity), von Willebrand disease (defect in the von Willebrand factor of factor VIII), hemophilia B (a sex-linked deficiency of factor IX activity), and other less common disorders. The sex-linked origin of some of these disorders means that hemophilia occurs almost exclusively in the male children of female carriers; men do not transmit the disease to their male children.

In elective surgery, levels of the deficient coagulation factor should be assayed 48 hours preoperatively and the level restored to 40% of normal before the surgical procedure. One unit of factor concentrate per kilogram of body weight normally increases the factor concentration by 2%. Thus, in an individual essentially devoid of activity, administration of 20 units/kg body weight would be required as an initial dose. Because the half-life is 6 to 10 hours for factor VIII and 8 to 16 hours for factor IX, approximately 1.5 units/hour/kg of factor VIII or 1.5 units/2 hours/kg of factor IX should be given. Additional administration of factors VIII and IX should be guided by the activity of the clotting factors for approximately 6 to 10 days postoperatively.

These factors are available in various preparations; the newer genetically engineered von Willebrand factor, cryoprecipitate, which contains 20 units/mL, is obtained from regular donors (the risk of hepatitis being 1 in 200 for 5-mL lots) or from fresh frozen plasma (which contains 1 unit/mL). Some risk of transmitting hepatitis virus and HIV (the agent of acquired immunodeficiency syndrome [AIDS]) accompanies transfusion but, with better testing, much less than formerly. Current screening of blood for aspartate or alanine aminotransferase levels is believed to result in a much lower risk of hepatitis C and even AIDS from transfusion. Theoretically, antigenic testing for HIV should further decrease the risk of transmission by blood products. Heat treatment is also reported to reduce the risk substantially. Factor IX, but not factor VIII, is contained in prothrombin complex concentrates; however, these concentrates may contain activated clotting factors, which can lead to disseminated intravascular coagulation (DIC) and a high risk for hepatitis. In addition, although EACA or tranexamic acid is sometimes administered as a fibrinolytic inhibitor, these substances carry with them a significant risk for DIC. Additional hazards of modern therapy include acute and chronic hepatitis, AIDS, hypersensitivity reactions, psychic trauma, chronic pain with narcotic addiction, and inhibition of factors, especially VIII.

An antibody that inactivates factor VIII or IX (fresh frozen plasma fails to increase clotting factor activity after incubation with the patient’s plasma) develops in approximately 10% of patients with either hemophilia A or B. These acquired anticoagulants are usually composed of IgG, are poorly removed by plasmapheresis, and are variably responsive to immunosuppressive drugs. The use of prothrombin complex concentrates can be lifesaving but carries the risk of DIC and hepatitis.
Vitamin K deficiency is discussed in the section on liver disease. To review, vitamin K–dependent clotting factors (II, VII, IX, and X) require vitamin K for the post-synthetic addition of γ-carboxyl groups to glutamate residues; administration of vitamin K or fresh frozen plasma can correct these deficiencies.

Patients who come to the operating room after having received many units of blood (as in massive GI bleeding) may have deficient clotting. This impaired clotting is initially caused by depletion of platelets, which occurs after administration of approximately 10 to 15 units of blood and, later, by depletion of coagulation factors (see Chapter 62). Treatment of these deficiencies can be corrected with platelet concentrates—each concentrate is normally suspended in 50 mL of fresh plasma; thus, coagulation factors are also replaced.

Urokinase, streptokinase, and tissue-type plasminogen activator (t-PA) have been used to treat pulmonary embolism, deep vein thrombosis, stroke, and arterial occlusive disease. These drugs accelerate the lysis of thrombi and emboli, in contrast to heparin, which may prevent, but does not dissolve a thrombus. Bleeding complications associated with these fibrinolytic agents are the result of dissolution of hemostatic plugs and can be quickly reversed by discontinuing the medication and replenishing plasma fibrinogen with cryoprecipitate or plasma. However, cryoprecipitate and plasma are seldom needed preoperatively because the fibrinolytic activity of urokinase and streptokinase usually dissolves within 1 hour of discontinuing their administration. Nonetheless, insufficient data have accumulated to prescribe the ideal preoperative preparation and intraoperative management of hemostasis in patients recently treated with urokinase, streptokinase, or t-PA. Postponing surgery for three half-lives of the drug (increases in plasmin activity in blood can be assayed ≥4 to 8 hours) may not be possible, and meticulous observation of the operative field for hemostasis may not suffice. The process may be even more complex in a patient with a vascular or cardiac condition who requires heparin administration intraoperatorically. To correct the fibrinogen deficiency in these patients, some clinicians administer fibrinogen preoperatively and EACA at heparin administration.

DDAVP has been used in operations associated with high blood loss as a routine measure to decrease bleeding and transfusion requirements. DDAVP therapy began as treatment of platelet dysfunction in von Willebrand disease but has since expanded to routine use in patients undergoing cardiovascular surgery and to frequent use in other high–blood loss operations. A meta-analysis of cardiac surgery concluded that DDAVP was not associated with a clinically significant reduction in exposure to blood transfusion in unselected patients, and therefore the authors were unable to recommend the routine use of DDAVP in patients exposed to CPB. However, DDAVP may reduce postoperative bleeding in patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 minutes, and patients with demonstrable platelet dysfunction. The authors suggested that DDAVP could be used selectively in these subgroups.

### ONCOLOGIC DISEASE

Patients with malignant tumors may be otherwise healthy or may be desperately ill with nutritional, neurologic, metabolic, endocrinologic, electrolyte, cardiac, pulmonary, renal, hepatic, hematologic, or pharmacologic disabilities. Thus, determining the other disabilities accompanying malignant tumors requires evaluation of all systems. Abnormalities frequently accompanying such tumors include hypercalcemia either by direct bone invasion or by ectopic elaboration of PTH or other bone-dissolving substance, uric acid nephropathy, hyponatremia (especially with small cell, or oat cell, carcinoma of the lung), nausea, vomiting, anorexia and cachexia, fever, tumor-induced hypoglycemia, intracranial metastases (10% to 20% of all cancers), peripheral nerve or spinal cord disorders, meningeal carcinomatosis, toxic neuropathies secondary to anticancer therapy, and paraneoplastic neurologic syndromes (dermatomyositis, Eaton-Lambert syndrome, myopathies, and distal neuropathies).

Many patients with malignant tumors are given large doses of analgesics and should be kept comfortable during the perioperative period. Avoiding drug dependence is of no practical importance in terminally ill patients. Marijuana (tetrahydrocannabinol) depresses the CNS vomiting center and may be more effective than the phenothiazines or butyrophenones in suppressing the nausea associated with cancer and its therapy; marijuana decreases anesthetic requirements 15% to 30%. Immunomodulators, stimulating factors or cytokines, gene identification, and drugs for treating side effects (e.g., midazolam or ondansetron) have given new hope for safer, more effective therapy with fewer limiting side effects. The effect of ondansetron in preventing vomiting and the effect of midazolam in preventing memory-stimulated vomiting have been important additions. The neurokinin-1 (NK-1) antagonists have also been approved for treatment in oncologic patients.

The toxicity of cancer chemotherapy is related to the drugs used and the dose. For radiation therapy, damage occurs when the following doses are exceeded: lungs, 1500 rad; kidneys, 2400 rad; heart, 3000 rad; spinal cord, 4000 rad; intestine, 5500 rad; brain, 6000 rad; and bone, 7500 rad. The toxicities of biologic and immunomodulating therapies are related to the change in immune function that they cause. Alkylating agents cause bone marrow depression, including thrombocytopenia, as well as alopecia, hemorrhagic cystitis, nausea, and vomiting. The alkylating agents, including cyclophosphamide and mechlorethamine, can act as an anticholinesterase and prolong neuromuscular blockade. The antineoplastic alkaloid vincristine produces peripheral neuropathy and SIADH, and vinblastine produces myelotoxicity. Cisplatin is also associated with peripheral neuropathy and severe nausea. Nitrosoureas can produce severe hepatic and renal damage, as well as bone marrow toxicity, myalgia, and paresthesia. Folic acid analogues such as methotrexate have been linked to bone marrow depression, ulcerative stomatitis, pulmonary interstitial infiltrates, GI toxicity, and occasionally, severe liver dysfunction. Fluorouracil
Chapter 39: Anesthetic Implications of Concurrent Diseases

and flouxuridine, both pyrimidine analogues, cause bone marrow toxicity, megaloblastic anemia, nervous system dysfunction, and hepatic and GI alterations. Purine analogues (mercaptopurine, thioguanine) have bone marrow depression as their primary toxic effect. Anthracycline antibiotics (doxorubicin, daunorubicin, mitrilmycin, mitomycin C, bleomycin) can all cause pulmonary infiltrates, cardiomyopathy (especially doxorubicin and daunorubicin), myelotoxicity, and GI, hepatic, and renal disturbances.

The wisdom of anesthetizing patients given bleomycin has been questioned. A retrospective study by Goldiner and coauthors reported postoperative deaths in 5 consecutive patients given bleomycin.429 All 5 patients died of postoperative respiratory failure. Using the same anesthetic technique, Goldiner and coauthors then anesthetized 12 patients, limited the inspired oxygen concentration to 22% to 25% perioperatively, and replaced much of the blood loss with colloids rather than crystalloids.429 None of the 12 patients died. These investigators postulated that bleomycin caused epithelial cell edema that progressed to necrosis of type I alveolar cells, leakage of fluid into the alveolar space, and the formation of hyaline membranes similar to those associated with oxygen toxicity. Goldiner and coauthors believe that this pathophysiologic similarity indicates a possible synergistic relationship between oxygen and bleomycin.429 However, LaMantia and co-workers retrospectively analyzed the changes in 16 patients undergoing surgery after bleomycin therapy.430 Thirteen patients were given oxygen at inspired concentrations of 37% to 45%. No instances of postoperative respiratory failure occurred. Using data from the Mayo Clinic registry, the incidence of postoperative ARDS after major surgery with general anesthesia is approximately 1.3% (95% CI, 0.6% to 2.6%).431 The authors found a history of smoking as a major risk factor. Therefore, general anesthesia appears safe with appropriate perioperative management.

PATIENTS GIVEN DRUG THERAPY FOR CHRONIC AND ACUTE MEDICAL CONDITIONS

A steadily increasing number of potent drugs are being used to treat disease, and the average hospitalized patient receives more than 10 drugs (see also Chapter 38). Many drugs have side effects that may make anesthesia more risky or patient management more difficult. Knowing the pharmacologic properties and potential side effects of commonly used drugs helps the anesthesiologist avoid pitfalls during anesthesia and surgery.

ANTIHYPERTENSIVE DRUGS

ACE inhibitors (captopril, enalapril, lisinopril, enalaprilat, and ramipril) and angiotensin II receptor blockers are being used increasingly as first-line drugs and appear to improve the quality of life of patients taking antihypertensive drugs. One of the angiotensin II receptor blockers—valsartan—when combined with a diuretic, actually increases libido in both men and women while decreasing arterial blood pressure. However, ACE inhibitors and angiotensin II receptor blockers may be associated with more peripheral vasodilation and hypotension on induction of anesthesia than are sympatholytic agents. Added to this group are the ACE receptor blocking agents. Both ACE inhibitors and ACE receptor blocking agents are associated with such severe hypotension with standard anesthetic induction that we discontinue or at least consider discontinuing the use of these drugs preoperatively (see earlier).

Catecholamine or sympathetic receptor blocking drugs affect the three major types of catecholamine receptors: α-adrenergic, β-adrenergic, and dopaminergic. The existence of subdivisions (e.g., β1 and β2) suggested the possibility that some drugs would be found to affect only one set of receptors. For example, terbutaline is used more frequently than isoproterenol because terbutaline is said to exert a preferential effect on β2 receptors (i.e., dilation of bronchial smooth muscle), thereby avoiding the cardiac stimulation produced by drugs that stimulate β1-receptors. In fact, the selectivity is dose related. At a certain dose, a direct β2-receptor stimulating drug affects only those receptors but, at a higher dose, stimulates both β1 and β2 receptors. The effect of a given dose varies with each patient. A certain dose may stimulate β1 and β2 receptors in one patient but neither receptor in another patient. More and more selective blocking drugs are being developed in hope of widening the margin among β1, β2, and α-adrenergic effects. Ultimately, however, even more selectivity is desired. It would be advantageous to be able to decrease the heart rate without changing myocardial contractility or to increase contractility without changing the heart rate. Such is the goal of much drug research and the development of dobutamine and fenoldopam. However, to date, all such selectivity appears to be dose related, even for dobutamine.

Metoprolol (Lopressor) and atenolol (Tenormin) (both β1-adrenergic receptor blocking drugs) and propranolol, betaxolol, timolol, esmolol, pindolol, oxprenolol, acebutolol, carteolol, penbutolol, and nadolol are widely available β-adrenergic receptor blocking drugs used for long-term therapy in the United States. Because nadolol has poor lipid solubility, it has a long elimination half-life (17 to 24 hours) and does not cross the blood-brain barrier readily. Although selective β-adrenergic receptor blocking drugs should be more appropriate in patients with increased airway resistance or diabetes, this advantage is apparent only when low doses are used. The use of β-adrenergic receptor blocking drugs has become widespread because these drugs treat everything from angina and hypertension to priapism and stage fright. These drugs appear to decrease morbidity and mortality in patients who have initially survived MI,432,433 and they may increase perioperative survival in selected patients.

When administration of β-adrenergic receptor blocking drugs is terminated, sympathetic stimulation often increases, as though the body had responded to the presence of these drugs by increasing sympathetic neuron activity. Thus, propranolol and nadolol (to name just two) withdrawal can be accompanied by a hyper-β-adrenergic condition that increases myocardial oxygen demands. Administering propranolol or metoprolol can cause bradycardia, CHF, fatigue, dizziness, depression, psychoses,
bronchospasm, and Peyronie disease. The POISE study emphasized the concerns that inadequate titration of these agents can lead to stroke or increased mortality. Side effects of dopaminergic receptor blocking drugs are discussed later. Prazosin (Minipress), terazosin, and oxazocin are α1-adrenergic receptor blocking drugs used to treat hypertension, ischemic cardiomyopathy, receding hairlines, and benign prostatic hypertrophy because they dilate both veins and arteries and reduce sphincter tone. These drugs are associated with vertigo, palpitations, depression, dizziness, weakness, and anticholinergic effects.

Some sympathomimetic drugs stimulate α-adrenergic receptors in the brainstem. Clonidine (Catapres), a drug with a half-life of 12 to 24 hours, guanabenz, and guanfacine (Tenex) are α2-adrenergic receptor stimulants. Presumably, α2-adrenergic agonists, including clonidine, guanabenz, and guanfacine, lower arterial blood pressure on a long-term basis through the central brainstem adrenergic stimulation referred to previously. They may also be used on a long-term basis to treat opiate, cocaine, food, and tobacco withdrawal. Occasionally, withdrawal from clonidine can precipitate a sudden hypertensive crisis, analogous to that occurring on withdrawal from propranolol, and it can cause a hyper–β-adrenergic condition. The degree of hypertensive crisis after clonidine withdrawal is now being debated. (Although intravenous clonidine is not available in the United States, a skin patch of clonidine is used preoperatively to ablate sympathomimetic responses perioperatively.) Tricyclic antidepressant drugs and presumably phenothiazines and the butyrophenones interfere with the action of clonidine. Although administration of a butyrophenone (e.g., droperidol) to a patient taking clonidine, guanabenz, or guanfacine on a long-term basis could theoretically precipitate a hypertensive crisis, this has not been reported. Clonidine administration can be accompanied by drowsiness, dry mouth, orthostatic hypotension, bradycardia, and impotence. Acute clonidine or dexmedetomidine administration decreases anesthetic requirements by at least 40% to 60%; long-term administration decreases requirements by 10% to 20%. Because of the relative safety of these drugs and their ability to decrease anesthetic requirements, block narcotic-induced muscle rigidity, and provide pain relief, their popularity preoperatively, intraoperatively, and in ICU sedation is increasing dramatically.

Three other classes of antihypertensive drugs affect the sympathetic nervous system indirectly: diuretics, arteriolar dilators, and slow-(calcium) channel blocking agents. Thiazide diuretic drugs are associated with hypochloremic alkalosis, hypokalemia, hyperglycemia, hyperuricemia, and hypercalcemia. The potassium-sparing diuretic spironolactone is associated with hyperkalemia, hyponatremia, gynecomastia, and impotence. All diuretic drugs can cause dehydration. The thiazide diuretics and furosemide appear to prolong neuromuscular blockade. The arteriolar dilator hydralazine can cause a lupus-like condition (usually with renal involvement), nasal congestion, headache, dizziness, CHF, angina, and GI disturbances. Such a syndrome is nonexistent with the other direct vasodilator on the U.S. market, minoxidil.

The slow-channel calcium ion antagonists (calcium channel blocking drugs) inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces the heart rate (negative chronotropy), depresses contractility (negative inotropy), decreases conduction velocity (negative dromotropy), and dilates coronary, cerebral, and systemic arterioles. The slow-channel calcium ion antagonists (calcium channel blocking drugs) inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces the heart rate (negative chronotropy), depresses contractility (negative inotropy), decreases conduction velocity (negative dromotropy), and dilates coronary, cerebral, and systemic arterioles.
produce such effects, but to varying degrees and apparently by similar, but different mechanisms. These mechanisms relate to the three different classes of calcium channel antagonists that they represent: the phenylalkylamines, the benzothiazepines, and the dihydropyridines, respectively. Nifedipine is the most potent of the three as a smooth muscle dilator, whereas verapamil and diltiazem have negative dromotropic and inotropic effects and vasodilating properties. Diltiazem has weak vasodilating properties when compared with nifedipine and has less of an AV conduction effect than does verapamil. Thus, verapamil and diltiazem can increase the PR interval and produce AV block. In fact, reflex activation of the sympathetic nervous system may be necessary during the administration of diltiazem, and especially during verapamil therapy, to maintain normal conduction. Clearly, verapamil and diltiazem must be titrated very carefully when a patient is already taking a β-adrenergic receptor blocking drug or when adding β-blocking drugs to a patient already taking verapamil or diltiazem.

The use of calcium channel blocking drugs has several important implications for anesthetic management.439-441 First, the effects of inhaled and narcotic anesthetics and nifedipine in decreasing systemic vascular resistance, arterial blood pressure, and contractility may be additive. Similarly, verapamil and anesthetics (inhaled anesthetics, nitrous oxide, and narcotics) increase AV conduction times and additively decrease arterial blood pressure, systemic vascular resistance, and contractility. Second, verapamil and presumably the other calcium channel blocking drugs have been found to decrease anesthetic requirements by 25%. These drugs can produce neuromuscular blockade, potentiate both depolarizing and nondepolarizing neuromuscular blocking drugs, and, in at least one type of myopathy (Duchenne muscular dystrophy), even precipitate respiratory failure. Finally, because slow-channel activation of calcium is necessary to cause spasms of cerebral and coronary vessels, bronchoconstriction, and normal platelet aggregation, these drugs may have a role in treating ischemia of the nervous system, bronchoconstriction, and unwanted clotting disorders perioperatively. All three drugs are highly protein bound and may displace or be displaced by other drugs that are also highly protein bound (e.g., lidocaine, bupivacaine, diazepam, disopyramide, and propranolol). Adverse consequences can be minimized by titrating the inhaled or narcotic drug to the hemodynamic and anesthetic effects. Hemodynamic, but not electrophysiologic, changes can usually be reversed by administering calcium. Reversal of the electrophysiologic effects may occur if “industrial” doses of β-adrenergic agonists are given.

**MOOD-ALTERING DRUGS**

Mood-altering drugs are the most frequently prescribed medications in the United States.442,443 They include MAOIs, SSRIs, phenothiazines, tricyclic antidepressant drugs, other antidepressants that do not fall into previous drug category classifications such as buproprion, and drugs of abuse such as cocaine. MAOIs, which include isocarboxazid (Marplan), phenelzine (Nardil), pargyline (Eutonyl), tranylcypromine (Parnate), and deprenyl, bind irreversibly to the enzyme MAO, thereby increasing intraneuronal levels of amine neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine, octopamine). This increase is associated with an antidepressant effect, an antihypertensive effect, an antinarcoleptic effect, elevation of liver enzymes, and delayed onset of Parkinson disease (deprenyl). Because two forms of the enzyme (MAO-A and MAO-B) are selective in vitro for substrate (MAO-A is selective for serotonin, dopamine, and norepinephrine; MAO-B for tyramine and phenylethylamine), presumably MAOIs selective for MAO-A or MAO-B would have different effects.444 This is not known for certain inasmuch as deprenyl (selegiline [Eldepryl]), an MAO-B-selective drug, improves a dopamine deficiency state, parkinsonism.

Interactions between MAOIs and a variety of foods and drugs containing indirect-acting sympathomimetic substances such as ephedrine or tyramine (found especially in aged cheeses) can occur for as long as 2 weeks after the last dose of MAOI is given. The most serious effects of this interaction are convulsions and hyperpyrexic coma (particularly after narcotics).

Anesthetic management of a patient given an MAOI can be chaotic; for this reason it is widely accepted practice to discontinue MAOIs at least 2 to 3 weeks before any planned operation.442-448 An alternative point of view has been expressed regarding severely psychotic patients or emergency surgery.444,449-451 Clearly, the risk of discontinuing MAOIs must be weighed against the risk of suicidal tendencies in some patients deprived of MAOIs. No reported experiences of interactions between narcotics and deprenyl have been published, so judgments about possible worsening of Parkinson disease and continuing MAOIs have no basis in data. Severe reactions have occurred when too short an interval existed between the administration of MAOIs and tricyclic antidepressants. Emergency surgery in patients given MAOIs can be punctuated by hemodynamic instability. A regional block can be attempted as treatment of postoperative pain to avoid having to give narcotics. Cases of hyperpyrexic coma after the administration of most narcotics have been reported in humans, and animal studies document a 10% to 50% incidence of hyperpyrexic coma in animals pretreated with MAOIs and then given a variety of narcotics.442-448 These reactions appear to be treated best by therapy supporting vital functions.

Alternative drugs for the treatment of severe depression include the tricyclic antidepressant drugs: amitriptyline (Elavil, Endep), imipramine (Tofranil, Preshane), desipramine (Norpramin), doxepin (Adapin, Sinequan), nortriptyline (Aventyl), fluoxetine (Prozac), trazodone (Desyrel), and others.442,443 Tricyclic antidepressant drugs also block the reuptake of neurotransmitters and cause their acute release. Given on a long-term basis, these drugs decrease stores of noradrenergic catecholamines. Tricyclic antidepressant drugs also produce side effects similar to those of atropine (dry mouth, tachycardia, delirium, urinary retention) and can cause changes on the ECG (changes in the T wave, prolongation of the QRS complex, bundle branch block or other conduction abnormalities, or PVCs). Although arrhythmias induced by tricyclic antidepressants have been treated
successfully with physostigmine, bradycardia has sometimes occurred.\textsuperscript{442,443} Drug interactions with tricyclic antidepressants include those related to blockade of the reuptake of norepinephrine (e.g., interference with the action of guanethidine) and fatal arrhythmias after halothane and pancuronium.\textsuperscript{452,453} Such interactions, although predictable for a population of patients, may not alter a patient's threshold for arrhythmias. The newer antidepressants (the SSRIs) can also have serious side effects. Fluoxetine, a tricyclic antidepressant that also has an SSRI effect, causes nausea, vomiting, headaches, nervousness, and possibly paranoia and ideas of suicide more commonly than do the other tricyclics\textsuperscript{442,443}; however, it is less likely to cause anticholinergic effects or orthostatic hypotension. Bupropion, which is fundamentally different than the SSRIs, may cause nausea, vomiting, seizures, agitation, tremor, excitement, and increased motor activity, but it only rarely causes anticholinergic effects or orthostatic hypotension. Discontinuing drugs can cause withdrawal symptoms or precipitate recurrence of psychiatric illness. Switching among drugs for depression can cause hyperpyrexia and coma. Thus, switching drugs preoperatively should not be requested casually.\textsuperscript{442,443}

The effectiveness of phenothiazines and butyrophenones in schizophrenia suggests a dopamine receptor blocking action. In addition, these drugs possess varying degrees of parasympathetic stimulation and ability to block \(\alpha\)-adrenergic receptors. The phenothiazines include chlorpromazine (Thoraze, Chlor-PZ), promazine (Spa-rine), triflupromazine (Vesprin), fluphenazine (Prolixin), trifluperazine, prochlorperazine (Compazine), and many others. The butyrophenones include droperidol and haloperidol (Haldol). Both the phenothiazines and butyrophenones produce sedation, depression, and antihistaminic, antiemetic, and hypothermic responses. They are also associated with cholstatic jaundice, impotence, dystonia, and photosensitivity. Other side effects associated with phenothiazines include orthostatic hypotension (partly as a result of \(\alpha\)-adrenergic blockade) and abnormalities on the ECG such as prolongation of the QT or PR intervals, blunting of T waves, depression of the ST segment, and on rare occasion, PVCs and torsades de pointes.\textsuperscript{442,443,452,453}

Although few data are available on the antidepressant drugs selective for serotonin (the SSRIs), occasional case reports of severe hypotension and cardiac arrest with severe bradycardia have been presented in abstract form.

Several important drug interactions are noteworthy for the phenothiazine derivatives. The effects of CNS depressants (especially narcotics and barbiturates) are enhanced by the concomitant administration of phenothiazines. In addition, the CNS seizure threshold is lowered by the administration of phenothiazines, which should be avoided in patients who are epileptic or withdrawing from any drug that depresses the CNS. The antihypertensive effects of guanethidine and guanadrel are blocked by tricyclic antidepressant drugs and the phenothiazines.\textsuperscript{454} Lithium carbonate is used to treat manic depression, but it is more effective in preventing mania than in relieving depression. In excitable cells, lithium mimics sodium and decreases the release of neurotransmitters both centrally and peripherally. Lithium prolongs neuromuscular blockade and may decrease anesthetic requirements because it blocks brainstem release of norepinephrine, epinephrine, and dopamine.

Psychoactive drugs such as the amphetamines (including methamphetamine and their smokable derivative in crystal form known as “ice”) and cocaine acutely release norepinephrine, epinephrine, and dopamine and block their reuptake. Taken on a long-term basis, they deplete nerve endings of these neurotransmitters.

Drugs that appear to increase central \(\alpha\)-adrenergic release increase anesthetic requirements, whereas drugs that appear to decrease central \(\alpha\)-adrenergic release decrease anesthetic requirements. (This may not be the mechanism by which they alter anesthetic requirements, but it is a convenient way of remembering the alteration.) Drugs that affect only the \(\beta\)-adrenergic receptors do not alter anesthetic requirements.

**ANTIARRHYTHMIC DRUGS**

Antiarrhythmic drugs include local anesthetics (lidocaine, procaine), anticonvulsant (phenytoin) or antihypertensive (propranolol) drugs, calcium channel blocking drugs, or primary antiarrhythmic drugs (see also Chapters 67 and 68). These drugs are classified into five major categories: local anesthetics that alter phase 0 and phase 4 depolarization (quinidine, procainamide, and flecainide), local anesthetics that affect only phase 4 depolarization (lidocaine, tocainide, phenytoin, encaïnide), \(\beta\)-adrenergic receptor antagonists, antiadrenergic drugs (bretylium, disopyramide, amiodarone), and calcium entry blockers. These drugs are discussed elsewhere in this chapter. A lack of adverse reports does not indicate that all these drugs should be continued through the time of surgery; pharmacokinetic studies have not yet determined whether anesthesia (or anesthesia with specific agents) alters the volume of distribution or clearance of these drugs to an extent sufficient to warrant changing the dosage or dosage schedule in the perioperative period. The dearth of reports on this subject may reflect a lack of significant drug interaction or a lack of awareness that untoward events could be caused by such an interaction.

The pharmacologic characteristics of the various antiarrhythmic drugs can affect anesthetic management. Disopyramide is similar to quinidine and procainamide in its antiarrhythmic effectiveness. Disopyramide is excreted mainly by the kidneys, but hepatic disease increases its half-life. This drug often produces anticholinergic effects, including tachycardia, urinary retention, and psychosis. Hepatitis has also been reported to have occurred after its use.\textsuperscript{455} Little is known of the interaction of bretylium with anesthetic agents. Because bretylium blocks the release of catecholamines, long-term therapy with this drug has been associated with hypersensitivity to vaso-pressors.\textsuperscript{455} Quinidine depends on the kidneys for excretion, can produce vagolytic effects that can decrease cardiovascular output and increase the risk of arrhythmias when given with other drugs, and is associated with blood dyscrasias and GI disturbances.\textsuperscript{455} Most of the antiarrhythmic drugs enhance nondepolarizing neuromuscular blockade. Reports have confirmed this enhancement for quinidine, phenytoin, lidocaine, procainamide, and propranolol.\textsuperscript{456-464} No data document such an effect for depolarizing muscle relaxants. Amiodarone, an antiadrenergic drug used to treat...
recurrent supraventricular and ventricular tachycardia, causes thyroid dysfunction as a result of the large amount of iodine in its structure (see the section on thyroid disorders earlier in this chapter), as well as peripheral neuropathy, and has been associated with hypertension, bradycardiac arrhythmias, and reduced cardiac output during anesthesia. The drug has a half-life of 29 days, and its pharmacologic effects persist for more than 45 days after discontinuance.

**ANTIBIOTICS**

Many antibacterial drugs are nephrotoxic or neurotoxic, or both, and many prolong neuromuscular blockade (see also Chapters 34 and 35). The only antibiotics devoid of neuromuscular effects appear to be penicillin G and the cephalosporins. Most enzyme-inducing drugs do not increase the metabolism of enflurane or isoflurane. However, isoniazid induces the microsomal enzymes responsible for the metabolism of at least enflurane and thereby increases the possibility of fluorine-associated renal damage after enflurane administration. Appropriate antibiotic prophylaxis for surgery requires a knowledge of the probability of infection for that type of surgical procedure and, if the incidence of infection warrants, the use of a drug regimen directed against the most likely infecting organisms.

**MEDICATIONS FOR GLAUCOMA**

Medications for glaucoma include two organophosphates: echothiophate and isofluorophate (see also Chapter 84). These drugs inhibit serum cholinesterase, which is responsible for the hydrolysis and inactivation of succinylcholine and ester-type local anesthetics such as procaine, chloroprocaine, and tetracaine (see also Chapters 34 and 36). These ester-type local anesthetics should be avoided in patients treated with eye drops containing organophosphate. Table 39-16 lists other medications related to anesthesia and their side effects (from the National Registry for Drug-Induced Ocular Side Effects,

---

**TABLE 39-16 COMMON OPHTHALMOLOGIC DRUGS AND THEIR ANESTHETICALLY IMPORTANT INTERACTIONS**

<table>
<thead>
<tr>
<th>Drug (Trade Name)</th>
<th>Toxicities and Specific Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glaucoma: Primary Goal Is to Reduce IOP By</strong></td>
<td></td>
</tr>
<tr>
<td>Miotics and epinephrine: increase outflow of aqueous humor</td>
<td></td>
</tr>
<tr>
<td>β-Blockade and carbonic anhydrase inhibitors: reduce production of aqueous humor</td>
<td></td>
</tr>
<tr>
<td>Osmotic drugs: transiently decrease volume</td>
<td></td>
</tr>
<tr>
<td><strong>Miotics</strong></td>
<td></td>
</tr>
<tr>
<td>Parasympathomimetics</td>
<td></td>
</tr>
<tr>
<td>Pilocarpine (Adsorbocarpine, Isopto Carpine, Pilocar, Pilocel)</td>
<td></td>
</tr>
<tr>
<td>Carbachol</td>
<td></td>
</tr>
<tr>
<td><strong>Acetylcholinesterase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Physostigmine</td>
<td></td>
</tr>
<tr>
<td>Demecarium</td>
<td></td>
</tr>
<tr>
<td>Isofurophate (Floropryl)</td>
<td></td>
</tr>
<tr>
<td>Echothiophate (Echodide, Phospholine)</td>
<td></td>
</tr>
<tr>
<td><strong>Epinephrine (Epitrate, Murocoll, Mytrate, Epifrin, Glaucan, Epinal, Eppy)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Timolol (Timoptic)</td>
<td></td>
</tr>
<tr>
<td>Betaxolol (Beoptic)</td>
<td></td>
</tr>
<tr>
<td>Levobunolol (Betagan)</td>
<td></td>
</tr>
<tr>
<td><strong>Carbonic Anhydrase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide (Diamox)</td>
<td></td>
</tr>
<tr>
<td>Dichlorphenamide (Daranide, Oratrol)</td>
<td></td>
</tr>
<tr>
<td>Ethoxzolamide (Cardrase, Ethamide)</td>
<td></td>
</tr>
<tr>
<td>Methazolamide (Neptazane)</td>
<td></td>
</tr>
<tr>
<td><strong>Osmotic Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Glycerin (Glyrol, Osmoglyn)</td>
<td></td>
</tr>
<tr>
<td>Isosorbide (Ismotic)</td>
<td></td>
</tr>
<tr>
<td>Urea (Urevert, Ureaphil)</td>
<td></td>
</tr>
<tr>
<td>Mannitol (Osmotrol)</td>
<td></td>
</tr>
<tr>
<td>Intraocular acetylcholine (Miochol)</td>
<td></td>
</tr>
<tr>
<td><strong>Mydriatics and Cycloplegics: Provide Pupillary Dilatation and Paralysis of Accommodation</strong></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics block muscarinic receptors; paralyzing in iris</td>
<td></td>
</tr>
<tr>
<td>α-Adrenergics contract the dilator of the iris</td>
<td></td>
</tr>
<tr>
<td>Tox: Hypersalivation, sweating, N/V, bradycardia, hypotension, bronchospasm, CNS effects, coma, respiratory arrest, death</td>
<td></td>
</tr>
<tr>
<td>Rx: Atropine, pralidoxime (Protopam)</td>
<td></td>
</tr>
<tr>
<td>Ix: Succinylcholine—prolonged apnea (drugs must be discontinued 4 wk before)</td>
<td></td>
</tr>
<tr>
<td>Tox: (rare) Tachycardia, PVCs, HTN, headache, tremors</td>
<td></td>
</tr>
<tr>
<td>Ix: Avoid drugs that sensitize to catecholamines (e.g., halothane)</td>
<td></td>
</tr>
<tr>
<td>Tox: β-Blockade with bradycardia, exacerbation of asthma, CNS depression, lethargy, confusion</td>
<td></td>
</tr>
<tr>
<td>Synergy noted with systemic drugs</td>
<td></td>
</tr>
<tr>
<td>Tox: Anorexia, GI disturbances, “general miserable feeling” and malaise, paresthesias, diuresis, hypokalemia (transient), renal colic and calculi, hyperuricemia, thrombocytopenia, aplastic anemia, acute respiratory failure in patients with COPD</td>
<td></td>
</tr>
<tr>
<td>Tox: Dehydration, hyperglycemia, nonketotic hyperosmolar coma (rare); fatalities with mannitol secondary to CHF or intracranial bleeding; urea may cause thrombosis</td>
<td></td>
</tr>
<tr>
<td>Tox: Hypotension, bradycardia</td>
<td></td>
</tr>
<tr>
<td>Rx: Atropine</td>
<td></td>
</tr>
</tbody>
</table>

Continued
### TABLE 39-16 COMMON OPHTHALMOLOGIC DRUGS AND THEIR ANESTHETICALLY IMPORTANT INTERACTIONS—cont’d

<table>
<thead>
<tr>
<th>Drug (Trade Name)</th>
<th>Toxities and Specific Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>Tachycardia, HTN, PVCs, myocardial ischemia, agitation</td>
</tr>
<tr>
<td>Atropine (Atropisol, Bufopto, Isoto Atropine)</td>
<td>Tox: Dry mouth, flushing, thirst, tachycardia, seizure, hyperactivity, transient psychosis, rare coma, and death</td>
</tr>
<tr>
<td>Cyclopentolate, alone (Cyclolgy) or with phenylephrine-homatropine (Cyclomydri)</td>
<td>Rx: Phystostigmine</td>
</tr>
<tr>
<td>Homatropine (Homatocrel, Isoto Homatropine)</td>
<td></td>
</tr>
<tr>
<td>Scopolamine (Isopto Hyoscine, Murocoll 19)</td>
<td></td>
</tr>
<tr>
<td>Tropicamide (Midriacyl)</td>
<td></td>
</tr>
<tr>
<td><strong>β-Adrenegics</strong></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine (Eriel, Mydfrin, Neo-Synephrine)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyamphetamine (Paredrine)</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from the National Registry for Drug-Induced Ocular Side Effects, Portland, Ore., Oregon Health Sciences University.*

**CHF,** Congestive heart failure; **CNS,** central nervous system; **COPD,** chronic obstructive pulmonary disease; **GI,** gastrointestinal; **HTN,** hypertension; **IOP,** intracocular pressure; **BR,** interaction; **N/V,** nausea and vomiting; **PVCs,** premature ventricular contractions; **Rx,** treatment; **Tox,** toxicity.

---

Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, Ore 97201; 503-279-8456).

**Complete references available online at expertconsult.com**

**Acknowledgment**

The editors and publisher would like to thank Drs. Michael F. Roizen and Lee A. Fleisher for contributing a chapter on this topic to the seventh edition of this work. It has served as the foundation for the current chapter.

**REFERENCES**

REFERENCES

27. Roizen MF: RealAge: are you as young as you can be? New York, 1999, HarperCollins.
References


63. Roizen MF: Should we all have a sympathectomy at birth? Or at least preoperatively? Anesthesiology 68:482, 1988.


References

References


References


References

References

343. Nichol KL, Nordin JD, Nelson DB, et al: Effectiveness of influ-
344. Sterns RH: Severe symptomatic hyponatremia: treatment and out-
345. Surawicz B: Relationship between electrocardiogram and electro-
349. Kharasch ED, Bowdle TA: Hypokalemia before induction of anes-
350. Allen M, Dunlay R, Copkney C: Nebulised albuterol for acute hy-
administration of potassium chloride to furosemide pretreated
352. Fahy TS, Cho CS, Lee KH: Clonidine premedication pre-
353. Lawson DH: Adverse reactions to potassium chloride, Q J Med
354. Vitez TS, Soper LE, Wong KC, Soper P: Chronic hypokalemia and
358. Adelsberger SE, Wolfe LC: Inherited disorders of the red cell membrane
359. Muretto P, Angelucci E, Lucarelli G: Reversibility of cirrhosis in
361. Messent M: Com: exchange transfusion is not required for sickle cell
368. Ould Amar K, Rouvillain JL, Loko G: Perioperative transfusion
management in patients with sickle cell anaemia undergoing a total hip arthroplasty: is there a role of red-cell exchange transfu-
sion? A retrospective study in the CHU of Fort-de-France Marti-
nique, Transfus Clin Biol 20:30-34, 2013.
thetist management of 21 patients undergoing laparotomy for
management of patients with carcinoid heart disease having val-
375. Watson JT, Badner NH, Ali MJ: The prophylactic use of octreotide
in a patient with ovarian carcinoid and valvular heart disease, Can
376. McCrillis A, Hickman J: Octreotide for carcinoid syndrome, Can
377. Quinlivan JK, Roberts WA: Intraoperative octreotide for refrac-
378. Dilger JA, Rho EH, Que FG, Sprung J: Octreotide-induced brady-
cardia and heart block during surgical resection of a carcinoid
prevent serotonin release and flushing during chemoembolization
in the irritable bowel syndrome: a multivariate study of patients
and non-patients with irritable bowel syndrome, Gastroenterology
381. Atkenhead AR, Robinson S: Influence of morphine and pethidine
on the incidence of anastomotic dehiscence after colonic surgery,
transfusions in children with sickle cell anemia and abnormal
results on transcranial Doppler ultrasonography, N Engl J Med
conservative and aggressive transfusion regimens in the peri-
operative management of sickle cell disease, N Engl J Med
leukocytes in sickle cell vascular occlusion: a new paradigm, Proc
caeaean section in a patient with sickle-cell trait, Can J Anaesth
388. Hemming AE: Pro: exchange transfusion is required for sickle cell
trait patients undergoing cardiopulmonary bypass, J Cardiovasc
389. Messent M: Con: exchange transfusion is not required for sickle cell
trait patients undergoing cardiopulmonary bypass, J Cardio-
use of transfusion therapy perioperatively in patients with sickle


