• Miller-Adrenocortical Malfunction

Three major classes of hormones—androgens, glucocorticoids, and mineralocorticoids—are secreted by the adrenal cortex. 105, 106 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. 107, 108, 109, 110, 111, 112, 113, 114, 115 Unfortunately, the lack of a wide variety of abdominal imaging procedures, plus the underuse of those procedures that do exist, has meant that many adrenal masses have been discovered only incidentally. 116, 117, 118 Because etomidate is an anesthetic that profoundly limits adrenal reserves, it is often the anesthesiologist who comes into contact with abnormalities of adrenocortical function.

Controlled comparisons of perioperative management for patients who have disorders of adrenal function are lacking. 105 However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable us 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, 119 constitute major sources of androgens in women. 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. 119 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 prior to surgery. 119 Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and consequently require supplementation of these hormones perioperatively (see later).

Glucocorticoids

The principal glucocorticoid, cortisol, is an essential regulator of carbohydrate, protein, lipid, and nucleic acid metabolism. Cortisol is believed to exert its biologic effects through a sequence of steps initiated by hormone binding to stereospecific intracellular cytoplasmic receptors. This bound complex stimulates nuclear transcription of specific messenger ribonucleic acids (mRNAs). These mRNAs are then translated to give rise to proteins that mediate the ultimate effects of hormones.

Most cortisol is bound to corticosterone-binding globulin (CBG, transcortin). It is the relatively small amounts of unbound cortisol that enter cells to induce actions or to be metabolized. Conditions that induce changes in the amount of CBG include liver disease and nephrotic syndrome, both of which result in decreased circulating levels of CBG, and estrogen administration and pregnancy, which result in increased CBG production. Total serum

cortisol levels may become elevated or depressed under these conditions that alter the amount of bound cortisol, and yet the unbound, active form of cortisol is present in normal amounts. The most accurate measure of cortisol activity is the level of urinary cortisol—that is, the amount of unbound, active cortisol filtered by the kidney.

The serum half-life of cortisol is 80 to 110 minutes. 111 However, because cortisol acts through intracellular receptors, pharmacokinetic data based on serum levels are not good indicators of cortisol activity. After a single dose of glucocorticoid, serum glucose is elevated for 12 to 24 hours; improvements in pulmonary function in patients with bronchial asthma can still be measured 24 hours after glucocorticoid administration. 111 Treatment schedules for glucocorticoid replacement are based, therefore, not on the measured serum half-life, but on the well-documented prolonged end-organ effect of these steroids. Hospitalized patients requiring chronic glucocorticoid replacement therapy are usually treated twice daily, with a slightly higher dose given in the morning than in the evening, to stimulate the normal diurnal variations in cortisol levels. 105 For patients who require parenteral "steroid coverage" during and after surgery (see later paragraphs), administration of glucocorticoid every 12 hours is appropriate. 109, 110 Relative potencies of glucocorticoids are listed in Table 25–7. Cortisol is inactivated primarily in the liver and is excreted as 17- hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into the urine.

TABLE 25–7. Relative Potency and Equivalent Doses for Commonly Used Glucocorticoids

The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (more than 30 mg/d), cortisol and cortisone bind to mineralocorticoid receptor sites and cause salt and water retention and loss of potassium and hydrogen ions. 111 When these steroids are administered in maintenance doses of 30 mg/d or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. 111 Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect 111 (see Table 25–7).

Secretion of glucocorticoids is regulated by pituitary adrenocorticotropic hormone (ACTH). ACTH is synthesized from a precursor molecule (preopiomelanocortin) that breaks down to form an endorphin (b-lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm normally greatest during the early morning hours in men, later in women, and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor 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 pituitary and hypothalamic levels to inhibit secretion of ACTH and corticotropin-releasing factor.

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. 120 This action is most prominent in the distal renal tubule but also occurs in salivary and

sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of the renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. 120 Renin splits the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by increased potassium concentration and, to a lesser degree, by ACTH. 120

Adrenocortical Hormone Excess

Glucocorticoid Excess

Glucocorticoid excess (Cushing syndrome) resulting from either endogenous oversecretion or chronic treatment with high-dose glucocorticoids produces a moon-faced plethoric individual having 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. These patients often have osteopenia due to 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 resulting from inhibition of peripheral use of glucose, as well as anti-insulin action and concomitant stimulation of gluconeogenesis.

The most common cause of Cushing syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies. 105 In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the preoperative period) by secreting more steroid. Thus, additional glucocorticoids may be required perioperatively (see the later section, *The Patient Taking Steroids for Other Reasons*). Spontaneous Cushing syndrome may be caused by pituitary production of ACTH (60–70% of all spontaneous cases), which is usually associated with pituitary microadenoma, or nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus). 121 Ten to twenty percent of cases of spontaneous Cushing syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.

Special preoperative considerations for patients having 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. 105 Treatment with the aldosterone antagonist spironolactone will stop the potassium loss and help 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. 105 In addition, glucocorticoids are lympholytic and immunosuppressive, increasing the patient's susceptibility to infection. 122, 123 The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by topical administration of vitamin A. 122

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. 121 Our perioperative treatment for patients who have Cushing disease and a pituitary microadenoma differs from that for patients who have a pituitary adenoma associated with amenorrhea and galactorrhea. 121 The patient with Cushing disease tends to bleed more easily and (on the basis of anecdotal evidence) tends to have a higher central venous pressure. Thus, during trans-sphenoidal tumor resection in such patients, the author routinely monitors central venous pressure and maintain it in the low end of the normal range. In other cases of trans-sphenoidal resection of microadenoma, such monitoring is needed only infrequently.

Ten to fifteen percent of patients with Cushing syndrome have adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. 105 If either unilateral or bilateral adrenal resection is planned, the author normally begins administering glucocorticoids at the start of resectioning of the tumor. Although no definitive studies exist, I normally give 100 mg of hydrocortisone hemisuccinate or hydrocortisone phosphate every 12 hours intravenously. I reduce this amount over 3 to 6 days until a maintenance dose is reached. Beginning on day 3, I also give a mineralocorticoid, 9a-fluorocortisol (0.05–0.1 mg/d). For certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For the patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. At the University of California, San Francisco, the incidence of pneumothorax in adrenal resection approached 20 percent during the early 1980s; this rate is similar to the incidence at the University of Chicago at present. The diagnosis of pneumothorax is sought and treatment is begun before the wound is closed.

Bilateral adrenalectomy with Cushing syndrome has a high incidence of postoperative complications and a perioperative mortality rate of 5 to 10 percent; it often results in permanent mineralocorticoid and glucocorticoid deficiency. Ten percent of patients with Cushing syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After reduction of high levels of cortisol by adrenalectomy, the pituitary tumor enlarges. 121 These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation. 121

Adrenal adenomas are generally treated surgically; often the contralateral gland resumes functioning after several months. Frequently, however, the effects of carcinomas are not cured by surgery. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (*o,p* Åå-DDD[2,2-bis(2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane]), may ameliorate some symptoms but may not improve survival. These drugs and the aldosterone antagonist spironolactone 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 chronic glucocorticoid replacement therapy (that is, 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, since most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. 124 These symptoms constitute primary hyperaldosteronism, or Conn syndrome (a cause of low-renin hypertension, as renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5 to 1.0 percent of hypertensive patients who have no other known cause of hypertension. 124 Primary hyperaldosteronism most often results from unilateral adenoma, although 25 to 40 percent 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. 124 A patient who has a serum potassium level of 2.9 mEq/L may have a deficit of body potassium of as little as 40 mEq or as much as 400 mEq. Frequently, at least 24 hours is required to restore potassium equilibrium. 125, 126, 127, 128 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. 129 A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when blood pressure and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive drugs were used. 106 However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly established. The author has 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. 105 The management of this type of glucocorticoid deficiency is discussed in the next section, *The Patient Taking Steroids for Other Reasons.* Other causes of adrenocortical insufficiency include 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 causes both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral. 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.

Autoimmune destruction of the adrenals may be associated with other autoimmune disorders, such as Hashimoto thyroiditis. Enzymatic defects in cortisol synthesis also cause glucocorticoid insufficiency, compensatory elevations of ACTH, and congenital adrenal hyperplasia. 119 Because adrenal insufficiency usually develops slowly, such patients develop marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (apparently secondary to chronic hypotension). 105

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 may result in hypopituitarism and consequent adrenal failure. 105

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress (for example, upper respiratory infection) is present. 105, 130 Preparation of such a patient for anesthesia and surgery should include treatment for hypovolemia, hyperkalemia, and hyponatremia. 113 Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids (about 200 mg hydrocortisone/70 kg body weight/d) perioperatively. However, Symreng and colleagues 109 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 the regimen using maximum doses (about 300 mg hydrocortisone per 70 kg body weight/d—see *The Patient Taking Steroids for Other Reasons*). Thus, I now recommend giving 100 mg of hydrocortisone phosphate intravenously every 12 hours. 105, 109, 110

Mineralocorticoid Deficiency

Hypoaldosteronism, a less common condition, 131 can be congenital or can occur after unilateral adrenalectomy or prolonged administration of heparin. 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 who have renal insufficiency. 131 Plasma renin activity levels are below normal and fail 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. 131 These defects can be treated successfully by administering mineralocorticoids (9a-fluorocortisol, 0.05–0.1 mg/d) preoperatively. 131 Doses must be carefully titrated and monitored to avoid an increase in hypertension.

The Patient Taking Steroids for Other Reasons

Perioperative Stress and the Need for Corticoid Supplementation

Many experimental studies and other reports (mostly anecdotal) concerning the adrenal responses of normal patients to the perioperative period, and the responses of patients taking steroids for other diseases, indicate the following:

1.
Perioperative stress relates to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia causes the usual intraoperative glucocorticoid surge to be postponed to the postoperative period. 132, 133
2.
Few patients who have suppressed adrenal function have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively. 108, 109, 110, 111, 112, 113, 114, 115
3.
Although a patient who chronically takes steroids occasionally becomes hypotensive perioperatively, only rarely has this event been documented sufficiently to implicate glucocorticoid or mineralocorticoid deficiency as the cause. 108, 109, 110, 111, 112, 113, 114, 115
4.
Acute adrenal insufficiency occurs only rarely but can be life-threatening. 108, 109, 110, 111, 112, 113, 114, 115
5.
There is little risk in giving these patients high-dose steroid coverage perioperatively. 109, 110, 130

In a recent well-controlled study of glucocorticoid replacement in primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement. 110 This study further defined the physiologic and hemodynamic consequences of inadequate cortisol replacement; an alternative dose regimen is suggested that has stood the test of a decade and has altered management methods to possibly improve patient safety. In this study, adrenalectomized primates and sham-operated controls were maintained on physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (one-tenth the normal cortisol production), physiologic, or supraphysiologic (ten 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 surgery. The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. The 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. The filling pressures of the heart were unchanged compared with those in control animals. There was no evidence of hypovolemia or severe congestive heart failure. Despite low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented

interaction of glucocorticoids and catecholamines, suggesting that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing by studying hydroxyproline accumulation. 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 long-standing intuitive impressions concerning patients who have inadequate adrenal function, either resulting from underlying disease or secondary to 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, there are at least theoretical negative consequences 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 for replacement therapy should be recommended. The authors of the previously discussed study on monkeys were reluctant to recommend simple physiologic steroid replacement doses for human patients perioperatively. 110 Our group agrees that a prospective, randomized double-blind trial in patients receiving physiologic doses of steroids is needed before current recommendations are modified. 109, 110 In any case, we never supplement perioperatively with a dose lower than what the patient has already been receiving. 111

Which patients definitely need supplementation? If in doubt, how can a patient's need for supplementation with glucocorticoids be determined? Because the risk is low, the author normally provides supplementation for any patient who has received steroids within a year. 107, 108, 109, 110, 111, 112, 113, 114, 115, 119, 120, 121, 122 The data indicate that topical application of steroids (even without use of occlusive dressings) can suppress normal adrenal responses for as long as 9 months to 1 year 107, 111 (Table 25–8).

TABLE 25–8. Recovery of Hypothalamic-Pituitary Adrenal Function After Withdrawal of Steroids

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 is impractical and probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of more than 25 mg/dL assuredly (and a value of >15 mg/dL probably) indicates normal pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 mg of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. 112 An increase in plasma cortisol of 6 to 20 mg/dL or more is normal. 134 A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates

pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.

Usually laboratory data defining pituitary-adrenal adequacy are not available before surgery. However, rather than delay surgery or test most patients, the author assumes that any patient who has taken steroids at any time during the preceding year has suppressed pituitary-adrenal functioning 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/d. 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 colectomy, and "minor surgery," by procedures such as herniorrhaphy. In one study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 mg/dL (range, 22–75 mg/dL). Values remained above 26 mg/dL for a maximum of 72 hours after surgery. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 mg/dL (range, 10–44 mg/dL).

Although the precise amount required has not been established, I usually administer intravenously the maximum amount of glucocorticoid that the body manufactures in response to a maximal stress (i.e., approximately 200 mg/d of hydrocortisone phosphate/70 kg body weight). 109, 110, 132, 133 For minor surgical procedures, I usually give hydrocortisone phosphate intravenously, 100 mg/70 kg body weight/d. Unless infection or some other perioperative complication develops, I decrease this dose by approximately 25 percent per day until oral intake can be resumed. At this point, the usual maintenance dose of glucocorticoids can be employed.

Risks of Supplementation

Rare complications of perioperative supplementation with steroids include aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbance. Although data are not available to assess the incidences of the following risks, two common complications of short-term perioperative supplementation with glucocorticoids are described in the literature: abnormal wound healing and increased rate of infections. 108, 109, 110, 111, 112, 113, 114, 115, 120, 121, 122, 123, 124, 135, 136 This evidence is inconclusive, however, as it relates to acute glucocorticoid administration and not to chronic administration of glucocorticoids with increased doses at times of stress. Ehrlich and Hunt 122 found that moderate to large doses of steroids exerted their morphologic effects best within 3 days of injury. They postulated that inhibition of the early inflammatory process by steroids after wounding was responsible for the delay in healing. Vitamin A was found to be somewhat protective against delayed healing, presumably because of its effect on stabilizing lysosomes. 122 In contrast to these studies that suggest a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study on primates suggests that high doses of glucocorticoids, administered perioperatively, did not impair sensitive measures of wound healing. 110 Other data provide no better insight into these problems. 108, 109, 110, 111, 112, 113, 114, 115, 120, 121, 122 These data are not conclusive

regarding a short-term increase in supplementation. However, 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 regarding the risk of infection from perioperative supplementation with glucocorticoids is also unclear. Winstone and Brooke 137 reported four cases of septicemia among 18 surgical patients given perioperative supplementation with glucocorticoids. No similar complications occurred in 17 others who were also taking glucocorticoids but who were not given perioperative supplementation. In a controlled study of 100 patients given perioperative supplementation with glucocorticoids, 11 wound infections occurred in the group treated with steroids, and only one occurred in the control group. 135 Test subjects and controls were not matched for underlying disease. By contrast, Jensen and Elb 136 found no change in the incidence of wound infections or of other infections in an uncontrolled series of 419 patients undergoing surgery and perioperative supplementation with glucocorticoids. Oh and Patterson 130 found only one minor suture abscess in 17 steroiddependent asthmatic patients undergoing 21 surgical procedures. Thus, although the data indicate that the risk of infection to the patient chronically taking steroids is real, these data are inadequate to conclude that perioperative supplementation with steroids increases that risk.

Adrenal Cortex Function in the Elderly

The adrenal gland shows a progressive decrease in production of androgens with age. 138 This decrease in androgen activity has no known implications for anesthesia. Plasma levels of cortisol are unaffected by increasing age. Levels of corticosterone-binding globulin are also unaffected by age; this suggests that a normal fraction of free cortisol (1–5%) is present in elderly patients. Several investigators have noted a progressively impaired ability of the aged patient 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 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 be due to impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30 percent lower in the elderly. This reduced secretion is an appropriate compensatory mechanism for maintaining a normal level of cortisol in the face of its decreased hepatic and renal clearance. It is important to the anesthesiologist that the reduced cortisol production can be overcome during periods of stress and that the elderly display an entirely normal adrenal response to 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. 121 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.

Also see Chapter 61.

Effect of Etomidate on Adrenal Function

Even a single dose of etomidate used for induction of anesthesia suppresses adrenal function. 139 The clinical significance of adrenal suppression by etomidate is unknown, but there is justifiable concern over continued use of etomidate without steroid supplementation.

Etomidate is an imidazole sedative-hypnotic that induces rapid loss of consciousness with minimal cardiovascular depression even in compromised patients. Etomidate has been administered in two clinical settings—as a bolus for induction of anesthesia and as a continuous infusion for prolonged sedation in the intensive care unit (ICU) setting. The pattern of adrenal suppression appears to be related to dose and time and differs with the duration of administration. 139

Etomidate inhibits two essential adrenocortical enzymes, 11b-hydroxylase and cholesterol side-chain cleavage enzyme, in rats and in humans. 139 I believe that it is important to clarify the difference between the adrenal suppression by etomidate and the stated goal of several anesthesiologists to provide stress-free anesthesia. It appears that providing a level of anesthesia that prevents grimacing, sweating, extreme elevations of blood pressure and heart rate, and an outpouring of the neurohumoral mediators of stress is evidence that we have adequately depressed CNS function and protected our patients from some of the unwanted side effects of surgery. This goal is different from the inhibition of peripheral adrenocortical enzymes of etomidate that occurs as an unwanted side effect of the drug.

Thus, it has been documented that adrenal reserve is compromised for at least 24 hours after a single induction dose of etomidate in most patients. 140 Should hypotension or electrolyte abnormalities associated with adrenal insufficiency (hyponatremia and hyperkalemia) occur in a patient who has recently received etomidate, I agree with previous suggestions 139 that corticosteroids should be administered in stress doses (e.g., cortisol, 100 mg bid) and be tapered as noted in the earlier section, *The Patient Taking Steroids for Other Reasons.*

Adrenal Incidentaloma

Adrenal tumors are found in as many as 9 percent of autopsies, and the increased use of imaging techniques brings many of these tumors to clinical attention before death. Previously, size was used as a discriminator: tumors larger than 6 cm were surgically removed because of the high probability of malignancy. Those smaller than 3 cm were followed up, and those 3 to 6 cm were investigated.

Recent data from three large series 116, 117, 118 and success from laparoscopic removal 141, 142 have called for a reevaluation. The three series found a significant number of adrenal carcinomas and pheochromocytomas (approximately 3% of each), an occasional

aldosteronoma (approximately 1%), as well as a not insignificant number of metastases from as yet uncovered primary tumors (approximately 10%). These data may indicate the need for a more aggressive approach to adrenal incidentalomas that are smaller than 6 cm.

Also see Chapter 9.

* Much of this section was modified from Lampe and Roizen. 105