TABLE 64-2 SYNDROMES OF ADRENOCORTICAL HYPOFUNCTION

PRIMARY ADRENAL DISORDERS
Combined Glucocorticoid and Mineralocorticoid Deficiency
Autoimmune
Isolated autoimmune disease (Addison's disease)
Polyglandular autoimmune syndrome, type I
Polyglandular autoimmune syndrome, type II
Infectious
Tuberculosis
Fungal
Cytomegalovirus
Human immunodeficiency virus
Vascular
Bilateral adrenal hemorrhage
Sepsis
Coagulopathy
Thrombosis, embolism
Adrenal infarction
Infiltration
Metastatic carcinoma and lymphoma
Sarcoidosis
Amyloidosis
Hemochromatosis
Congenital
Congenital adrenal hyperplasia
21-Hydroxylase deficiency
3β-ol Dehydrogenase deficiency
20,22-Desmolase deficiency
Adrenal unresponsiveness to ACTH
Congenital adrenal hypoplasia
Adrenoleukodystrophy
Adrenomyeloneuropathy
Iatrogenic
Bilateral adrenalectomy
Drugs: metyrapone, aminoglutethimide, trilostane, ketoconazole, *o,p′*-DDD, mifepristone, pasireotide
Mineralocorticoid Deficiency without Glucocorticoid Deficiency
Corticosterone methyl oxidase deficiency
Isolated zona glomerulosa defect
Heparin therapy
Critical illness
Angiogensin-converting enzyme inhibitors
SECONDARY ADRENAL DISORDERS
Secondary Adrenal Insufficiency
Hypothalamic-pituitary dysfunction
Exogenous glucocorticoids
After removal of an ACTH-secreting tumor
Hyporeninemic Hypoaldosteronism
Diabetic nephropathy
Tubulointerstitial diseases
Obstructive uropathy
Autonomic neuropathy
Nonsteroidal anti-inflammatory drugs
β-Adrenergic drugs

ACTH, Adrenocorticotropic hormone; *o,p′*-DDD, *o,p′*-dichlorodiphenyldichloroethane (mitotane).

secondary adrenal insufficiency. An upright PRA value greater than 3 ng/mL/hour in the setting of a suppressed aldosterone level is consistent with primary adrenal insufficiency, whereas a value lower than 3 ng/mL/hour probably represents secondary adrenal insufficiency. The 1-hour cosyntropin test is suppressed in both primary and secondary adrenal insufficiency.

Secondary adrenal insufficiency occurs commonly after the discontinuation of glucocorticoids. Alternate-day glucocorticoid treatment, if feasible, results in less suppression of the HPA axis than does daily glucocorticoid therapy. Complete recovery of the HPA axis can take 1 year or more, and the rate-limiting step appears to be recovery of the CRH-producing neurons.

Under stress, cortisol secretion is increased. Therefore, the concept of adrenal fatigue, proposed by some alternative providers, has no biologic validity.

After stabilization of acute adrenal insufficiency, patients with Addison's disease require lifelong replacement therapy with both glucocorticoids and mineralocorticoids. Many patients are overtreated with glucocorticoids and undertreated with mineralocorticoids. Because overtreatment with glucocorticoids results in insidious weight gain and osteoporosis, the minimal cortisol dose that can be tolerated without symptoms of glucocorticoid insufficiency (usually joint pain, abdominal pain, or diarrhea) is recommended. An initial regimen of 15 to 20 mg hydrocortisone first thing in the morning plus 5 mg hydrocortisone at about 3:00 PM mimics the physiologic dose and is recommended; a third dose is occasionally needed. Whereas glucocorticoid replacement is fairly uniform in most patients, the requirement for mineralocorticoid replacement varies greatly. The initial dose of the synthetic mineralocorticoid fludrocortisone should be 100 μg/day (often in divided doses), and the dosage should be adjusted to keep the standing PRA value between 1 and 3 ng/mL/hour.

Under the stress of a minor illness (e.g., nausea, vomiting, fever >100.5° F), the hydrocortisone dose should be doubled for as short a period as possible. An inability to ingest hydrocortisone pills may necessitate parenteral hydrocortisone administration. Patients undergoing a major stressful event (e.g., surgery necessitating general anesthesia, major trauma) should receive 150 to 300 mg parenteral hydrocortisone daily (in three divided doses) with a rapid taper to normal replacement during recovery. All patients should wear a medical information bracelet and should be instructed in the use of intramuscular emergency hydrocortisone injections.

Hyporeninemic Hypoaldosteronism

Mineralocorticoid deficiency can result from decreased renin secretion by the kidneys. Resultant hypoangiotensinemia leads to hypoaldosteronism with hyperkalemia and hyperchloremic metabolic acidosis. The plasma sodium concentration is usually normal, but total plasma volume is often deficient. PRA and aldosterone levels are low and unresponsive to stimuli, including hypokalemia. Diabetes mellitus and chronic tubulointerstitial diseases of the kidney are the most common underlying conditions leading to impairment of the juxtaglomerular apparatus. A subset of hyporeninemic hypoaldosteronism is caused by autonomic insufficiency and is a frequent cause of orthostatic hypotension. Stimuli such as upright posture or volume depletion, mediated by baroreceptors, do not cause a normal renin response. Administration of pharmacologic agents such as nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, and β-adrenergic antagonists can also produce conditions of hypoaldosteronism. Salt administration often with fludrocortisone and the α_1-receptor agonist midodrine are effective in correcting the orthostatic hypotension and electrolyte abnormalities caused by hypoaldosteronism.