accelerated clearance of dexamethasone as in patients receiving hepatic enzyme–inducing drugs, such as phenytoin. In these patients, measurements of plasma dexamethasone is useful to gauge the effective blood concentration.

The CRH stimulation test produces exaggerated ACTH or cortisol responses, or both, in about 90% of patients with Cushing disease.[3] Poor responses occur in patients with adrenal tumors and in most patients with nonendocrine ACTH-secreting tumors (usually those having elevated basal concentrations of plasma ACTH). Patients with depression and anorexia nervosa usually do not exhibit exaggerated responses of ACTH to CRH injections. CRH testing has no major advantage over the high-dose dexamethasone suppression test. If the cause of Cushing syndrome is uncertain, measurement of ACTH from inferior petrosal vein specimens before and after CRH stimulation may be helpful.

Concentrations of adrenal androgens and plasma DHEA-S are measured in the differential diagnosis of hirsutism without Cushing syndrome.[1,10] For example, in patients with Cushing syndrome, plasma DHEA-S concentrations are usually normal or moderately elevated (plasma DHEA-S ~5 μg/mL). Those patients with an adrenal adenoma usually have low age-adjusted concentrations of DHEA-S. The concentrations for plasma DHEA-S in patients with nonendocrine ACTH-secreting tumors vary from normal to elevated. In patients with congenital adrenal hyperplasia (CAH), adrenal androgens suppress normally with the administration of 0.75 mg of dexamethasone for 2 to 3 weeks, but suppression does not occur in those patients with adrenal tumors and nonendocrine ACTH-secreting tumors.

In addition to suppression and stimulation testing, methods of anatomical localization should be used to document the diagnosis of Cushing syndrome. Computed tomography (CT) of the adrenal glands has been helpful in localizing (1) adrenal tumors, (2) macronodular hyperplasia, and (3) bilateral hyperplasia of the adrenal glands. CT in combination with magnetic resonance imaging (MRI) of the pituitary gland has been used to help detect pituitary microadenomas.

Conditions That Mimic Cushing Syndrome

Alcohol abuse has been known to induce a "pseudo-Cushing syndrome" that mimics the clinical and biochemical features of the actual disease. The abnormalities are all reversible once alcohol abuse by the patient is eliminated. The clinician must therefore use considerable judgment in detecting the cause of Cushing syndrome before therapy. Human immunodeficiency virus (HIV), anorexia nervosa, and depression are associated with elevated serum cortisol concentrations, and patients with these disorders may have positive low-dose overnight dexamethasone suppression tests. However, the clinical features of patients with HIV and anorexia nervosa are not typical of those with Cushing syndrome. Measurement of urinary free cortisol and plasma cortisol with the dexamethasone suppression test improves the predictive value in the diagnosis of both Cushing syndrome and depression.[10]

Obese patients also have presented with clinical features that mimic true Cushing syndrome. Features of Cushing syndrome that occur in normal, obese subjects include (1) truncal obesity, (2) striae, and (3) the excretion of elevated concentrations of 17-hydroxysteroids. Urinary free cortisol, however, is normal in the obese individual. This effectively differentiates normal subjects from those with true Cushing syndrome.

Congenital Adrenal Hyperplasia (Adrenogenital Syndrome)

The biosynthesis of cortisol and aldosterone from cholesterol requires the action of specific enzymes in the adrenal cortex for the chemical modification and introduction of the different functional groups. CAH[1] is characterized by the congenital absence or deficiency of one or more of the biosynthetic enzymes that lead to cortisol biosynthesis. As noted in Figure 40-3, a defect or deficiency in any one or all of the four key enzymes of adrenocorticoid biosynthesis can occur. As a result, cortisol biosynthesis is impaired, leading to a compensatory increase in ACTH release. ACTH then stimulates steroid biosynthesis to the point of the enzyme block.

The term CAH is used to denote the congenital presentation of this disorder (usually at birth) and the adrenocortical hyperplasia that results from the compensatory ACTH response to cortisol deficiency. "Adrenogenital syndrome" is also used to describe this disorder in that it affects the genitalia and secondary sex characteristics of the newborn. In girls, particularly, the diagnosis of CAH in the neonatal period is commonly suggested first by the observed presence of ambiguous genitalia. In boys the abnormality may not be suspected until signs of precocious puberty or accelerated growth are present. Because aldosterone production has been observed to be compromised with accumulation and diversion of intermediate steroids to other pathways, hypertension and salt wasting may also be present. The adrenogenital syndrome is recognized with increased frequency in adults, with affected people presenting with subtle abnormalities at the time of puberty that go unrecognized. In adult women, the clinical presentation may be indistinguishable from the polycystic ovary syndrome (PCOS) or idiopathic hirsutism.[1]

Deficiency of the 21-hydroxylase enzyme is the most common form of CAH, with more than 90% of cases caused by 21-hydroxylase deficiency. A deficiency *of 11β-hydroxylase* is the second most common form of CAH, with an incidence of 1 per 100,000 births, and is associated with (1) manifestations of virilization, (2) elevated concentrations of plasma androstenedione and DHEA-S, and (3) hypertension. A deficiency of *3β-hydroxysteroid dehydrogenase-isomerase* has been observed to lead to an elevation in the ratio of 17α-hydroxypregnenolone to 17α-hydroxyprogesterone and to an increased ratio of DHEA to androstenedione. In severe forms of this rare disorder, female infants have pseudohermaphroditism, and male infants present with incomplete masculinization.

A reduction in the conversion of 17-hydroxypregnenolone to DHEA and of 17-hydroxyprogesterone to androstenedione results from a deficiency of *C-17,20-lyase/17α-hydroxylase*. A defect of this enzyme complex in the gonads of genetic females results in pubertal failure, and a defect in genetic males causes pseudohermaphroditism. The synthesis of cortisol, androgens, and estrogens is decreased, and the production of progesterone, corticosterone, and DOC is increased. In the complete form, hypertension and hyperkalemia with a lack of

sexual development are observed in girls, whereas male pseudohermaphroditism is seen in boys. The diagnosis is usually made at the time of puberty when patients present with hypogonadism in association with hypertension and hypokalemia.

The effectiveness of a treatment program for CAH is judged on the basis of the presence or absence of normal linear growth, normal sexual development, and suppression of abnormal blood and urine steroid concentrations into the reference interval.

Adrenal Tumors

Plasma DHEA-S, DHEA, androstenedione, and testosterone concentrations are elevated in patients with virilizing adrenal adenomas and Cushing syndrome. The plasma concentrations of DHEA also may be elevated in women with virilizing ovarian tumors. CT scans along with MRI are useful in differentiating the sites of the tumors. Aldosterone-secreting adenomas referred to as Conn syndrome are typically small microadenomas found in the zona glomerulosa that hypersecrete aldosterone, producing the syndrome characterized by low renin hypertension.

Adrenal carcinomas are rare, with an incidence of only 1 per million population, and may cause only virilization and not the typical features of Cushing syndrome. Women are more commonly affected than men in a 2.5 : 1 ratio. Plasma DHEA-S, DHEA, and androstenedione concentrations are markedly elevated in patients with adrenal carcinoma along with raised concentrations of cortisol. The concentrations of DHEA-S often exceed 10 µg/mL in patients presenting with adrenal carcinoma and are usually diagnostic of this malignancy. High-dose glucocorticoids do not suppress the elevated androgen concentrations.

Feminizing adrenocortical carcinomas are also rare. They result in elevation of plasma (1) DHEA-S, (2) DHEA, (3) androstenedione, (4) estrone, and (5) estradiol concentrations. Serum cortisol concentrations may be normal or elevated in those patients with Cushing syndrome. Gynecomastia and sexual dysfunction occur in men and precocious pseudopuberty in women. Steroid hormone production fails to decrease normally after treatment with dexamethasone.

Nonfunctioning Adrenocortical Tumors

Approximately 2% of the general population have an adrenal tumor; most of these tumors are nonfunctioning and are sometimes called incidentalomas. They are found when CT scans of the abdomen are performed that are able to easily detect small tumors 1 cm in diameter or 5 g in weight. No virilizing tumors smaller than 1 cm in diameter have been reported. Carcinomas are usually more than 30 g in weight.

Mineralocorticoid Excess (Hyperaldosteronism)

Hyperaldosteronism, commonly referred to as Conn syndrome, is a syndrome associated with hypersecretion of the major mineralocorticoid, aldosterone (Table 40-8). *Primary and secondary* are the two types of hyperaldosteronism.

Primary Aldosteronism

In *primary aldosteronism*, excessive aldosterone production originates from within the adrenal gland; it was first described by Conn in 1955 and is characterized by an elevated plasma concentration of aldosterone along with hypertension and hypokalemia. Overproduction of aldosterone may be due to (1) an autonomous and inappropriate secretion of aldosterone by an adenoma of one adrenal gland (*aldosterone-producing adrenal adenoma* [APA] or *Conn syndrome*), (2) hyperplasia of aldosterone-producing cells in both glands (*idiopathic adrenal hyperplasia* [IAH]), (3) an aldosterone-producing adrenal carcinoma, or (4) a rare familial condition known as *glucocorticoid-suppressible aldosteronism*. The clinical features of primary aldosteronism are generally related to the consequences of aldosterone overproduction. They include (1) increased retention of sodium through the effects of aldosterone on the renal tubular handling of sodium, (2) expansion of extracellular fluid volume, and (3) increased tubular secretion of potassium and hydrogen ions. Hypokalemia and metabolic alkalosis result as a consequence of a progressive renal depletion of body potassium. As a consequence of sodium retention, there is a modest expansion of extracellular fluid volume and an increase in arterial blood pressure.

TABLE 40-8 Differential Diagnosis of Hyperaldosteronism

	Plasma Renin	Plasma Aldosterone	Blood Pressure	Serum Potassium
Primary aldosteronism	Low	High	High	Low
Secondary hypertension				
Edematous disorder	High	High	Normal	Low
Malignant hypertension	High	High	High	Low
Renovascular hypertension	Normal or high	Normal or high	High	Normal or low
Renin-secreting tumors	High	High	High	Normal or low
CAH (11- and 17-hydroxylase deficiency)	Low	Low	High	Low
Cushing syndrome	Normal or low	Normal or low	High	Low
Liddle syndrome	Low	Low	High	Low
Bartter syndrome	High	High	Normal or low	Low
Licorice ingestion	Low	Low	High	Low
Low-renin essential hypertension	Low	Normal or low	High	Normal
Ingestion of exogenous mineralocorticoids	Low	Low	High	Low

CAH, *Congenital adrenal hyperplasia.*