morphologically identical to other cortical neoplasms and will be discussed later.

Congenital adrenal hyperplasia **stems from several autosomal-recessive, inherited metabolic errors, each characterized by a deficiency or total lack of a particular enzyme involved in the biosynthesis of cortical steroids, particularly cortisol (Fig. 24-46).** Steroid precursors that build behind the defective step in the pathway are channeled into other pathways, resulting in increased production of androgens, which accounts for virilization. Simultaneously, the deficiency of cortisol leads to increased secretion of ACTH, culminating in adrenal hyperplasia. Certain enzyme defects may also impair aldosterone secretion, adding *salt wasting* to the virilizing syndrome. Other enzyme deficiencies may be incompatible with life or, in rare instances, may involve only the aldosterone pathway without involving cortisol synthesis.

21-hydroxylase deficiency (caused by mutations of *CYP21A2*) is by far the most common, accounting for over 90% of cases. Figure 24-46 illustrates normal adrenal steroidogenesis and the consequences of 21-hydroxylase deficiency, which may range from a total lack to a mild loss, depending on the nature of the *CYP21A2* mutation. Three distinctive syndromes have been described: (1) salt-wasting ("classic") adrenogenitalism, (2) simple virilizing adrenogenitalism, and (3) "nonclassic" adrenogenitalism.

- The *salt-wasting syndrome* results from an inability to convert progesterone into deoxycorticosterone because of a total lack of the hydroxylase. Thus, there is virtually no synthesis of mineralocorticoids, and concomitantly, there is a block in the conversion of hydroxyprogesterone into deoxycortisol resulting in deficient cortisol synthesis. This pattern usually comes to light soon after birth, because in utero the electrolytes and fluids can be maintained by the maternal kidneys. There is *salt wasting*, *hyponatremia,* and *hyperkalemia*, which induce acidosis, *hypotension*, cardiovascular collapse, and possibly death. The concomitant block in cortisol synthesis and excess production of androgens, however, lead to virilization, which is easily recognized in the female at birth or in utero. Males with this disorder are generally unrecognized at birth but come to clinical attention 5 to 15 days later because of some salt-losing crisis.
- *Simple virilizing adrenogenital syndrome without salt wasting* (presenting as genital ambiguity) occurs in approximately a third of patients with 21-hydroxylase deficiency. These patients generate sufficient mineralocorticoid to prevent a salt-wasting "crisis." However, the lowered glucocorticoid level fails to cause feedback inhibition of ACTH secretion. Thus, the level of testosterone is increased, with resultant progressive virilization.
- *Nonclassic or late-onset adrenal virilism* is significantly more common than the classic patterns already described. There is only a partial deficiency in 21-hydroxylase function, which accounts for the later onset. Individuals with this syndrome may be virtually asymptomatic or have mild manifestations, such as hirsutism, acne, and menstrual irregularities. Nonclassic CAH cannot be diagnosed on routine newborn screening, and the diagnosis is usually rendered by demonstration of biosynthetic defects in steroidogenesis.

MORPHOLOGY

In all cases of CAH the adrenals are bilaterally hyperplastic, sometimes increasing to 10 to 15 times their normal weights because of the sustained elevation in ACTH. The adrenal cortex is thickened and nodular, and on cut section the widened cortex appears brown, because of total depletion of all lipid. The proliferating cells are mostly compact, eosinophilic, lipid-depleted cells, intermixed with lipid-laden clear cells. Hyperplasia of corticotroph (ACTH-producing) cells is present in the anterior pituitary in most persons with CAH.

Clinical Course. The clinical features of these disorders are determined by the specific enzyme deficiency and include abnormalities related to *androgen excess*, with or without *aldosterone* and *glucocorticoid deficiency*. CAH affects not only adrenal cortical enzymes but also products synthesized in the medulla. High levels of intra-adrenal glucocorticoids are required to facilitate medullary catecholamine (epinephrine and norepinephrine) synthesis. In patients with severe salt-wasting 21-hydroxylase deficiency, a combination of low cortisol levels and developmental defects of the medulla *(adrenomedullary dysplasia)* profoundly affects catecholamine secretion, further predisposing these individuals to hypotension and circulatory collapse.

Depending on the nature and severity of the enzymatic defect, the onset of clinical symptoms may occur in the perinatal period, later childhood, or, less commonly, adulthood. For example, in 21-hydroxylase deficiency excessive androgenic activity causes signs of masculinization in females, ranging from clitoral hypertrophy and pseudohermaphroditism in infants, to oligomenorrhea, hirsutism, and acne in postpubertal females. In males, androgen excess is associated with enlargement of the external genitalia and other evidence of precocious puberty in prepubertal patients and oligospermia in older males.

CAH should be suspected in any neonate with ambiguous genitalia. Severe enzyme deficiency in infancy can be a life-threatening condition with vomiting, dehydration, and salt wasting. Individuals with CAH are treated with exogenous glucocorticoids, which, in addition to providing adequate levels of glucocorticoids, also suppress ACTH levels and thus decrease the excessive synthesis of the steroid hormones responsible for many of the clinical abnormalities. Mineralocorticoid supplementation is required in the salt-wasting variants of CAH. With the availability of routine neonatal metabolic screens for CAH and the feasibility of molecular testing for antenatal detection of 21-hydroxylase mutations, the outcome for even the most severe variants has improved significantly.

KEY CONCEPTS

Adrenogenital Syndromes

- The adrenal cortex can secrete excess androgens in either of two settings: adrenocortical neoplasms (usually *virilizing* carcinomas) or congenital adrenal hyperplasia (CAH).
- CAH consists of a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually