cortisol; the most common subtype is caused by deficiency of the enzyme 21-hydroxylase.

- Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production. Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males, and in some instances, salt (sodium) wasting and hypotension.
- Bilateral hyperplasia of the adrenal cortex is characteristic, and a subset of 21-hydroxylase-deficient patients also demonstrates *adrenomedullary dysplasia.*

Adrenocortical Insufficiency

Adrenocortical insufficiency, or hypofunction, may be caused by either primary adrenal disease (primary hypoadrenalism) or decreased stimulation of the adrenals due to a deficiency of ACTH (secondary hypoadrenalism) (Table 24-10). The patterns of adrenocortical insufficiency can be considered under the following headings: (1) primary *acute* adrenocortical insufficiency (adrenal crisis), (2) primary *chronic* adrenocortical insufficiency *(Addison disease)*, and (3) secondary adrenocortical insufficiency.

Primary Acute Adrenocortical Insufficiency

Acute adrenal cortical insufficiency occurs in a variety of clinical settings.

Table 24-10 Adrenocortical Insufficiency

Primary Insufficiency
Loss of Cortical Cells
Congenital adrenal *hypo*plasia
X-linked adrenal hypoplasia (*DAX1* gene on Xp21)
"Miniature"-type adrenal hypoplasia (unknown cause)
Adrenoleukodystrophy (*ALD* gene on Xq28)
Autoimmune adrenal insufficiency
Autoimmune polyendocrinopathy syndrome type 1 (*AIRE1* gene on 21q22)
Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
Isolated autoimmune adrenalitis (polygenic)
Infection
Acquired immune deficiency syndrome
Tuberculosis
Fungi
Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome*)
Amyloidosis, sarcoidosis, hemochromatosis
Metastatic carcinoma
Metabolic Failure in Hormone Production
Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virilization)
Drug- and steroid-induced inhibition of ACTH or cortical cell function
Secondary Insufficiency
Hypothalamic Pituitary Disease
Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic Pituitary Suppression
Long-term steroid administration
Steroid-producing neoplasms

ACTH, Adrenocorticotropic hormone.

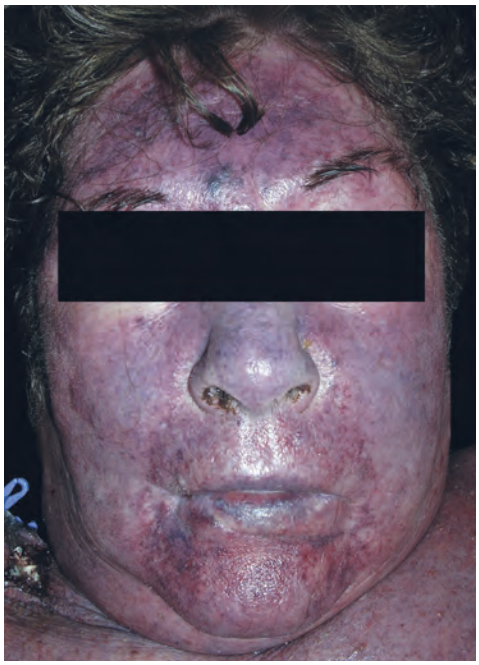

Figure 24-47 Diffuse purpuric rash in a patient with Waterhouse-Friderichsen syndrome. (Reproduced with permission from C. Vincentelli et al, Am J Emerg Med, 27:751, 2009).

- As a *crisis* in individuals with chronic adrenocortical insufficiency precipitated by any form of stress that requires an immediate increase in steroid output from glands incapable of responding
- In patients maintained on exogenous corticosteroids, in whom *rapid withdrawal of steroids* or failure to increase steroid doses in response to an acute stress may precipitate an adrenal crisis, because of the inability of the atrophic adrenals to produce glucocorticoid hormones
- As a result of *massive adrenal hemorrhage*, which damages the adrenal cortex sufficiently to cause acute adrenocortical insufficiency—as occurs in newborns following prolonged and difficult delivery with considerable trauma and hypoxia. It also occurs in some patients maintained on anticoagulant therapy, in postsurgical patients who develop disseminated intravascular coagulation and consequent hemorrhagic infarction of the adrenals, and as a complication of disseminated bacterial infection; in this last setting, it is called *Waterhouse-Friderichsen syndrome*.

Waterhouse-Friderichsen Syndrome

This uncommon but catastrophic syndrome is characterized by the following:

- Overwhelming bacterial infection, classically *Neisseria meningitidis* septicemia but occasionally caused by other highly virulent organisms, such as *Pseudomonas* species, pneumococci, *Haemophilus influenzae*, or even staphylococci
- Rapidly progressive hypotension leading to shock
- Disseminated intravascular coagulation associated with widespread purpura, particularly of the skin (Fig. 24-47)