Table 24-9 Clinical Features of Cushing Syndrome

Feature	Percent
Obesity or weight gain	95%*
Facial plethora	90%
Rounded face	90%
Decreased libido	90%
Thin skin	85%
Decrease in linear growth in children	70-80%
Menstrual irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression/emotional liability	70%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Osteopenia or fracture	50%
Nephrolithiasis	50%

*100% in children.
Adapted from Newell-Price J, et al: Cushing syndrome. Lancet 367:1605-1616, 2006.

Clinical Course. Cushing syndrome develops slowly and can be quite subtle in its early manifestations. Early stages of the disorder may present with hypertension and weight gain (Table 24-9). With time the more characteristic central pattern of adipose tissue deposition becomes apparent in the form of truncal obesity, moon facies, and accumulation of fat in the posterior neck and back *(buffalo hump)*. Hypercortisolism causes selective atrophy of fast-twitch (type 2) myofibers, resulting in decreased muscle mass and proximal limb weakness. Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant *hyperglycemia*, *glucosuria* and *polydipsia (secondary diabetes)*. The catabolic effects cause loss of collagen and resorption of bones. Consequently the *skin is thin, fragile, and easily bruised*; wound healing is poor; and cutaneous striae are particularly common in the abdominal area (Fig. 24-44). Bone resorption results in the development of *osteoporosis*, with consequent backache and increased susceptibility to fractures. Persons with Cushing syndrome are at increased risk for a variety of infections, because glucocorticoids suppress the immune response. Additional manifestations include several *mental disturbances*, including mood swings, depression, and frank psychosis, as well as *hirsutism* and *menstrual abnormalities*.

The laboratory diagnosis of Cushing syndrome is based on the following: (1) the 24-hour urine free-cortisol concentration, which is increased, and (2) loss of normal diurnal pattern of cortisol secretion. Determining the cause of Cushing syndrome depends on the serum ACTH and measurement of urinary steroid excretion after administration of dexamethasone (dexamethasone suppression test). The results of these tests fall into three general patterns:

- In pituitary Cushing syndrome, the most common form, ACTH levels are elevated and cannot be suppressed by the administration of a low dose of dexamethasone. Hence, there is no reduction in urinary excretion of 17-hydroxycorticosteroids. After higher doses of injected dexamethasone, however, the pituitary responds by reducing ACTH secretion, which is reflected by suppression of urinary steroid secretion.
- Ectopic ACTH secretion results in an elevated level of ACTH, but its secretion is completely insensitive to low or high doses of exogenous dexamethasone.
- When Cushing syndrome is caused by an adrenal tumor, the ACTH level is quite low because of feedback inhibition of the pituitary. As with ectopic ACTH secretion, both low-dose and high-dose dexamethasone fail to suppress cortisol excretion.

KEY CONCEPTS

Hypercortisolism (Cushing Syndrome)

- The most common cause of hypercortisolism is exogenous administration of steroids.
- Endogenous hypercortisolism most often is secondary to an ACTH-producing pituitary microadenoma (*Cushing disease*), followed by primary adrenal neoplasms (*ACTH-independent* hypercortisolism) and paraneoplastic ACTH production by tumors (e.g., small cell lung cancer).
- The morphologic features in the adrenal vary from bilateral cortical atrophy (in exogenous steroid-induced disease), to bilateral diffuse or nodular hyperplasia (most common finding in endogenous Cushing syndrome), to an adrenocortical neoplasm.

Primary Hyperaldosteronism

Hyperaldosteronism is the generic term for a group of closely related conditions characterized by chronic excess aldosterone secretion. Hyperaldosteronism may be primary, or it

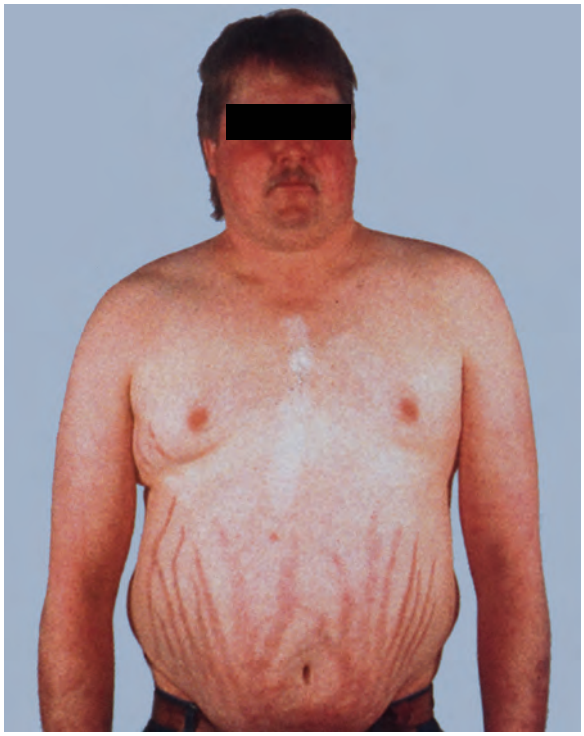

Figure 24-44 A patient with Cushing syndrome demonstrating central obesity, "moon facies," and abdominal striae. (Reproduced with permission from Lloyd RV, et al (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)