Adrenocortical Hyperfunction (Hyperadrenalism)

The syndromes of adrenal hyperfunction are caused by overproduction of the three major hormones of the adrenal cortex (1) *Cushing syndrome*, characterized by an excess of cortisol; (2) *hyperaldosteronism* as a result of excessive aldosterone; and (3) *adrenogenital or virilizing syndromes* caused by an excess of androgens. The clinical features of these syndromes overlap somewhat because of the overlapping functions of some of the adrenal steroids.

Hypercortisolism (Cushing Syndrome)

Pathogenesis. **This disorder is caused by conditions that produce elevated glucocorticoid levels.** Cushing syndrome can be broadly divided into *exogenous* and *endogenous* causes. The vast majority of cases of Cushing syndrome are the result of the administration of exogenous glucocorticoids ("iatrogenic" Cushing syndrome). The endogenous causes can, in turn, be divided into those that are *ACTH dependent* and those that are *ACTH independent* (Table 24-8).

ACTH-secreting pituitary adenomas account for approximately 70% of cases of endogenous hypercortisolism. In recognition of Harvey Cushing, the neurosurgeon who first published the full description of this syndrome, the pituitary form is referred to as *Cushing disease*. The disorder affects women about four times more frequently than men and occurs most frequently in young adults. In the vast majority of cases it is caused by an *ACTH-producing pituitary microadenoma*. In some cases there is an underlying macroadenoma and rarely there is *corticotroph cell hyperplasia* without a discrete adenoma. Corticotroph cell hyperplasia may be primary or arise secondarily from excessive stimulation of ACTH release by a hypothalamic corticotrophin-releasing hormone (CRH)-producing tumor. The adrenal glands in individuals with Cushing disease are characterized by variable degrees of nodular cortical hyperplasia (discussed later), caused by the elevated levels of ACTH. The cortical hyperplasia, in turn, is responsible for hypercortisolism.

Secretion of ectopic ACTH by nonpituitary tumors accounts for about 10% of ACTH-dependent Cushing syndrome. In many instances the responsible tumor is a *small-cell carcinoma of the lung*, although other neoplasms, including carcinoids, medullary carcinomas of the thyroid, and islet cell tumors, have been associated with the syndrome. In addition to tumors that elaborate ectopic ACTH, occasionally a neuroendocrine neoplasm may produce ectopic corticotrophin releasing hormone (CRH), which, in turn, causes ACTH secretion and hypercortisolism. As in the pituitary variant, the adrenal glands undergo bilateral cortical hyperplasia, but the rapid downhill course of patients with these cancers often limits the extent of the adrenal enlargement. This variant of Cushing syndrome is more common in men and usually occurs in the 40s and 50s.

Primary adrenal neoplasms, such as adrenal adenoma (~10%) and carcinoma (~5%) are the most common underlying causes for ACTH-independent Cushing syndrome. The biochemical *sine qua non* of ACTH-independent Cushing syndrome is elevated serum levels of cortisol with low levels of ACTH. Cortical carcinomas tend to produce more marked hypercortisolism than adenomas or hyperplasias. In instances of a unilateral neoplasm, the uninvolved adrenal cortex and the cortex in the opposite gland undergo atrophy because of suppression of ACTH secretion.

The overwhelming majority of hyperplastic adrenals are ACTH dependent, and *primary cortical hyperplasia* (i.e., ACTH-independent hyperplasia) is uncommon. In *macronodular hyperplasia* the nodules are usually greater than 3 mm in diameter. Macronodular hyperplasia is typically a sporadic (nonsyndromic) condition observed in adults. It is now known that, although the condition is ACTH independent, it is not entirely "autonomous." Specifically, cortisol production is regulated by non-ACTH circulating hormones, because of ectopic overexpression of their corresponding receptors in the adrenocortical cells. Such non-ACTH hormones include gastric inhibitory peptide, LH and ADH; their receptors are overexpressed on hyperplastic adrenal cortical cells. The mechanism by which these receptors for non-ACTH hormones are overexpressed in adrenocortical tissues is not known. A subset of macronodular hyperplasia arises in the setting of McCune-Albright syndrome (Chapter 26), characterized by somatic mutations that activate *GNAS*, which encodes a stimulatory $G_s\alpha$. This $G_s\alpha$ mutation causes hyperplasia by increasing intracellular levels of cAMP, which you will recall is an important second messenger in many endocrine cell types. Given this, it is not surprising that mutations in several other proteins that are involved in cAMP signaling, such as the regulatory subunit of cAMP-dependent protein kinase (encoded by the *PRKAR1A* gene) and a phosphodiesterase (an enzyme that breaks down cAMP, encoded by the *PDE11A* gene), are also associated with primary cortical hyperplasia.

Table 24-8 Endogenous Causes of Cushing Syndrome

Cause	Relative Frequency (%)	Ratio of Females to Males
ACTH-Dependent		
Cushing disease (pituitary adenoma; rarely CRH	70	3.5:1
Ectopic corticotropin syndrome (ACTH)	10	1:1
ACTH-Independent		
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1
Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors)	<2	1:1
Primary pigmented nodular adrenal disease (*PRKARIA* and *PDE11* mutations)	<2	1:1
McCune-Albright syndrome (*GNAS* mutations)	<2	1:1

ACTH, Adrenocorticotropic hormone; GIPR, gastric inhibitory polypeptide receptor; LHR, luteinizing hormone receptor; *PRKAR1A*, protein kinase A regulatory subunit 1α; *PDE11*, phosphodiesterase 11A.

Note: These etiologies are responsible for endogenous Cushing syndrome. The most common overall cause of Cushing syndrome is exogenous glucocorticoid administration (iatrogenic Cushing syndrome).

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