# GLUCOCORTICOID AND ADRENAL ANDROGENS

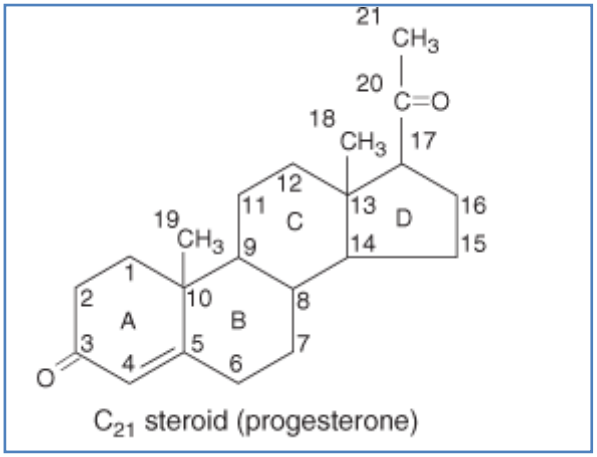
The adrenal cortex produces many steroid hormones of which the most important are cortisol, aldosterone, and adrenal androgens. The adult adrenal cortex comprises 90% of the adrenal weight and the inner medulla about 10%. The adrenal cortex is composed of three zones: an outer zona glomerulosa, a zona fasiculata, and an inner zona rticularis. The **zona glomerulosa**, which produces aldosterone and constitutes ~15% of adult cortical volume, is deficient in 17α-hydroxylase activity and thus cannot produce cortisol or androgen.

The **zona fasiculata** is the thickest layer of the adrenal cortex ~75% of the cortex, and produces cortisol and androgens. The inner **zona reticularis** surrounds the medulla and also produces cortisol and androgen. The zona fasiculata and reticularis are regulated by ACTH; excess or deficiency of this hormone alters their structure and function.

## Biosynthesis of Cortisol and Adrenal Androgens

### Steroidogenesis

The major hormones secreted by the adrenal cortex are cortisol, the androgens, and aldosterone. The carbon atoms in the steroid molecule are numbered as shown in Fig. 9-3 and the major biosynthetic pathways and hormonal intermediates in Fig. 9-4 and Fig. 9-5.



$C_{21}$ steroid (progesterone)

Figure 9-3. **Structure of adrenocortical steroids**. The letters in the formula for progesterone identify the A, B, C, and D rings; the numbers show the positions in the basic C-21 steroid structure

**A. Zones of Steroidogenesis:**
Because of enzymatic differences between the zona glomerulosa and the inner two zones, the adrenal cortex functions as two separate units, with differing regulation and secretory products. The synthesis of aldosterone by zona glomerulosa is primarily regulated by the renin–angiotensin system and by $K^+$. The zona fasiculata and zona reticularis produce cortisol, androgens, and small amounts of estrogens. These zones are regulated primarily by ACTH.

**B. Cholesterol Uptake and Synthesis**
Synthesis of cortisol and the androgens by the zonae fasiculata and reticularis begins with cholesterol, as does the synthesis of all steroid hormones. Plasma lipoproteins are the major source of adrenal cholesterol, though synthesis within the gland from acetate also occurs. Low–density lipoprotein (LDL) accounts for ~80% of cholesterol delivered to the adrenal gland.

When the adrenal is stimulated, there is also increased hydrolysis of stored cholestryl esters to free cholesterol, increased uptake of plasma lipoproteins, and increased cholesterol synthesis within the gland. The acute response to a steroidogenic response is medicated by the steroidogenic acute regulatory protein (StAR). This mitochondrial phosphoprotein

enhances cholesterol transport from the outer to the inner mitochondrial membrane where side-chain cleavage of cholesterol -the first step in steroidogenesis– occurs.

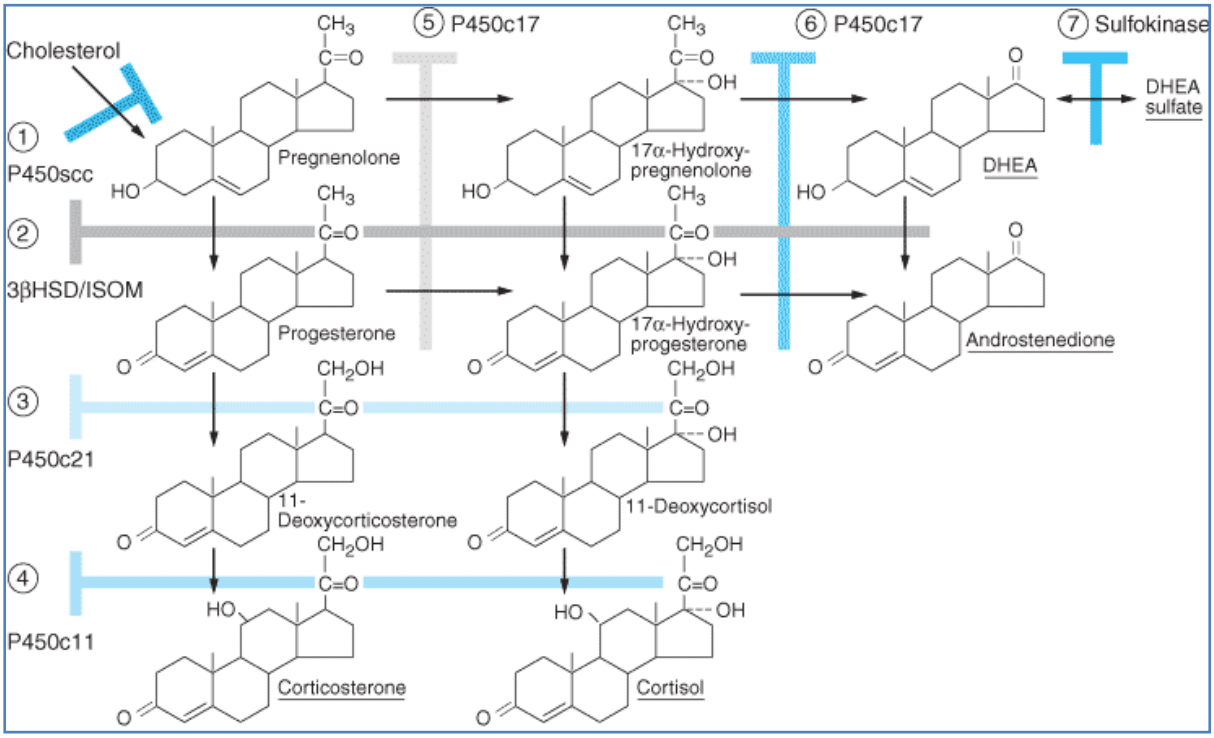
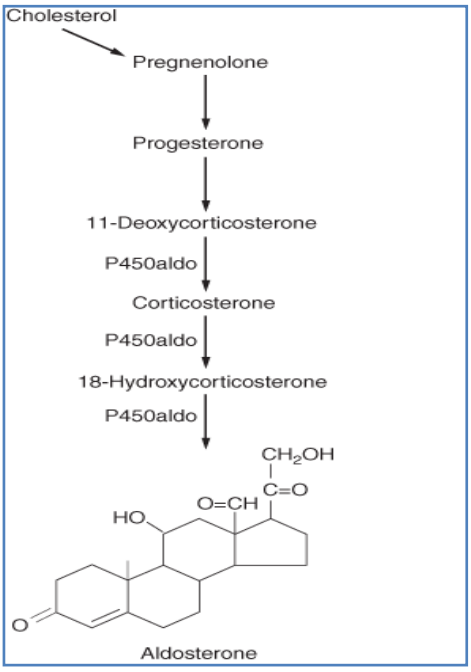



**Figure 9-4**. **Steroid biosynthesis in the zona fasciculata and zona reticularis of the adrenal cortex.** The major secretory products are underlined. The enzymes for the reactions are numbered on the left and at the top of the chart, with the steps catalyzed shown by the shaded bars. 1 P450scc, cholesterol 20,22-hydroxylase:20,22 desmolase activity; 2 3βHSD/ISOM, 3-hydroxy-steroid dehydrogenase; $\Delta^5$-oxosteroid isomerase activity; 3 P450c21, 21α-hydroxylase activity; 4 P450c11= 11β-hydroxylase activity; 5 P450c17, 17α-hydroxylase activity; 6 P450c17, 17,20-lyase/desmolase activity; 7 sulfokinase

**Figure 9-5**. **Steroid biosynthesis in the zona glomerulosa.** The steps from cholesterol to 11-deoxycorticosterone are the same as in the zona fasciculata and zona reticularis. However, the zona glomerulosa lacks 17α-hydroxylase activity and thus cannot produce cortisol. Only the zona glomerulosa can convert corticosterone to 18-hydroxycorticosterone and aldosterone. The single enzyme P450aldo catalyzes the conversion of 11-deoxycorticosterone to corticosterone to 18-hydroxycorticosterone to aldosterone




## C. Cholesterol metabolism

The conversion of cholesterol to pregnenolone is the rate – limiting step in adrenal steroidogenesis and the major site of ACTH action on the adrenal. This step is catalyzed by the enzyme $P_{450scc}$ (side-chain cleavage enzyme). Pregnenolone is then transported outside the mitochondria.

### D. Synthesis of Cortisol

Cortisol synthesis proceeds by 17α-hydroxylation of pregnenolone to 17α-hydroxypregnessolone. This is converted to 17α-hydroxprogesterone by 3β-hydroxysteroid dehydrogenase $\Delta^{4,5}$ isomerase activity. An alternative but apparently less important pathway in the zonae fasiculata and reticularis is from pregnenolone → progesterone →17α-hydroxy-progesterone. The next step, which is again microsomal, involves the 21-hydroxylation by 21α hydroxylase of 17α-hydroxyprogesterone to form 11-deoxycortisol; this compound is further hydroxylated within mitochondria by 11β-hydroxylase to form cortisol. The zona fasiculata and zona reticularis also produce 11-deoxycorticosterone (DOC), 18-hydroxydeoxycorticosterone, and corticosterone.

### E. Synthesis of Androgens

The production of adrenal androgens from pregnenolone and progesterone requires prior 17α-hydroxylation and thus does not occur in the zona glomerulosa. The major production of androgens is the conversion of 17α-hydroxpregnenolone to DHEA and its sulfated conjugate DHEA sulfate. The other major adrenal androgen, androstenedione, is produced from DHEA by 3β-hydroxysteroid steroid dehydrogenase/isomerase activity, and possibly from 17α-hydroxprogesterone by 17,20–lyase/desmolase activity. DHEA and DHEA sulfate as well as androstenedione contribute to androgenicity by their peripheral conversion to the more potent androgens testosterone and dihydrotestosterone.

## Regulation of Secretion

### A. Secretion of CRH and ACTH

ACTH is the trophic hormone of the zonae fasiculata and reticularis and the major regulator of cortisol and adrenal androgen production, although other factors produced within the adrenal including neurotransmitters, neuropeptides and nitric oxide also play a role. ACTH in turn is regulated by the hypothalamus and CNS via neurotransmitters and corticotropin – releasing hormone (CRH) and arginine vasopressin (AVP).

### B. ACTH Effects on the Adrenal Cortex

ACTH increases the synthesis and secretion of steroid hormone. ACTH increases RNA, DNA, and protein synthesis. Chronic stimulation leads to adrenocortical hyperplasia and hypertrophy; conversely, ACTH deficiency results in decreased steroidogenesis and is accompanied by adrenocortical atrophy, and decreased gland weight.

### C. ACTH and Steroidogenesis

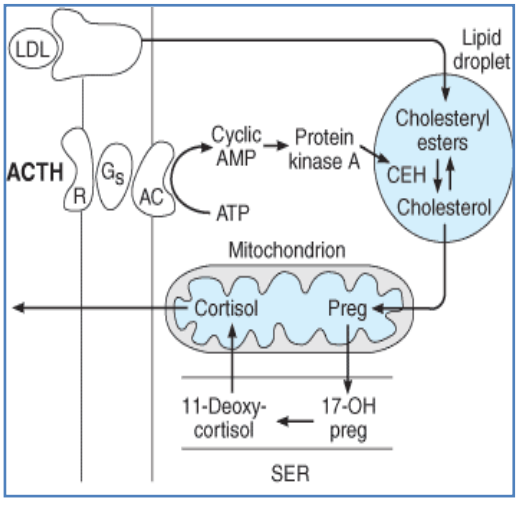



**Figure 9-6. Mechanism of action of ACTH on cortisol-secreting cells in the inner two zones of the adrenal cortex**. When ACTH binds to its receptor (R), adenylyl cyclase (AC) is activated via $G_s$. The resulting increase in cAMP activates protein kinase A, and the kinase phosphorylates cholesteryl ester hydrolase (CEH), increasing its activity. Consequently, more free cholesterol is formed and converted to pregnenolone in the mitochondria. Note that in the subsequent steps in steroid biosynthesis, products are shuttled between the mitochondria and the smooth endoplasmic reticulum (SER).

ACTH binds to high affinity plasma membrane receptors, thereby activating adenylyl cyclase and increasing cAMP, which in turn activates intracellular phosphoprotein kinases (Fig. 9-6) including (StAR). ACTH action results in increased free cholesterol formation as a consequence of increased cholesterol esterase activity as well as increased lipoprotein uptake by the adrenal cortex. This process stimulates the rate-limiting step-cholesterol delivery to the side–chain cleavage enzyme for conversion to $\Delta^5$-pregnenolone, thereby initiating steroidogenesis.

### D. Neuroendocrine Control

Cortisol secretion is closely regulated by ACTH, and plasma cortisol levels parallel those of ACTH. There are three mechanisms of neuroendocrine control: (1) episodic secretion and the circadian rhythm of ACTH, (2) stress responsiveness of the hypothalamic – pituitary adrenal axis, and (3) feedback inhibition by cortisol of ACTH secretion

1. **Circadian rhythm:** circadian rhythm is superimposed on episodic secretion; it is the result of CNS events that regulate both the number and magnitude of CRH and ACTH secretory episodes. Cortisol secretion is low in the late evening and continues to decline in the first several hours of sleep. During the third and fifth hours of sleep there is an increase in secretion; but the major secretory episodes begin in the sixth to eighth hours of sleep (Fig 9-7) and then begin to decline as wakefulness occurs. The rhythm is changed by (1) physical stresses such as major illness, surgery, trauma, or starvation; (2) psychological stress; (3) CNS and pituitary disorders; (4) Cushing's syndrome; (5) liver disease; (6) chronic renal failures, and (7) alcoholism.

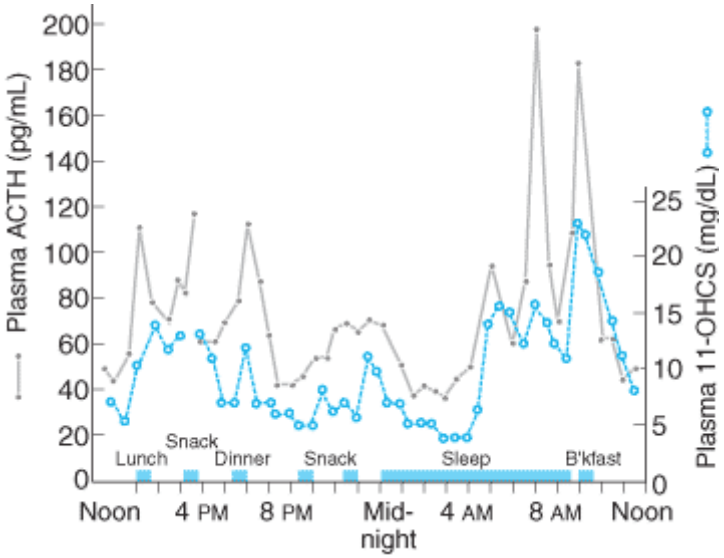



**Figure 9-7**. Fluctuations in plasma ACTH and glucocorticoids (11-OHCS) throughout the day. Note the greater ACTH and glucocorticoid rises in the morning before awakening.

2. **Stress responsiveness:** plasma ACTH and cortisol secretion are also responsive to physical stress. Plasma ACTH and cortisol are secreted within minutes following the onset of stress such as surgery and hypoglycemia, and these responses abolish circadian periodicity if the stress is prolonged. Stress responses originate in the CNS and increase hypothalamic CRH and thus pituitary ACTH secretion.

3. **Feedback inhibition:** The third major regulator of ACTH and cortisol secretion is that of feedback inhibition by glucocorticoids of CRH, ACTH, and cortisol secretion. Glucocorticoid feedback inhibition involves fast and delayed feedback inhibition. The fast feedback inhibition is mediated by a noncytosolic glucocorticoid receptor mechanism. Delayed feedback appears to act via the classic glucocorticoid receptor mechanism.

## Circulation of Cortisol and Adrenal Androgens

Cortisol and the adrenal androgens circulate bound to plasma proteins. Cortisol binds mainly to corticosterone-binding globulin (CBG or trancortin) and to a lesser extent to albumin, whereas, the androgens bind chiefly to albumin. Bound steroids are biologically inactive; the unbound or free fraction is active. CBG levels are increased in high-estrogen states (pregnancy, estrogen or oral contraceptive use), hyperthyroidism, diabetes, and on a genetic basis. CBG concentrations are decreased is familial CBG deficiency, hypothyroidism, and protein deficiency states such as severe liver disease or nephritic syndrome.

Under basal conditions, ~10% of the circulating cortisol is free, about 75% is bound to CGB and 15% to albumin. Albumin has a much greater capacity for cortisol binding but a lower affinity. Androstenedione, DHEA, and DHEA sulfate circulate weakly bound to albumin. However, testosterone is bound mainly to a specific globulin, sex hormone – binding globulin (SHBG).

## Metabolism of Cortisol

The metabolism of the steroids renders them inactive and increases their water solubility, as does their subsequent conjugation with glucuronide or sulfate groups. These inactive conjugated metabolites are more readily excreted by the kidney. The liver is the major site of steroid catabolism and conjugation, and 90% of theses metabolized steroids are excreted by the kidney.

### Hepatic Conversion

Hepatic metabolism of cortisol involves a number of metabolic conversions of which the most important is the irreversible inactivation of the steroid by $\Delta^4$ reductases to dihydrocortisol and then to tetrahydrocortisol. Cortisol is also converted by 11β-hydroxysteroid dehydrogenase to the biologically inactive cortisone and then to tetra hydrocortisone.

### Cortisol-Cortisone Shunt

Aldosterone is the principal mineralocorticoid controlling $Na^+$ and $K^+$ exchange in the distal nephron. Mineralocorticoid receptors in the kidney are responsible for this effect, and the sensitivities of both the glucocorticoid receptor and the mineralocorticoid receptor for cortisol in vitro are similar. Small changes in aldosterone affect $Na^+$ and $K^+$ exchange in the kidney while cortisol does not. This is explained by an intracellular enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that metabolizes cortisol in the kidney to the inactive cortisone and protects the mineralocorticoid receptor from cortisol binding (Fig. 9-8). However, when circulating cortisol is extremely high (as in sever Cushing's syndrome), this pre receptor metabolism of cortisol is over whelmed and the mineralocorticoid receptor is activated by cortisol, resulting in volume expansion, hypertension, and hypokalemia.

In addition, some tissues can actually convert the inactive cortisone to cortisol by the enzyme11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). The skin expresses this enzyme, explaining why cortisone cream can be effective. More importantly, the liver expresses 11β-HSD1 and can activate cortisone to cortisol, thereby completing the "cortisol-cortisone shunt". The expression of 11β-HSD1 in adipose tissue may contribute to abdominal obesity seen in syndrome X without biochemical hypercortisolism.

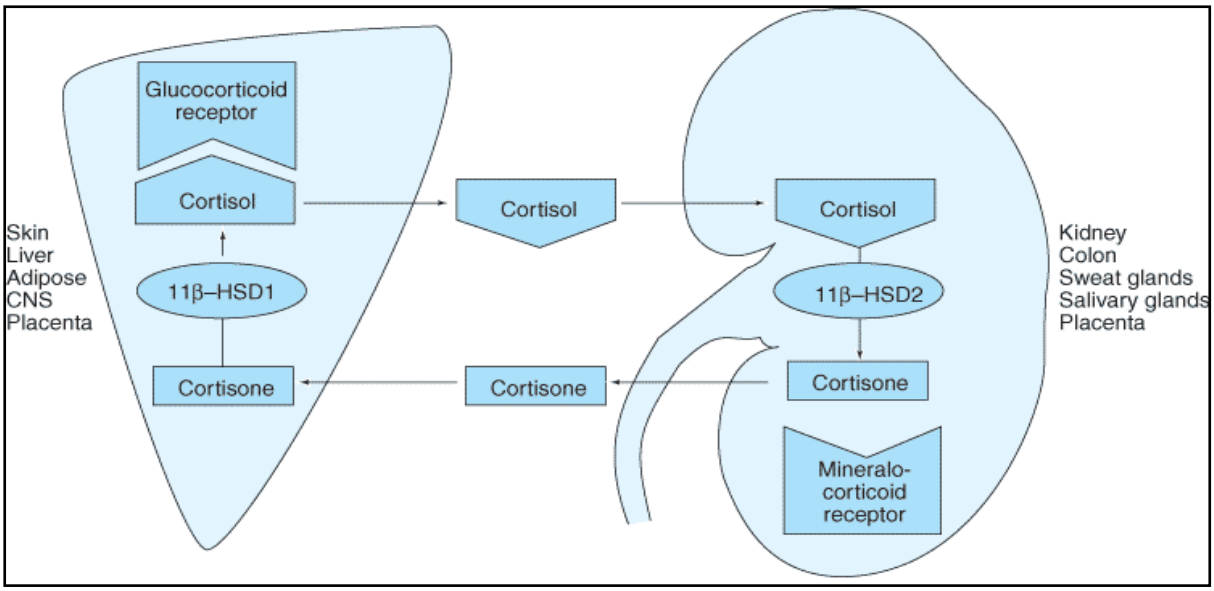



**Figure 9-8**. **Cortisol-cortisone shunt**. Contrasting functions of the isozymes of 11β-HSD. 11β-HSD2 is an exclusive 11β-dehydrogenase that acts in classical aldosterone target tissues to exclude cortisol from otherwise nonselective mineralocorticoid receptors. Inactivation of cortisol also occurs in placenta. 11β-HSD1 is a predominant 11β-reductase in vivo that acts in many tissues to increase local intracellular glucocorticoid concentrations and thereby maintain adequate exposure of relatively low affinity glucocorticoid receptors to their ligand.

## Biological Effects of Adrenal Steroids

### Glucocorticoids

Although glucocorticoids were originally so called because of their influence on glucose metabolism, they are currently defined as steroids that exert their effects by binding to specific cytosolic receptors which mediate the actions of these hormones. Alterations in the structure of the glucocorticoids have led to the development of synthetic compounds with greater glucocorticoid activity. The increased activity of these synthetic compounds is due to increased affinity for the glucocorticoid receptors and delayed plasma clearance, which increases exposure.

### Molecular Mechanisms

Glucocorticoid action is initiated by entry of the steroid into the cell and binding to the cytosolic glucocorticoid receptor proteins. The most abundant cytoplasmic glucocorticoid receptor complex includes two subunits of the 90 KDa heat shock protein hsp90. After binding, hsp90 subunits dissociate and activated hormone–receptor complexes enter the nucleus and interact with nuclear chromatin acceptor sites. The DNA binding domain of the receptor is a cysteine-rich region called a "zinc finger". The receptor–glucocorticoid complex acts via two mechanisms: (1) binding to specific sites in nuclear DNA, the glucocorticoid regulatory elements; and (2) interaction with other transcription factors such as nuclear factor κB, an important regulator of cytokine genes. These result in altered expression of specific genes and the transcription of specific mRNAs. The resulting proteins elicit the glucocorticoid response, which may be inhibitory or stimulatory depending on the specific gene and tissue affected. There are marked structural and amino acid sequence homology between glucocorticoid receptors and receptors for other steroid hormones (e.g. mineralocorticoids, estrogen, progesterone) as well as for thyroid hormone and the oncogene v-erb A.

### Glucocorticoid Agonists and Antagonists

In addition to agonists and antagonists, there are steroids with mixed effects termed partial agonists, partial antagonists, or partial agonist – partial antagonists.

In humans, cortisol, synthetic glucocorticoids (e.g. prednisolone) corticosterone, and aldosterone are glucocorticoid agonists. The synthetic glucocorticoids have substantially higher affinity for the glucocorticoid receptor, and these have greater glucocorticoid activity than cortisol.

Glucocorticoid antagonists bind to the glucocorticoid receptors but do not elicit the nuclear events required to cause a glucocorticoid response. These steroids compete with agonist steroids such as cortisol for the receptors and thus inhibit agonist responses. Other steroid have partial agonist activity when present alone; i.e. they elicit a partial glucocorticoid response. Steroids such as progesterone, 11-dexycortisol, DOC, testosterone, and 17β-estradiol have antagonist or partial agonist – partial antagonist effects. The antiprogestational agent RU486 (mifepristone) has substantial glucocorticoid antagonist properties and has been used to block glucocorticoid action in patients with Cushing's syndrome.

## Intermediary Metabolism

Glucocorticoids in general inhibit DNA synthesis. In addition, in most tissues they inhibit RNA and protein synthesis and accelerate protein catabolism. Accelerated catabolism also accounts for the deleterious effects of glucocorticoids on muscle, bone, connective tissue, and lymphatic tissues. In contrast, RNA and protein synthesis in liver is stimulated.

#### A. Hepatic Glucose Metabolism:

Glucocorticoids increase hepatic gluconeogenesis by stimulating the gluconeogenic enzymes phosphoenolpyruvate carboxykinase and glucose 6-phosphatase. Glucocorticoids have a permissive effect in that they increase hepatic responsiveness to the gluconeogenic hormone glucagon, and they also increase the release of substrates for gluconeogenesis from peripheral tissues, particularly muscle; amino acid uptake by peripheral tissue and protein synthesis are reduced. Glucocorticoids also increase glycerol and free fatty acid release by lipolysis and increase muscle lactate release. They enhance hepatic glycogen synthesis and storage by stimulating glycogen synthetase activity.

#### B. Peripheral Glucose Metabolism

Glucocorticoids also alter carbohydrate metabolism by inhibiting peripheral glucose uptake in muscle and adipose tissue. Insulin secretion may increase in states of chronic glucocorticoid excess.

#### C. Effects on Adipose Tissue

In adipose tissue, the predominant effect is increased lipolysis with release of glycerol and free fatty acids. This is partially due to direct stimulation of lipolysis by glucocorticoids, but it is also contributed to by decreased glucose uptake and enhancement by glucocorticoids the effects of lipolytic hormones. Although glucocorticoids are lipolytic, increased fat deposition is a classic manifestation of glucocorticoid excess. This paradox may be explained by the increased appetite caused by high level of these steroids and by the lipogenic effects of the hyperinsulinemia that

occurs in this state. The reason for abnormal fat deposition and distribution in state of cortisol excess is unknown. In these instances, fat is classically deposited centrally in the face, cervical area, trunk, and abdomen; the extremities are usually spared.

**D. Summary**

The effects of the glucocorticoids on intermediary metabolism can be summarized as follows:

1. Effects are minimal in the fed state. However, during fasting, glucocorticoids contribute to the maintenance of plasma glucose levels by increasing gluconeogenesis, glycogen deposition, and the peripheral release of gluconeogenic substrate.
2. Hepatic glucose production is enhanced, as is hepatic RNA and protein synthesis.
3. The effects on muscle are catabolic, i.e. decreased glucose uptake and metabolism, decreased protein synthesis, and increased release of amino acids.
4. In adipose tissue, lipolysis is stimulated.
5. In glucocorticoid deficiency, hypoglycemia may result, whereas in states of glucocorticoid excess there may be hyperglycemia, hyperinsulinemia, muscle wasting, and weight gain with abnormal fat distribution.

**Effects on Other Tissues and Functions**

**A. Connective Tissue:** Glucocorticoid in excess inhibit fibroblasts, lead to loss of collagen and connective tissue and thus result in thinning of the skin, easy bruising and weight gain with abnormal fat distribution.

**B. Bone:** The physiologic role of glucocorticoids in bone metabolism and calcium homeostasis is unknown; however, in excess, they have major deleterious effects. Glucocorticoids directly inhibit bone formation by decreasing cell proliferation and the synthesis of RNA, protein, collagen and hyaluronate. Glucocorticoids also directly stimulate bone-resorbing cells, leading to osteolysis. In addition, they potentiate the actions of PTH and $1,25(OH)_2$ $D_3$ on bone, and this may further contribute to net bone resorption.

**C. Calcium Metabolism:** Glucocorticoids markedly reduce intestinal calcium absorption, which tends to lower serum calcium. This results in a secondary increase in PTH secretion. In addition, glucocorticoids may directly stimulate PTH release. The mechanism of decreased intestinal calcium absorption is unknown, it is not mediated by $1,25(OH)_2$ $D_3$; in fact, $1,25(OH)_2$ $D_3$ levels are normal or even increased in the presence of glucocorticoid excess. Glucocorticoids also increase urinary calcium excretion. Serum calcium levels are maintained, but at the expense of net bone resorption, that results in osteoporosis.

**D. Growth and Development**: Glucocorticoids accelerate the development of a number of systems and organs in fetal and differentiating tissue, although the mechanisms are unclear. These stimulatory effects may be due to glucocorticoid interaction with other growth factors. Examples are increased surfactant production in the fetal lung and the accelerated development of hepatic and gastrointestinal enzyme systems. Glucocorticoids in excess inhibit growth in children, and this adverse effect is a major

complication of therapy. This may be a direct effect on bone cells, although decreased GH and somatomedin also contribute.

**E. Blood Cells and Immunologic Function**:

1. **Erythrocytes:** Glucocorticoids have little effect on erythropoiesis and hemoglobin concentration.

2. **Leukocytes:** Glucocorticoids influence both leukocyte movement and function. Glucocorticoids reduce the number of circulating lymphocytes, monocytes, and eosinophils, mainly by increasing their movement out of the circulation. Glucocorticoids also decrease the migration of inflammatory cells (polymorphonuclear leukocytes – PMNs, monocytes and lymphocytes) to sites of injury, and this is probably a major mechanism of anti-inflammatory actions and increase susceptibility to infections that occur following chronic administration. Glucocorticoids also affect functions of these cells.

3. **Immunologic Effects:** Glucocorticoids influence multiple aspects of immunologic and inflammatory responsiveness, including the mobilization and function of leukocytes. They inhibit phospholipase $A_2$, a key enzyme in the synthesis of prostaglandins. They also impair release of effector substances such as the lymphokine interleukin–1 (IL-1), antigen processing, antibody production, and other specific bone marrow-derived and thymus–derived lymphocyte functions.

**F. Cardiovascular Function:** Glucocorticoid may increase cardiac output, and they also increase peripheral vascular tone. Glucocorticoids also regulate expression of adrenergic receptors. Thus, refractory shock may occur when the glucocorticoid – deficient individual is subjected to stress.

**G. Renal Function:** Glucocorticoids affect water and electrolyte balance by actions mediated either by mineralocorticoid receptors ($Na^+$ retention, hypokalemia, and hypertension) or via glucocorticoid receptors (increased GFR due to increased cardiac output or due to direct renal effects on salt and water retention).

**H. Central Nervous System Function:** Glucocorticoids readily enter the brain, and although their physiological role in CNS function is unknown, their excess or deficiency may profoundly alter behavior and cognitive function.

**I. Effects on Other Hormones:**

1) **Thyroid function**: TSH synthesis and release are inhibited by Glucocorticoids, and TSH responsiveness to TRH is subnormal. Manifestations of hypothyroidism are not apparent.

2) **Gonadal Function:** in males, glucocorticoids inhibit gonadotropin secretion as evident by decreased responsiveness to GnRH and subnormal plasma testosterone concentration. In females, glucocorticoids also suppress LH responsiveness to GnRH, resulting in suppression of estrogens and progestins with inhibition of ovulation and amenorrhea.

## Adrenal Androgens

The direct biologic activity of adrenal androgens (androstenedione, DHEA, DHEA sulfate) is minimal, and they function primarily as precursors for T and DHT. In males with normal gonadal function, the physiologic effect of adrenal androgens is negligible. In females, the adrenal androgens substantially contribute to total androgen production. Abnormal adrenal function as seen in Cushing's syndrome, adrenal carcinoma, and congenital adrenal hyperplasia results in excessive secretion of adrenal androgen, manifested by acne, hirsutism, and virilization.

# Disorders of Adrenocortical Insufficiency

Deficient adrenal production of glucocorticoids or mineralocorticoids result in adrenocortical insufficiency, which is either the consequence of destruction or dysfunction of the adrenal cortex (primary adrenocortical insufficiency, or Addison's disease) or secondary to deficient pituitary ACTH secretion (secondary adrenocortical insufficiency). Glucocorticoid therapy is the most common cause of secondary adrenocortical insufficiency.

## Primary Adrenocortical Insufficiency (Addison's Disease)

### Etiology and Pathology (Fig. 9-9)

Tuberculosis was the major cause of adrenocortical insufficiency. Since 1950, autoimmune adrenalitis with adrenal atrophy has accounted for about 80% of cases. Primary adrenocortical insufficiency, or Addison's disease, is rare. It is more common in females. **Autoimmune** Addison's disease is frequently accompanied by other immune disorders. It is often associated with hepatitis, dystrophy of dental enamel and nails, and may be accompanied by hypofunction of the gonads, thyroid, pancreatic B cells, and gastric parietal cells. Autoantibodies against the cholesterol side–chain cleavage enzyme and others have been described in patients with this disorder. This disorder has no relationship to HLA.

The more common presentation of autoimmune adrenocortical insufficiency is associated with HLA-related disorders including type I diabetes mellitus and autoimmune thyroid disease. This disorder is often referred to as polyglandular autoimmune syndrome type II (Schmidt’s syndrome). The genetic susceptibility to this disorder is linked to HLA-DR3 or DR4 (or both). These patients have antiadrenal cytoplasmic antibodies and autoantibodies directed against 21α-hydroxylase.

Bilateral **adrenal hemorrhage** is a common cause. This may result from adrenal vein thrombosis. **Infections** such as systemic fungal infection and AIDS can involve and destroy the adrenal cortex.

X-linked **adrenoleukodystrophy** is an important cause of adrenal insufficiency in men. This disorder represents two distinct entities that may cause malfunction of the adrenal cortex and demyelination in the CNS. These disorders are characterized by abnormally high level of very long chain fatty acids due to their defective beta oxidation within peroxisomes. The abnormal accumulation of these fatty acids in the brain, adrenal cortex, testes, and liver, result in the clinical manifestations of this disorder.

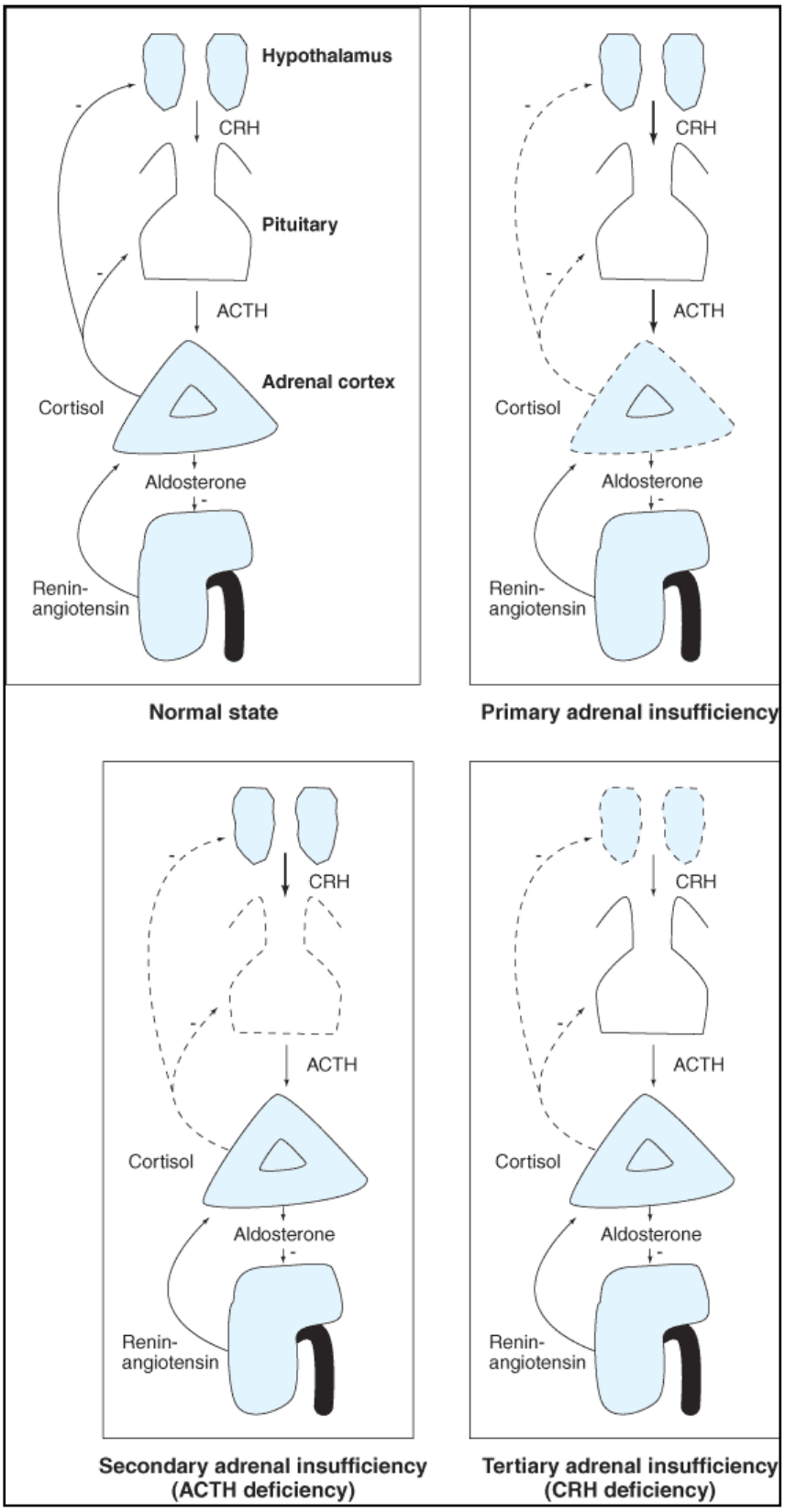



**Figure 9-9**. **Hypothalamic-pituitary axis in adrenal insufficiency of different causes**. These panels illustrate hormone secretion in the normal state (upper left), primary adrenal insufficiency (upper right), secondary adrenal insufficiency–ACTH deficiency (lower left), and tertiary adrenal insufficiency–CRH deficiency (lower right). Renin-angiotensin system is also illustrated. In contrast to normal secretion and hormone levels, decreased hormonal secretion is indicated by a dotted line and increased secretion by a dark solid line.

**Familial glucocorticoid deficiency** is a rare disorder in which there is hereditary adrenocortical unresponsiveness to ACTH, aldosterone secretion is preserved. Two distinct types of this disorder have been described. One type is associated with mutation in the ACTH receptor on the cells of the adrenal cortex. Another type is often associated with achalasia and progressive neurologic impairment.

Primary **cortisol resistance** is an unusual disorder representing target cell resistance to cortisol due to abnormalities of glucocorticoid receptor. This is characterized by hypercortisolism without clinical manifestations of glucocorticoid excess. Pituitary resistance to cortisol results in hypersecretion of ACTH, which stimulates the adrenal gland to produce excessive amounts of cortisol, mineralocorticoids and adrenal androgens. The increased production of these nonglucocorticoid adrenal steroids may cause hypertension, hypokalemia, virilization, and sexual precocity.

### Clinical Features

Cortisol deficiency causes weakness, fatigue, anorexia and vomiting, hypotension, hyponatremia and hypoglycemia. Mineralocorticoid deficiency produces renal sodium wasting and potassium retention and can lead to severe dehydration, hypotension, hyponatremia, hyperkalemia, and acidosis. Amenorrhea is common in Addison's disease. It may be due to weight loss and chronic illness and to primary ovarian failure.

## Secondary Adrenocortical Insufficiency

Secondary adrenocortical insufficiency due to ACTH deficiency is most commonly a result of exogenous glucocorticoid therapy. Pituitary and hypothalamic tumors are the most common causes of naturally occurring pituitary ACTH hyposecretion.

ACTH deficiency is the primary event and leads to decreased cortisol and adrenal androgen secretion. Aldosterone secretion remains normal except in a few cases. The clinical features of secondary adrenal insufficiency differ from those of primary adrenocortical insufficiency in that pituitary secretion of ACTH is deficient and hyperpigmentation is therefore not present.

# Cushing's Syndrome

Chronic glucocorticoid excess, whatever its cause, leads to Cushing's syndrome. Cushing's syndrome is caused by abnormalities of the pituitary or adrenal or may occur as a consequence of ACTH or CRH secretion by nonpituitary tumors (ectopic ACTH syndrome; ectopic CRH syndrome). Cushing's disease is defined as the specific type of Cushing's syndrome due to excessive pituitary ACTH secretion from pituitary tumors.

### Classification

Cushing's syndrome is conveniently classified as either ACTH–dependent or ACTH independent. These ACTH-dependent types of Cushing's syndrome–ectopic ACTH syndrome and Cushing's disease – are characterized by chronic ACTH hypersecretion, which results in hyperplasia of the adrenal zonae fasciculate and reticularis and therefore increased adrenocortical secretion of cortisol androgens and DOC.

ACTH–independent Cushing's syndrome may be caused by a primary adrenal neoplasm (adenoma or carcinoma) or nodular adrenal hyperplasia. In these cases, the cortisol excess suppresses pituitary ACTH secretion.

**A. Cushing's Disease**

This is the most frequent type of Cushing's syndrome and is responsible for about 70% of reported cases. Cushing's disease is much more common in women than in men (8:1) and the age may range from childhood to 70 years.

**B. Ectopic ACTH Hypersecretion**

This disorder accounts for 15-20% of patients with ACTH-dependent Cushing's syndrome. The production of ACTH from a tumor of non pituitary origin may result in severe hypercortisolism. The clinical presentation of ectopic ACTH secretion is most frequently seen in patients with small cell carcinoma of the lung. The ectopic ACTH syndrome is more common in men.

**C. Primary Adrenal Tumors**

Primary adrenal tumors cause ~10% of cases of Cushing's syndrome. Most of these patients have benign adrenocortical adenomas. Adrenocortical carcinomas are uncommon.

**D. Childhood Cushing's Syndrome**

In contrast to the incidence in adults, adrenal carcinoma is the most frequent cause of Cushing's syndrome in childhood and adolescence (51%) and adrenal adenomas are present in 14%. They occur between the ages 1-8 years, more common in girls, in adolescence the sex incidence is equal.

**Pathophysiology (Fig. 9-12)**

**A. Cushing's Disease**

In Cushing's disease, ACTH hypersecretion is random and episodic and causes cortisol hypersecretion with absence of normal circadian rhythm. ACTH hypersecretion persists despite elevated cortisol secretion and results in chronic glucocorticoid excess.

1. **Abnormalities of ACTH secretion:** despite ACTH hypersecretion, stress responsiveness is absent; stimuli such as hypoglycemia or surgery fail to further elevate ACTH and cortisol secretion. This is probably due to suppression of hypothalamic CRH secretion by hypercortisolism.

2. **Effect of cortisol excess:** cortisol excess not only inhibits normal pituitary and hypothalamic function, affecting ACTH, thyrotropin, GH, and gonadotropin release, but also results in all systemic affects of glucocorticoid excess.

3. **Androgen Excess:** secretion of adrenal androgen (DHEA, DHEA sulfate, androstenedione) is also increased in Cushing's disease. The peripheral conversion of these hormones to T and DHT leads to androgen excess. In women, this cause hirsutism, acne, and amenorrhea. In men with Cushing's disease, cortisol suppression of LH secretion decreases testicular testosterone secretion, resulting in decreased libido and impotence. The increased adrenal androgens are insufficient to compensate for the decreased gonadal testosterone production.

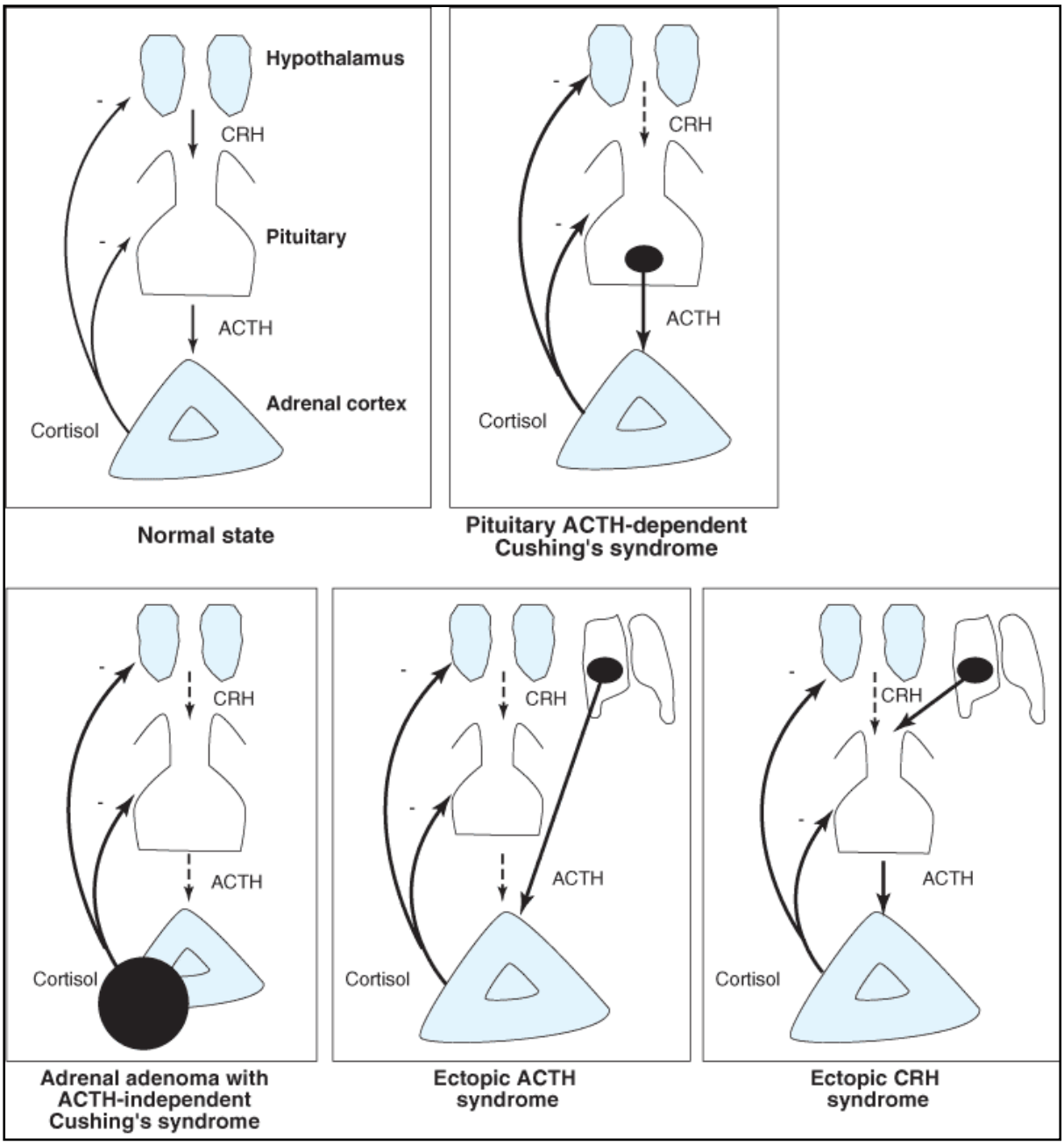



**Figure 9-12**. **Hypothalamic-pituitary axis in Cushing's syndrome of different causes**. These panels illustrate hormone secretion in the normal state (upper left), and four types of cortisol excess: Pituitary ACTH-dependent (with an ACTH-secreting pituitary tumor) (upper right), adrenal tumor (lower left), ectopic ACTH syndrome due to an ACTH-secreting lung cancer (lower middle), and ectopic CRH syndrome due to a CRH-secreting lung tumor. In contrast to normal secretion and hormone levels, decreased hormonal secretion is indicated by a dotted line and increased secretion by a dark solid line.

## B. Ectopic ACTH Syndrome

Hypersecretion of ACTH and cortisol is usually greater in patients with ectopic ACTH syndrome than in those with Cushing's disease. ACTH secretion by ectopic tumors is not subject to negative feed-back control. Features of mineralocorticoid excess (hypertension and hypokalemia) are frequently present and have been attributed to

increased secretion of DOC and the mineralocorticoid effects of cortisol. With ectopic CRH secretion, pituitary ACTH cell hyperplasia and ACTH hypersecretion are observed along with resistance to negative feedback by cortisol.

### C. Adrenal Tumors

1. **Autonomous secretion:** primary adrenal tumors, both adenomas and carcinomas autonomously hypersecrete cortisol. Circulating plasma ACTH levels are suppressed, resulting in cortical atrophy of the uninvolved adrenal.

2. **Adrenal Adenoma:** Adrenal adenomas causing Cushing's syndrome typically present solely with clinical manifestations of glucocorticoid excess, since they usually secrete only cortisol. Thus the presence of androgen or mineralocorticoid excess should suggest that the tumor is an adrenocortical carcinoma.

3. **Adrenal Carcinomas:** Adrenal carcinomas frequently hypersecrete multiple adrenocortical steroids and their precursors. Cortisol and androgens are the steroids most frequently secreted in excess; 11-deoxycortisol is often elevated, and there may be increased secretion of DOC, aldosterone, or estrogens.

### Clinical Features (Table 9-12)

1. **Obesity:** Obesity is the most common manifestation, and weight gain is usually the initial symptom. It is classically central, affecting mainly the face, neck, trunk and abdomen, with relative sparing of the extremities. Accumulation of fat in the face leads to the typical "moon faces", which is present in 75% of cases. Fat accumulation around the neck is prominent which is responsible for the "buffalo hump".

2. **Skin Changes:** Skin changes are frequent. Atrophy of the epidermis and its underlying connective tissue leads to thinning and facial plethora, easy bruisability. Striae are most commonly abdominal but may also occur over the breasts, hips, buttocks, thighs … Acne may result from hyperandrogenism.

3. **Hirsutism:** Hirsutism is resent in 80% of female patients owing to hypersecretion of adrenal androgens. Facial hirsutism is most common, but increased hair growth may also occur over the abdomen, breasts, chest, and upper thighs. Virilism is unusual except in cases of adrenal carcinoma.

4. **Hypertension:** Hypertension is a classic feature of spontaneous Cushing's syndrome; it is present in about 75% of cases. And the diastolic blood pressure is greater than 100 mmHg in over 50%.

5. **Gonadal Dysfunction:** This is very common as a result of elevated androgens (in females) and cortisol (in males and to a lesser extent in females). Amenorrhea occurs in 75% of premenopausal women and is usually accompanied by infertility. Decreased libido is frequent in males.

6. **CNS and Psychologic Disturbances:** Psychological disturbances occur in the majority of patients. Mild symptoms consist of emotional lability and increases irritability. Anxiety, depression poor concentration and poor memory may also be present. Sleep disorder are present with either insomnia or early morning awakening.

Severe psychologic disorders occur in a few patients and include severe depression, psychosis with delusions or hallucinations, and paranoia.

7. **Muscle Weakness:** It is usually most prominent in lower extremities. Hypercortisolism is associated with both low fat-free muscle mass and low total body protein.

8. **Osteoporosis:** Owing to the profound effects of glucocorticoids on the skeleton, patients with Cushing's syndrome frequently have evidence of significant osteopenia and osteoporosis. Patients may present with frequent unexplained fractures, typically of the feet, ribs, or vertebrae. Back pain may be the initial complain.

9. **Renal Calculi:** Calculi secondary to glucocorticoid induced hypercalciuria occur in ~15% of patients, and renal colic may occasionally be a presenting complaint.

10. **Thirst and Polyuria:** It is usually due to glucocorticoid inhibition of ADH secretion and the direct enhancement of renal free water clearance by cortisol.

**Table 9–12**. Clinical Features of Cushing's Syndrome (% Prevalence).

| |
|---|
| **General** |
| Obesity 90% |
| Hypertension 85% |
| **Skin** |
| Plethora 70% |
| Hirsutism 75% |
| Striae 50% |
| Acne 35% |
| Bruising 35% |
| **Musculoskeletal** |
| Osteopenia 80% |
| Weakness 65% |
| **Neuropsychiatric 85%** |
| Emotional lability |
| Euphoria |
| Depression |
| Psychosis |
| **Gonadal dysfunction** |
| Menstrual disorders 70% |
| Impotence, decreased libido 85% |
| **Metabolic** |
| Glucose intolerance 75% |
| Diabetes 20% |
| Hyperlipidemia 70% |
| Polyuria 30% |
| Kidney stones 15% |