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Adrenocortical Hormones and Drugs Affecting the Adrenal Cortex

Ronald P. Rubin

DRUG LIST

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Aminoglutethimide	700	Hydrocortisone	692
Beclomethasone	692	Ketoconazole	700
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Clobetasol	692	Mifepristone (RU 486)	701
Corticotropin	699	Mitotane	700
Cosyntropin	699	Prednisolone	692
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The steroidal nature of adrenocortical hormones was established in 1937, when Reichstein synthesized desoxycorticosterone. Eventually it was clearly established that the adrenal cortex elaborated a number of hormones and that these compounds differed in their amount of inherent metabolic (glucocorticoid) and electrolyte regulating (mineralocorticoid) activity. The actions of these hormones extend to almost every cell in the body. In humans, hydrocortisone (cortisol) is the main carbohydrate-regulating steroid, and aldosterone is the main electrolyte-regulating steroid.

STEROID PHYSIOLOGY

Anatomy of the Adrenal Cortex

The mammalian adrenal cortex is divided into three concentric zones: the zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa produces hormones, such as aldosterone, that are responsible for regulating salt and water metabolism; the zona fasciculata produces glucocorticoids; and the zona reticularis produces adrenal androgens. While secretion by the two inner zones is controlled by pituitary adrenocorticotropic hormone (corticotrophin, ACTH), aldosterone produced by the zona glomerulosa is principally controlled by the renin–angiotensin system. Desoxycorticosterone, a mineralocorticoid produced in the zona fasciculata, is under corticotrophin control.
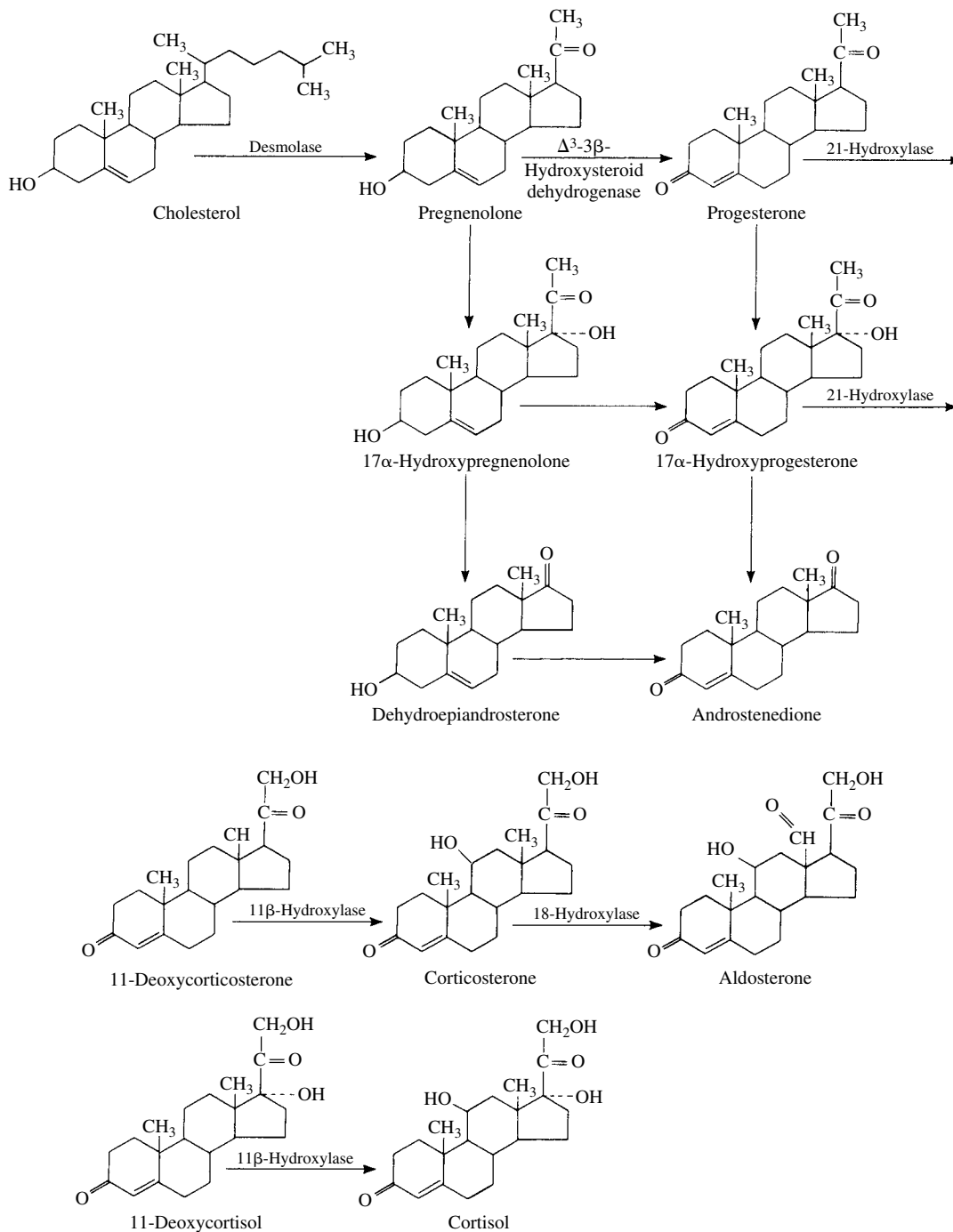
Steroid Biosynthesis

Although the adrenal cortex is primarily involved in the synthesis and secretion of corticosteroids, it is also capable of producing and secreting such steroid intermediates as progesterone, androgens, and estrogens. The adrenal gland synthesizes steroids from cholesterol, which is derived from plasma lipoproteins via the low- and high-density lipoprotein pathways. Additionally, cholesterol is enzymatically released extramitochondrially from cholesterol esters catalyzed by a cholesterol

ester hydrolase. The corticotrophin-dependent stimulation of cholesterol ester hydrolase activity provides an additional source of cholesterol for steroidogenesis.

Cholesterol is transported into the mitochondria of steroidogenic tissue, where side chain cleavage is carried out. In common with other mixed-function oxidase systems, the cholesterol side chain cleavage requires reduced nicotinamide-adenine dinucleotide phosphate

(NADPH), oxygen, and a specific cytochrome P450. *The rate-limiting step in steroid biosynthesis is the conversion of cholesterol to pregnenolone* (Fig. 60.1).

Pregnenolone leaves the mitochondria to become the obligatory precursor of corticosteroids and adrenal androgens. The biosynthetic pathway next branches into two separate routes. One route passes through progesterone and corticosterone to aldosterone, and the other

FIGURE 60.1
Metabolic pathways of corticosteroid biosynthesis.

proceeds from 17α-hydroxyprogesterone and 1-deoxy-cortisol to yield cortisol. Thus, steroid intermediates are converted to steroid end products by sequential 17-, 21-, and 11-hydroxylation reactions. 11-β-Hydroxylation is essential for glucocorticoid and mineralocorticoid activity of a steroid. The steroid hydroxylase system has the characteristics of a mixed-function oxidase, since two substrates, steroid and NADPH, are oxidized. All hydroxylases seem to be associated with a specific cytochrome P450.

The 17- and 21-hydroxylase enzymes are associated with microsomes, whereas the 11-β-hydroxylase has a mitochondrial origin. Since the last-named enzyme is not detectable in other steroid-producing tissues, the term 11-oxygenated steroids is considered synonymous with adrenal steroids. Aldosterone synthesis involves an essential 18-hydroxylation step catalyzed by $P450_{c18}$ with corticosterone as the precursor; this reaction also takes place within the mitochondria.

Steroid Transport in Blood

Glucocorticoids secreted into the systemic circulation are reversibly bound to a specific α-globulin known as *transcortin* or *corticosteroid-binding globulin*. This binding system has a high affinity and low capacity for corticosteroids, which contrasts with the low-affinity binding of these compounds to plasma albumin. Approximately 80% of the normal cortisol content in human plasma (12 μg/dL) is bound to corticosteroid-binding globulin, while 10% is bound to serum albumin; the remaining 10% is the biologically active unbound hormone.

Transcortin acts as a reservoir from which a constant supply of unbound cortisol may be provided to target cells. In addition, when serum albumin levels are low, less circulating cortisol becomes bound, which yields a greater physiological effect. Not only does protein binding control the amount of biologically active cortisol available, but it also reduces the rate at which steroids are cleared from the blood and thus limits steroid suppression of corticotrophin release from the pituitary gland.

The binding affinity of human transcortin is not limited to corticoids. Progesterone and the synthetic glucocorticoid prednisone also can bind to this macromolecule. High estrogen states (pregnancy, estrogen administration, use of oral contraceptives) greatly increase circulating transcortin levels. Thyroxine also stimulates transcortin formation, while androgen administration will decrease transcortin levels and the amount of bound glucocorticoids.

Steroid Metabolism

Most of the cortisol circulating in the blood is metabolized before its excretion. The metabolism of adrenal steroids occurs primarily in the liver, and when metabolic processes are altered, as occurs in liver disease, the half-life of cortisol may increase from 100 minutes to 7 hours.

Two major steps are involved in the metabolism of cortisol. The first is reduction of double bonds and introduction of a hydroxyl group in the A ring to form tetrahydric derivatives; this pathway accounts for 20 to 30% of the cortisol excreted. The glucocorticoid-metabolizing microsomal enzymes 11β-hydroxysteroid dehydrogenases (11β-HSD) play a crucial role in determining the availability of glucocorticoids. 11 β-HSD-1 acts as a reductase, regenerating active glucocorticoids, whereas 11β-HSD-2 acts as a dehydrogenase, converting cortisol to its inactive 11-keto derivative (cortisone). By inactivating glucocorticoids, 11β-HSD-2 protects the mineralocorticoid receptor from occupation by glucocorticoids, thereby endowing specificity to the aldosterone regulatory effects despite the predominance of glucocorticoids in the circulation. By contrast, congenital deficiency of 11β-HSD-2 results in inappropriate activation of the mineralocorticoid receptor by cortisol, leading to hypertension and hypokalemia. The second step in the metabolism of cortisol is a glucuronic acid or sulfate conjugation to form more soluble derivatives that are poorly bound to plasma proteins and readily pass into the urine. Adrenal androgens also are excreted, primarily as sulfates; they constitute about two-thirds of the total urinary 17-ketosteroids excreted. In the male, the other third is contributed by gonadal secretions. Knowledge of corticosteroid metabolism is important to the clinician, since alterations in adrenocortical function can be determined by measuring the amounts of 17-hydroxycorticosteroids. However, radioimmunoassay of urinary free cortisol (and plasma cortisol) is supplanting measurements of urinary metabolites.

Since the metabolism of steroid hormones occurs in part through the action of the hepatic oxidative drug-metabolizing enzymes, concomitant administration of anticonvulsant drugs (e.g., phenytoin and carbamazepine), which are potent inducers of glucocorticoid metabolism, will augment the elimination of methylprednisolone severalfold. Also, since steroids such as prednisone lack glucocorticoid activity until converted to prednisolone by hepatic enzymes, patients with liver disease should be treated with prednisolone rather than prednisone.

ACTIONS OF THE CORTICOSTEROIDS

The pharmacological actions of steroids are generally an extension of their physiological effects. Adrenal corticosteroids exert effects on almost every organ in the body. In normal physiological concentrations, they are

essential for homeostasis, for coping with stress, and for the very maintenance of life.

The designation "glucocorticoid activity" is arbitrary, since naturally occurring glucocorticoids, such as cortisol, also possess mineralocorticoid activity, and the principal mineralocorticoid, aldosterone, when administered in very high doses, has glucocorticoid activity. Moreover, hydrocortisone, as well as certain synthetic glucocorticoids, such as prednisone and dexamethasone, binds to mineralocorticoid receptors. However, the distinction between these two groups serves a useful purpose when dissociation of the basic actions becomes crucial for optimizing steroids' therapeutic efficiency.

Carbohydrate, Protein, and Fat Metabolism

The glucocorticoids increase blood glucose and liver glycogen levels by stimulating gluconeogenesis. The source of this augmented carbohydrate production is protein, and the protein catabolic actions of the glucocorticoids result in a negative nitrogen balance. The inhibition of protein synthesis by glucocorticoids brings about a transfer of amino acids from muscle and bone to liver, where amino acids are converted to glucose.

Supraphysiological concentrations of glucocorticoids will induce the synthesis of specific proteins in various tissues. For instance, glucocorticoids stimulate the synthesis of enzymes involved in glucose and amino acid metabolism, including glucose 6-phosphatase and tyrosine transaminase. The relation of this action of glucocorticoids to their overall effects on general metabolic processes remains obscure, although the latency of their therapeutic actions (several hours) is consistent with the fact that steroids regulate RNA and protein synthesis.

Glucocorticoids not only break down protein but also stimulate the catabolism of lipids in adipose tissue and enhance the actions of other lipolytic agents. This occurrence results in an increase in plasma free fatty acids and an enhanced tendency to ketosis. The mechanism of this lipolytic action is unknown. The net effect of the biochemical changes induced by the glucocorticoids is antagonism of the actions of insulin. These biochemical events promote hyperglycemia and glycosuria, which are similar to the diabetic state.

Electrolyte and Water Metabolism

Another major function of the adrenal cortex is the regulation of water and electrolyte metabolism. The principal mineralocorticoid, aldosterone, can increase the rate of sodium reabsorption and potassium excretion severalfold. This will occur physiologically in response to sodium or volume depletion or both. The primary site of this effect is the distal tubule (see Chapter 21). The steroid-binding specificity of mineralocorticoid and glucocorticoid receptors overlaps in the distal cortical cells and collecting tubules, so that glucocorticoids may mediate mineralocorticoid-like effects. Glucocorticoids also decrease the intestinal transport of calcium by antagonizing the action of 1,25-dihydroxyvitamin D_3 and promote calcium excretion by the kidney (see Chapter 66).

Cardiovascular Function

Glucocorticoids directly stimulate cardiac output and potentiate the responses of vascular smooth muscle to the pressor effects of catecholamines and other vasoconstrictor agents. Such actions on vascular smooth muscle may be secondary to effects mediated through the central nervous system or on circulating volume. However, the presence of steroid receptors on vascular smooth muscle suggests a direct effect on vasomotor activity. *Thus, corticosteroids appear to play an important role in the regulation of blood pressure by modulating vascular smooth muscle tone, by having a direct action on the heart, and through stimulating renal mineralocorticoid and glucocorticoid receptors.* The resulting hypertension may predispose patients to coronary heart disease if a prolonged course of rigorous glucocorticoid therapy is employed.

Immune and Defense Mechanisms

The inflammatory response is a highly complex process that involves a number of cell types of the reticuloendothelial system and a number of chemical mediators, including prostaglandins, leukotrienes, kinins, and biogenic amines (See Chapter 36). The inhibitory effects of glucocorticoids on various aspects of the inflammatory and immunological responses constitute the basis for their therapeutic efficacy. All steps of the inflammatory process are blocked: there is a diminution in heat, erythema, swelling, and tenderness. Both the early components (edema, fibrin deposition, neutrophil migration, and phagocytosis) and late components (collagen synthesis and deposition) may be retarded.

Glucocorticoids promote apoptosis and reduce survival, differentiation, and proliferation of a variety of inflammatory cells, including T lymphocytes and macrophages. These effects are mediated by changes in the production and activity of inflammatory cytokines, such as interleukin (IL) 6 and IL-β, tumor necrosis factor-α, and interferon-γ. Many of the antiinflammatory actions of glucocorticoids are mediated by cross-talk between the activated glucocorticoid receptor and transcription factors, such as the proinflammatory nuclear factor-κ-B (NF-κB) and activator protein (AP) 1. These transcription factors, which promote the expression of a number of inflammatory genes, are potential targets for

antiinflammatory therapy as observed in asthma, for example.

A prominent histological feature of glucocorticoid action on the late-phase response to bronchial inhalation challenge with antigen is inhibition of the influx of polymorphonuclear leukocytes, eosinophils, basophils, mononuclear cells, and lymphocytes into tissues (Fig. 60.2). The ability of glucocorticoids to alter reticuloendothelial cell traffic, which is a prominent antiinflammatory action of glucocorticoids, is regulated by adhesion molecules. Glucocorticoids reduce the expression of adhesion molecules through the inhibition of proinflammatory cytokines and by direct inhibitory effects on the expression of adhesion molecules. Chemotactic cytokines, such as IL-8, which attract immune cells to the inflammatory site, are also inhibited by glucocorticoids. In addition to their ability to inhibit the adherence of inflammatory cells, particularly neutrophils, to the vascular endothelium, steroids are vasoconstrictors. This action would further impede inflammatory cell migration into tissues.

As mentioned previously, glucocorticoids promote apoptosis and reduce survival, differentiation, and proliferation of a number of inflammatory cells. While there is an increase in the number of polymorphonuclear leukocytes in the circulation, corticosteroids cause the involution and atrophy of all lymphoid tissue and decrease the number of circulating lymphocytes. The striking lymphocytopenia is caused in large part by an inhibition of lymphocyte proliferation, although diminished growth with preferential accumulation of cells in the G_1-phase of the cell cycle is followed by cell death. These effects are mainly mediated by alterations in cytokine production and action.

Another important aspect of the inflammatory cascade is arachidonic acid metabolism, leading to the synthesis of the proinflammatory prostaglandins and leukotrienes. Through the formation of lipocortin, an inhibitor of phospholipase A_2, glucocorticoids depress the release of arachidonic acid from phospholipids and hence the production of arachidonic acid metabolites.

Other Endocrine Organs

Since the synthesis and release of cortisol are regulated by pituitary corticotrophin, removal of the pituitary gland results in decreased function and eventual atrophy of the zona fasciculata and zona reticularis. Infusion of supraphysiological concentrations of cortisol will suppress corticotrophin secretion from the pituitary and will markedly decrease circulating corticotrophin levels. This occurrence implies a negative feedback control for corticotrophin and corticosteroid release (Fig. 60.3).

In addition to the humoral control of corticotrophin release, direct nervous control is mediated through the median eminence of the hypothalamus (Fig. 60.3). Nerve terminals in the median eminence store and release various hormones and neurotransmitters, including corticotropin-releasing factor (CRF), which is under the control of higher neural centers. During stress, CRF is released into the pituitary portal system to stimulate corticotrophin release. Activation of the hypothalamic–pituitary system also accounts for the diurnal, or circadian, nature of cortisol secretion; plasma cortisol concentrations reach a maximum between 6 and 8 A.M. and then slowly decrease through the afternoon and evening. Human and animal studies suggest the existence of an early (fast) and more prolonged (delayed,
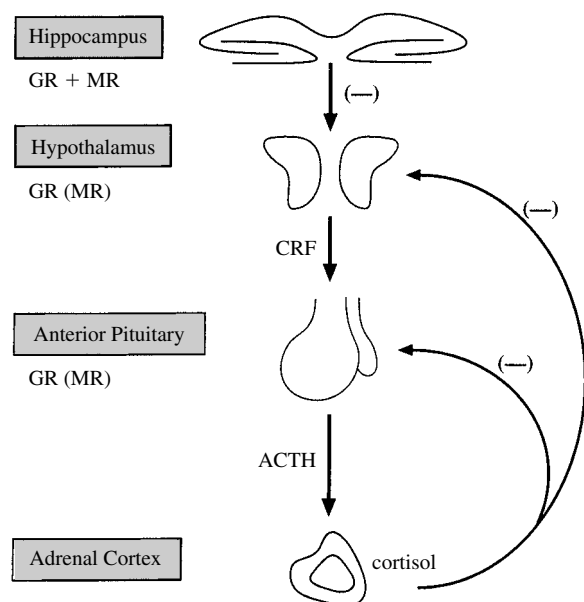
FIGURE 60.3

The role of the hypothalamic–pituitary axis in the regulation of adrenocortical hormone synthesis and release. The major physiological stimulus for the synthesis and release of glucocorticoids is corticotropin (ACTH) secreted from the anterior pituitary gland. ACTH secretion is regulated by corticotropin-releasing factor (CRF) from the paraventricular region of the hypothalamus. The release of CRF in turn is controlled by glucocorticoid levels and by input from the hippocampus. Both endogenous and exogenous glucocorticoids feed back negatively to regulate the secretion of ACTH and CRF. Glucocorticoid and mineralocorticoid receptors (GR and MR) in the hippocampus also negatively modulate CRF synthesis and release.

>2 hours) feedback of corticotrophin suppression. Both inhibitory systems are operative at the hypothalamic and pituitary levels. The hippocampus also highly expresses glucocorticoid and mineralocorticoid receptors, which when activated, decrease the synthesis and release of CRF. This results in a decrease in basal and corticotrophin-induced cortisol secretion (Fig. 60.3).

Corticosteroids also affect adrenomedullary function by increasing epinephrine production; the mechanism is exertion of a stimulatory action on two of the enzymes that regulate catecholamine synthesis, tyrosine hydroxylase, the rate-limiting enzyme, and phenylethanolamine *N*-methyltransferase, which catalyzes the conversion of norepinephrine to epinephrine. Steroids also influence the metabolism of circulating catecholamines by inhibiting their uptake from the circulation by nonneuronal tissues (i.e., extraneuronal uptake; see Chapter 9). This effect of corticoids may explain their permissive action in potentiating the hemodynamic effects of circulating catecholamines.

Finally, steroids can exert suppressive actions on certain endocrine systems. Glucocorticoids inhibit thyroid-stimulating hormone pulsatility and the nocturnal surge of this hormone by depressing thyrotropin-releasing hormone secretion at the hypothalamic level. In addition to hypercortisolism being associated with insulin resistance, glucocorticoids are inhibitors of linear growth and skeletal maturation in humans. A pivotal component of this inhibition is the depression of growth hormone secretion. The anticalcemic effect of the glucocorticoids, which is associated with an amplification of the actions of parathyroid hormone, also may retard bone growth. The inhibitory action of high levels of glucocorticoids on reproductive function is probably because of attenuation of luteinizing hormone secretion and direct action on the reproductive organs.

GENERAL PHARMACOLOGY OF CORTICOSTEROIDS

### *Structure-Activity Relationships*
Natural Corticosteroids

Within the basic structure of the steroid molecule (Fig. 60.4), a 4,5 double bond and a 3-ketone group are needed for typical steroid activity. A hydroxyl group on C11 is needed for glucocorticoid activity (corticosterone) but is not required for sodium-retaining activity (desoxycorticosterone). The addition of a hydroxyl group on C17, which converts corticosterone to cortisol, also increases glucocorticoid activity.

Synthetic Corticosteroids

The ultimate aim in altering the steroid molecule is to decrease sodium-retaining activity and to increase anti-inflammatory glucocorticoid activity.

Ring A
The addition of a double bond at the 1,2 position of cortisol or cortisone yields prednisone or prednisolone, respectively, and increases the ratio of carbohydrate to
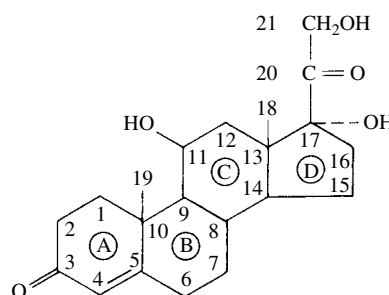
FIGURE 60.4
Basic corticosteroid nucleus.

sodium-retaining potency. Prednisone is inactive and must be converted to prednisolone in the liver by re-duction at the 11-keto position.

Ring B

The inclusion of an α-methyl group in position 6 of prednisolone will yield 6-α-methylprednisolone, a com-pound with slightly greater glucocorticoid potency. This small structural modification greatly diminishes the binding of methylprednisolone to transcortin.

Ring C

The addition of a fluoride group on the 9 position of cortisol to give 9-α-fluorocortisol will greatly increase all biological activity.

Ring D

Hydroxylation or methylation at the 16 position of α-fluoroprednisolone to give triamcinolone, dexam-ethasone, or betamethasone increases antiinflammatory potency and drastically diminishes sodium-retaining activity.

The relative antiinflammatory potency of each of the synthetic analogues is compared with cortisol in Table 60.1 and is roughly correlated with its biological half-life. Hydrocortisone is considered a short-acting steroid; triamcinolone and prednisolone, intermediate-acting; and betamethasone and dexamethasone, long-acting. Thus, prednisone 5 mg, dexamethasone 0.75 mg, and hydrocortisone 20 mg should possess equal gluco-corticoid potency.

The synthetic analogues (except 9-α-fluorocortisol) share an advantage over hydrocortisone in that sodium retention is not as marked at equipotent antiinflamma-tory doses. However, all of the other undesirable side effects of supraphysiological concentrations of hydro-cortisone have been observed with the synthetic ana-logues.

Steroid Preparations

Glucocorticoids are available in a wide range of prepa-rations, so that they can be administered parenterally, orally, topically, or by inhalation. Obviously the oral route is preferred for prolonged therapy. However, par-enteral administration is required in certain circum-stances. Intramuscular injection of a water-soluble ester (phosphate or succinate) formed by esterification of the C21 steroid alcohol produces peak plasma steroid levels within 1 hour. Such preparations are useful in emergen-cies. By contrast, acetate and tertiary butylacetate esters must be injected locally as suspensions and are slowly absorbed from the injection site, which prolongs their effectiveness to approximately 8 hours.

Topical preparations usually contain relatively insol-uble steroids, such as clobetasol propionate, triamcin-olone acetonide, or triamcinolone diacetate. Side effects of this mode of drug application are usually milder and more transient than those seen after systemically ad-ministered steroids. However, potent topical cortico-steroids, such as clobetasol propionate (*Temovate*), can suppress adrenal function when used in large amounts for a long time, especially when the skin surface is de-nuded or when occlusive dressings are employed. Since the high potency topical preparations carry a higher risk of local side effects, their use should be held in reserve.

Inhaled glucocorticoid preparations, such as be-clomethasone dipropionate and betamethasone valer-ate, provide an effective alternative to systemic steroids in the treatment of chronic asthma, with lesser side ef-fects than oral or parenteral glucocorticoids (see Chapter 39). In fact, inhaled glucocorticoids have be-come a mainstay of asthma therapy. Inhalation delivers the agent directly to the target site in relatively low doses, with the potential for more frequent administra-tion. Moreover, inhaled glucocorticoids are metabolized in the lung before they are absorbed, which reduces their systemic effects. However, even modest doses of

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T A B L E 60.1   General Classification of Glucocorticoids

Steroid	Carbohydrate Potency[a] (mg)	Antiinflam-matory Potency	Sodium-retaining Potency	Biological Half-life (hr)
Cortisol	20.0	1	1.00	8–12
Prednisolone (Δ¹-cortisone)	5.0	4	0.50	12–36
6-α-Methylprednisolone	4.0	5	0.50	12–36
9-α-Fluorocortisol	0.1	10	125.00	12–36
Triamcinolone (9-α-fluoro-16-hydroxyprednisolone)	4.0	5	0.10	12–36
Betamethasone (9-α-16-β-methylprednisolone)	0.6	25	0.05	36–54
Dexamethasone (9-α-fluoro-16-α-methylprednisolone)	1.0	30	0.05	36–54

[a]Carbohydrate action of glucocorticoids is defined as the stimulation of glucose formation, diminution of its use, and promotion of its storage as glycogen.

inhaled steroid can have a measurable effect on the hypothalamic–pituitary axis, although the clinical effects may be marginal. There is also a close association in adults between the heavy use of inhaled glucocorticoids and the risk of posterior subcapsular cataract. Since the dose–response curve to inhaled glucocorticoids is relatively flat, the use of steroid-sparing agents (long-acting inhaled β-adrenergic agonists, low-dose theophylline, or antileukotrienes) is recommended instead of increasing the dose of glucocorticoid. This strategy will also limit the severity of hypothalamic–pituitary–adrenal depression and other side effects.

ADVERSE EFFECTS

General Considerations

Short-term glucocorticoid therapy of life-threatening diseases, such as status asthmaticus, provides dramatic improvement with few complications. However, when administered in pharmacological doses for long periods, steroids generally produce serious toxic effects that are extensions of their pharmacological actions. No route or preparation is free from the diverse side effects (Table 60.2), although individuals receiving comparable doses of glucocorticoids exhibit variations in side effects.

Glucocorticoids are cautiously employed in various disease states, such as rheumatoid arthritis, although they still should be regarded as adjunctive rather than primary treatment in the overall management scheme. The toxic effects of steroids are severe enough that a number of factors must be considered when their prolonged use is contemplated.

The first point is that treatment with steroids is generally palliative rather than curative, and only in a very few diseases, such as leukemia and nephrotic syndrome, do corticosteroids alter prognosis. One must also consider which is worse, the disease to be treated or possible induced hypercortisolism. The patient's age can be an important factor, since such adverse effects as hypertension are more apt to occur in old and infirm individuals, especially in those with underlying cardiovascular disease. Glucocorticoids should be used with caution during pregnancy. If steroids are to be employed, prednisone or prednisolone should be used, since they cross the placenta poorly.

Once steroid therapy is decided upon, the lowest possible dose that can provide the desired therapeutic effect should be employed. Relationships of dosage, duration, and host responses are essential elements in determining adverse effects. Increasing attention is being given to the use of lower doses of glucocorticoids in combination with other drugs that can have a synergistic effect on a given disease. Moreover, the lowered dose levels of steroid will minimize the side effects.

TABLE 60.2 Complications of Glucocorticoid Therapy

Hematological and immunological	Central nervous system
Leukocytosis	Insomnia
Lymphopenia	Depression
Eosinopenia	Nervousness
Altered inflammatory response	Psychosis
Gastrointestinal	Fluid and electrolyte
Peptic ulceration	Na^+ retention
Fatty liver	K^+ loss
Pancreatitis	Negative Ca^{++} balance
Nausea, vomiting	Hypertension
Metabolic	Endocrinological
Hyperglycemia	Suppression of HPA axis[a]
Protein wasting	Antagonisms with insulin, parathyroid, thyroid
Hyperlipidemia	Skin
Obesity	Thinning of skin
Musculoskeletal	Striae purpurae
Myopathy	Ecchymoses
Growth failure	Acne
Osteopenia	Hirsutism
Ocular	General
Posterior subcapsular cataracts	Cushingoid features
Increased intraocular pressure	Truncal obesity
	Withdrawal syndrome

[a]Hypothalamic-pituitary-adrenocortical axis.

Osteoporosis

The most damaging and therapeutically limiting adverse effect of long-term glucocorticoid therapy is impairment of bone formation. This effect is associated with a decrease in serum levels of osteocalcin, a marker of osteoblastic function. In fact, *glucocorticoid administration is the most common cause of drug-induced osteoporosis.* Most patients receiving chronic steroid therapy develop osteoporosis, particularly during the first year of therapy, and more than 50% will have a bone fracture. Trabecular bone is particularly affected.

Systemic glucocorticoid therapy increases the probability of osteoporosis even with dosages sufficiently low so as not to affect the hypothalamic–pituitary–adrenal axis. By enhancing bone resorption and decreasing bone formation, glucocorticoids decrease bone mass and increase the risk of fractures. The overall effects appear to be due to direct actions of glucocorticoids on osteoblasts and to indirect effects, such as impaired Ca^{++} absorption and a compensatory increase in parathyroid hormone secretion. Inhibition of bone growth is a well-known side effect of long-term systemic glucocorticoid therapy in children with bronchial asthma, even in those receiving alternate-day therapy. Glucocorticoids can also augment bone loss, decreasing testosterone levels in men and estrogen levels in women

by direct effects on the gonads and inhibition of gonadotropin release. Thus, patients taking glucocorticoids can also develop hypogonadism. It is recommended that all patients who receive long-term glucocorticoid treatment should have measurements of bone density, gonadal steroids, vitamin D, and 24-hour urinary Ca^{++}. Deficiencies in either testosterone or estradiol increase bone loss and should be corrected if possible. Bisphosphonates (etidronate, alendronate, or risedronate) and calcitonin, which inhibit bone resorption, have become increasingly popular for treating osteoporosis.

The Infectious Process

Steroids can alter host–parasite interactions, suppress fever, decrease inflammation, and change the usual character of the symptoms produced by most infectious organisms. There is a heightened susceptibility to serious bacterial, viral, and fungal infections. Local infections may reactivate and spread, and infections acquired during the course of therapy may become more severe and even more difficult to recognize. By interfering with fibroblast proliferation and collagen synthesis, glucocorticoids cause dehiscence of surgical incisions, increase risk of wound infection, and delay healing of open wounds. This untoward effect of steroids may make it mandatory to administer antibiotics with the steroids, especially when there is a history of a chronic infectious process (e.g., tuberculosis). On the other hand, individuals with normal defenses who are treated with low to moderate doses of glucocorticoids are not at great risk of infection. While the incidence of infections has probably decreased with the increased use of inhaled steroids and combination therapy, inhaled steroids carry an increase in the incidence of oral candidiasis that can be reduced by using proper doses. Nevertheless, glucocorticoids are used to treat herpes zoster, bacterial meningitis, and skin infections.

Effects on Gastric Mucosa

Steroid administration was once thought to lead to the formation of peptic ulcers, with hemorrhage or perforation or reactivation of a healed ulcer. It is now realized that this effect is principally observed in patients who have received concomitant nonsteroidal antiinflammatory treatment. Since there is a minimal increase in the incidence of ulcers in patients receiving glucocorticoid treatment alone, prophylactic antiulcer regimens are usually not necessary.

Hyperglycemic Action

In about one-fourth to one-third of the patients receiving prolonged steroid therapy, the hyperglycemic effects of glucocorticoids lead to decreased glucose tolerance, decreased responsiveness to insulin, and even glycosuria. Ketoacidosis occurs very rarely. Pharmacological concentrations of steroids may precipitate frank diabetes in individuals who cannot produce the necessary additional insulin. Mild hyperglycemia can often be managed with oral hypoglycemic agents. The effects of glucocorticoids on hyperglycemia are usually reversed within 48 hours following discontinuation of steroid therapy. If glucocorticoid therapy is continued for an extended period, the alterations of glucose metabolism and the resulting hyperinsulinemia may lead to enhanced cardiovascular risk.

Ophthalmic Effects

Glucocorticoids induce cataract formation, particularly in patients with rheumatoid arthritis. An increase in intraocular pressure related to a decreased outflow of aqueous humor is also a frequent side effect of periocular, topical, or systemic administration. Induction of ocular hypertension, which occurs in about 35% of the general population after glucocorticoid administration, depends on the specific drug, the dose, the frequency of administration, and the glucocorticoid responsiveness of the patient.

Central Nervous System Effects

Treatment with steroids may initially evoke euphoria. This reaction can be a consequence of the salutary effects of the steroids on the inflammatory process or a direct effect on the psyche. The expression of the unpredictable and often profound effects exerted by steroids on mental processes generally reflects the personality of the individual. Psychiatric side effects induced by glucocorticoids may include mania, depression, or mood disturbances. Restlessness and early-morning insomnia may be forerunners of severe psychotic reactions. In such situations, cessation of treatment might be considered, especially in patients with a history of personality disorders. In addition, patients may become psychically dependent on steroids as a result of their euphoric effect, and withdrawal of the treatment may precipitate an emotional crisis, with suicide or psychosis as a consequence. Patients with Cushing's syndrome may also exhibit mood changes, which are reversed by effective treatment of the hypercortisolism.

The hippocampus is a principal neural target for glucocorticoids. It contains high concentrations of glucocorticoid and mineralocorticoid receptors and has marked sensitivity to these hormones.

Fluid and Electrolyte Disturbances

The normal subject may retain sodium and water during steroid therapy, although the synthetic steroid ana-

logues represent a lesser risk in this regard. Prednisolone produces some edema in doses greater than 30 mg; triamcinolone and dexamethasone are much less liable to elicit this effect. Glucocorticoids may also produce an increase in potassium excretion. Muscle weakness and wasting of skeletal muscle mass frequently accompany this potassium-depleting action. The expansion of the extracellular fluid volume produced by steroids is secondary to sodium and water retention. However, the presence of specific steroid receptors in vascular smooth muscle suggests that glucocorticoids are also more directly involved in the regulation of blood pressure. The major adverse effects of glucocorticoids on the cardiovascular system include dyslipidemia and hypertension, which may predispose patients to coronary artery disease. A separate entity, steroid myopathy, is also improved by decreasing steroid dosage.

Pseudorheumatism

In certain patients, whose large dosages of corticosteroids for rheumatoid arthritis are gradually diminished, new symptoms develop that may be mistaken for a flare-up of the joint disease. These can include emotional lability, fever, muscle aches, and general fatigue. It is tempting to increase the dosage of steroid in this situation, but continued maintenance at the lower dosage with a subsequent gradual decrease in the dose usually improves symptoms.

Additional Effects

Other side effects include acne, striae, truncal obesity, deposition of fat in the cheeks (moon face) and upper part of the back (buffalo hump), and dysmenorrhea. Topical administration may produce local skin atrophy. In patients with AIDS who are treated with glucocorticoids, Kaposi's sarcoma becomes activated or progresses more rapidly.

Iatrogenic Adrenal Insufficiency

In addition to the dangers associated with long-term use of corticosteroids in supraphysiological concentrations, withdrawal of steroid therapy presents problems. The suppression of the hypothalamic–pituitary axis observed with modest doses and short courses of glucocorticoid therapy is usually readily reversible. However, steroid therapy with modest to high doses for 2 weeks or longer will depress hypothalamic and pituitary activity and result in a decrease in endogenous adrenal steroid secretion and eventual adrenal atrophy. These patients have a limited ability to respond to stress and an enhanced probability that shock will develop. Long-acting steroids, such as dexamethasone and betamethasone, suppress the hypothalamic–pituitary axis more than do other steroids. The functional state of the hypothalamic–pituitary axis can be evaluated by tests involving basal plasma cortisol determinations, low and high doses of cosyntropin (peptide fragment of corticotrophin), insulin hypoglycemia, metyrapone, and corticotrophin-releasing hormone.

Glucocorticoids are not withdrawn abruptly but are tapered. The doses are altered so that the condition being treated will not flare up and recovery of the hypothalamic–pituitary axis will be facilitated. Tapering the dose may reduce the potential for the development of Addison-like symptoms associated with steroid withdrawal. Alternate-day therapy will relieve the clinical manifestations of the inflammatory diseases while allowing a day for reactivation of endogenous corticosteroid output, thereby causing less severe and less sustained hypothalamic–pituitary suppression. This is feasible with doses of shorter-acting corticosteroids, such as prednisolone. The usual daily dose is doubled and is given in the early morning to simulate the natural circadian variation that occurs in endogenous corticosteroid secretion. The benefits of alternate-day therapy are seen only when steroids are used for a long period and are particularly useful for tapering the dose of glucocorticoid.

Although not always predictable, the degree to which a given corticosteroid will suppress pituitary activity is related to the route of administration, the size of the dose, and the length of treatment. The parenteral route causes the greatest suppression, followed by the oral route, and finally topical application. Hypothalamic–pituitary suppression also may result if large doses of a steroid aerosol spray are used to treat bronchial asthma. Patients given high concentrations of steroids for long periods and subsequently exposed to undue stress (e.g., severe infection, surgery) face the danger of adrenal crisis. These patients must be given supplemental steroids to compensate for their lack of adrenal reserve and to sustain them during the crisis.

Acute adrenal insufficiency will, of course, occur from an abrupt cessation of steroid therapy. The causation of fever, myalgia, arthralgia, and malaise may be difficult to distinguish from reactivation of rheumatic disease. Steroid treatment should be reduced gradually over several months to avoid this potentially serious problem. Also, continued suppression may be avoided by administering daily physiological replacement doses (5 mg prednisone) until adrenal function is restored. Although tapering of dose may not facilitate recovery of the hypothalamic–pituitary–adrenal axis, it may reduce the possibility of adrenal insufficiency. This is important, since severe hypotension caused by adrenal insufficiency may evoke a medical emergency. Adrenal insufficiency should always be considered in patients who are being withdrawn from prolonged glucocorticoid therapy unless metyrapone or insulin hypoglycemia tests are performed to exclude this possibility.

An additional problem associated with glucocorticoid therapy is that certain side effects can be caused by the diseases for which glucocorticoids are administered. Thus, osteoporosis can be a sequela of rheumatoid arthritis, and the physician is left to determine whether the untoward effect is iatrogenic or is merely a sign of the disease being treated. In addition to these problems, the physician must also be aware of the patient's natural reluctance to reduce the dose of steroid because of its salutary effects, both on the inflammatory process and on the psyche. Thus, the problems associated with withdrawal from long-term steroid therapy in rheumatoid arthritis are additional reasons steroid treatment should be initiated only after rest, physiotherapy, and nonsteroidal antiinflammatory drugs or after methotrexate, gold, and D-penicillamine have been used.

THERAPEUTIC USES OF STEROID HORMONES

Replacement Therapy

Adrenal insufficiency may result from hypofunction of the adrenal cortex (primary adrenal insufficiency, Addison's disease) or from a malfunctioning of the hypothalamic–pituitary system (secondary adrenal insufficiency). In treating primary adrenal insufficiency, one should administer sufficient cortisol to diminish hyperpigmentation and abolish postural hypotension; these are the cardinal signs of Addison's disease.

Although patients may require varying amounts of replacement steroid, 20 to 30 mg/day of cortisol supplemented with the mineralocorticoid 9-α-fluorocortisol (0.1 mg/day) is generally adequate. A doubling of the cortisol dose may be required during minor stresses or infections. In patients who require high-dose supplementation, prednisone can be substituted for cortisol to avoid fluid retention.

In the treatment of secondary adrenocortical insufficiency, lower doses of cortisol are generally effective, and fluid and electrolyte disturbances do not have to be considered, since patients with deficient corticotrophin secretion generally do not have abnormal function of the zona glomerulosa. Since cortisol replacement therapy is required for life, adequate assessment of patients is critical to avoid the serious long-term consequences of excessive or insufficient treatment. In many cases, the doses of glucocorticoid used in replacement therapy are probably too high. Patients should ideally be administered three or more doses daily. To limit the risk of osteoporosis, replacement therapy should be carefully assessed on an individual basis and overtreatment avoided.

Inflammatory States

Since glucocorticoids possess a wide range of effects on virtually every phase and component of the inflammatory and immune responses, they have assumed a major role in the treatment of a wide spectrum of diseases with an inflammatory or immune-mediated component. Rheumatoid arthritis is the original condition for which antiinflammatory steroids were used, and they remain a mainstay of therapy. Intraarticular glucocorticoid injections have proven to be efficacious, particularly in children. However, the detrimental effects of glucocorticoids on growth are significant for children with active arthritis. Although steroids offer symptomatic relief from this disorder by abolishing the swelling, redness, pain, and effusions, they do not cure. Progressive deterioration of joint structures continues, and the disease process may be exacerbated after steroid therapy is terminated (see Chapter 36).

Based on the concept that asthma is an inflammatory disease that leads to airway obstruction, inhaled glucocorticoids are the first-line treatment for moderate to severe asthma. Inhaled preparations are particularly effective when used to prevent recurrent attacks. This therapy is often combined with an inhaled bronchodilator such as a β-adrenergic agonist. The use of β-adrenergic agonists or theophylline enables use of a lower dose of glucocorticoid, especially in patients relatively resistant to therapy (see Chapter 39).

Steroids are used in other collagen diseases, such as lupus erythematosus; in hypersensitivity or allergic states, such as nephrotic syndrome, ulcerative colitis, and Crohn's disease; in granulomatous disease, such as sarcoid; and in a wide range of dermatological and ophthalmological conditions. Glucocorticoids may also be used at lower doses in combination with other drugs for the treatment of vasculitis, lupus nephritis, and amyloidosis. Steroids are valuable in the prevention and treatment of organ transplant rejection and in the improvement of muscle function in polymyositis.

Corticosteroids are the mainstay of therapy for inflammatory demyelinating polyneuropathies. In Guillain-Barré syndrome glucocorticoids reduce the inflammatory attack and improve final outcome, while in chronic inflammatory demyelinating polyneuropathy glucocorticoids suppress the immune reaction but may not retard the progression of the disease. Glucocorticoids also exert a facilitatory action on neuromuscular transmission that may contribute to their efficacy in certain neuromuscular disorders. The fact that acetylcholine receptor antibodies are responsible for the neuromuscular transmission defect in myasthenia gravis has provided a rationale for exploiting the immunosuppressive effects of glucocorticoids (see Chapter 28).

Although infections are generally thought to be particularly frequent and possibly severe in patients treated with steroids, they have been used as short-term adjunctive therapy to reduce the severe symptoms associated with such bacterial infections as acute *H. influenzae* and miliary tuberculosis and in viral infections, such as hepatitis and infectious mononucleosis.

Glucocorticoids are also used in the treatment of a number of HIV-related disorders, including *Pneumocystis carinii* pneumonia, demyelinating peripheral neuropathies, tuberculous meningitis, and nephropathy. Glucocorticoids are used as adjunctive therapy in Pneumo cystitis carinii pneumonia to decrease the inflammatory response and allow time for antimicrobial agents to exert their effects. In patients who are immunocompromised because of HIV infection, adjunctive steroids may be less beneficial in promoting survival.

Leukemia

Steroids are important components in the treatment of hematopoietic malignancies. Their efficacy in chronic lymphocytic leukemia and multiple myeloma stems from their lympholytic effects to reduce cell proliferation, promote cell cycle arrest, and induce cell death by apoptosis. A complication of chronic lymphocytic leukemia, that is, autoimmune hemolytic anemia, also responds favorably to steroids. However, the development of resistance may limit the effectiveness of steroid therapy.

Shock

Prompt intensive treatment with corticosteroids may be lifesaving when an excessive inflammatory reaction has resulted in septic shock. A massive infusion of corticosteroids can restore cardiac output and reverse hypotension by sensitizing the response of adrenoceptors in the heart and blood vessels to the stimulating action of catecholamines. This protective role of steroids may be due to a direct effect on vascular smooth muscle. The combination of glucocorticoids and dopamine therapy preserves renal blood flow during shock.

Congenital Adrenal Hyperplasia

Congenital enzymatic defects in the adrenal biosynthetic pathways lead to diminished cortisol and aldosterone production and release. In these conditions, corticotrophin secretion is increased, and adrenal hyperplasia occurs, accompanied by enhanced secretion of steroid intermediates, especially adrenal androgens. More than 90% of cases of congenital adrenal hyperplasia are due to 21-hydroxylase deficiency, which is created by mutations in the CYP21 gene encoding the en-

zyme. Overproduction of androgens causes virilization, accelerated growth, and early epiphysial fusion. Treatment of this condition requires administration of glucocorticoid in amounts adequate to suppress adrenal androgen secretion but insufficient to compromise bone growth and mineralization. Approximately 75% of patients have concomitant mineralocorticoid deficiency and therefore cannot synthesize sufficient aldosterone to maintain sodium balance. These patients may develop potentially fatal salt-wasting if not treated.

PROPOSED MECHANISM OF STEROID ACTION

While certain properties of glucocorticoid action are a result of direct posttranscriptional effects, most are a consequence of effects on gene expression. Steroids transported by transcortin enter the target cell by diffusion and then form a complex with its cytosolic receptor protein. Glucocorticoids bind to cytoplasmic glucocorticoid receptors containing two subunits of the heat shock protein that belong to the 90-kDa family. The heat shock protein dissociates, allowing rapid nuclear translocation of the receptor–steroid complex. Within the nucleus, the glucocorticoid receptor induces gene transcription by binding to specific sequences on DNA called glucocorticoid response elements in the promoter–enhancer regions of responsive genes (Fig. 60.5). In certain cases, the glucocorticoid receptor can interact with nuclear factor-κB and AP-1 to inhibit gene expression activated by these proinflammatory transcription factors. Because their side effects are thought to be a consequence of gene induction, glucocorticoids that can repress inflammatory genes without inducing gene transcription are in development.

The pivotal role that the glucocorticoid receptor plays in hormone action is illustrated by the fact that the magnitude of induction of a regulatable gene and cellular responsiveness are directly proportional to the number of occupied receptors. A decrease in glucocorticoid receptor number (down-regulation) produced by protein degradation may be responsible for the increase in steroid resistance observed clinically. Down-regulation of glucocorticoid receptors also is a potential mechanism for terminating glucocorticoid-dependent responses and for curtailing excessive cell stimulation when circulating levels of steroids are high. The effectiveness of glucocorticoids will also be compromised by the concomitant administration of other drugs that enhance the clearance of glucocorticoids (ephedrine, phenytoin, rifampin). Glucocorticoids, which bind to mineralocorticoid receptors in the kidney to regulate salt balance, are inactivated by l1-β-hydroxysteroid reductase so that they do not elicit mineralocorticoid
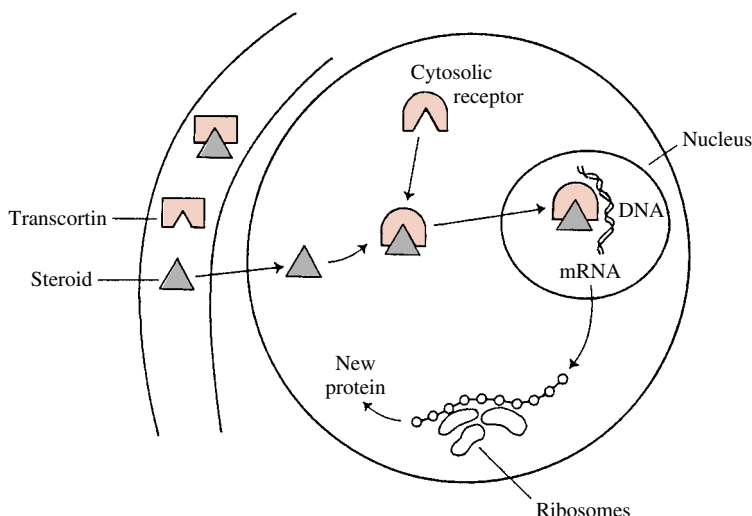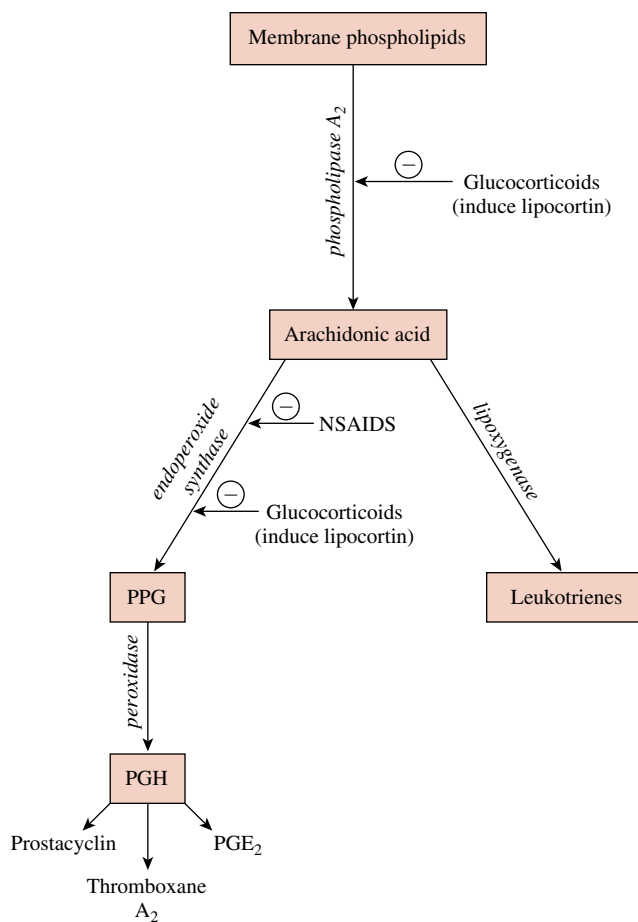
FIGURE 60.5
Mechanism of action of glucocorticoids.

actions in this tissue. However, in other tissues glucocorticoids may exert their actions through mineralocorticoid receptors. Several actions of glucocorticoids that are too rapid to be explained by actions on transcription are mediated by effects on membrane receptors.

Because glucocorticoids regulate gene expression and protein synthesis, there is generally a lag of several hours before their effects are manifest. Moreover, the duration of various responses can endure after steroid levels fall. This may account for the fact that side effects elicited by steroids can be minimized by alternate-day therapy.

Metabolites of arachidonic acid, including prostaglandins (PG), thromboxanes, and leukotrienes, are considered strong candidates as mediators of the inflammatory process. Steroids may exert a primary effect at the inflammatory site by inducing the synthesis of a group of proteins called lipocortins. These proteins suppress the activation of phospholipase A_2, thereby decreasing the release of arachidonic acid and the production of proinflammatory eicosanoids (Fig. 60.6).

Another possible glucocorticoid-sensitive step is the PG endoperoxide H synthase (or cyclooxygenase) (COX) mediated conversion of arachidonate to PG endoperoxides (Fig. 60-6). The endoperoxides (PGG and PGH) are the precursors of PGE_2, thromboxane A2 (TBXA2), and PGI_2, (prostacyclin). PG endoperoxide H synthase has two isoforms: one is constitutively expressed (PGHS-1, or COX-1), and another is induced by growth factors, cytokines, and endotoxins (PGHS-2, or COX-2). One component of the antiinflammatory action of glucocorticoids appears to involve the suppression of PGHS-2 induction in inflammatory cells by

FIGURE 60.6
Possible site or sites of action of glucocorticoids on prostanoid production.

proinflammatory stimuli. Inhibition of the production and effects of inflammatory cytokines (IL-6 and IL-β) by the transcription factors nuclear factor-κB and AP-1 may also contribute to the antiinflammatory effects of glucocorticoids.

DRUGS USED IN THE DIAGNOSIS OR TREATMENT OF ADRENOCORTICAL ABNORMALITIES

Corticotropin

Corticotropin (*ACTH, Acthar, Cortrophin Gel*) is an open-chain polypeptide that consists of 39 amino acid residues, the first 24 of which are essential for its biological activity. The remainder of the amino acids are also clinically important, since they may be involved in stimulating antibody formation and causing allergic reactions. This is true especially when corticotropin of animal origin is injected into humans. Commercially available corticotropin is prepared from animal pituitary glands.

Absorption, Metabolism, Excretion

Corticotropin is rapidly inactivated by gastrointestinal proteolytic enzymes and therefore must be administered parenterally. It is rapidly removed from the circulation ($T_{1/2}$, 15 minutes) and is probably inactivated in body tissues, since no intact compound is found in the urine.

Clinical Uses

The rationale for using corticotropin instead of pharmacological concentrations of glucocorticoids stems from the fact that corticotropin provides enhanced amounts of all endogenously secreted adrenocortical hormones, including androgens. However, obvious disadvantages are associated with the use of this polypeptide: (1) It must be given daily parenterally. (2) It is quite expensive. (3) It is antigenic and thus can produce resistance and hypersensitivity reactions. Corticotropin is used as a diagnostic tool for the identification of primary adrenal insufficiency or as a method for evaluating the hypothalamic–pituitary–adrenal axis before surgery in patients previously treated with glucocorticoids.

Adverse Effects

Aside from hypersensitivity and allergic reactions, corticotropin administration has been associated with electrolyte disturbances and masculinization in women.

Cosyntropin

Cosyntropin (*Cortrosyn*) is a polypeptide that consists solely of the first 24 amino acids of corticotropin. It appears to offer an advantage over the naturally occurring hormone in that it has a longer duration of action and lacks the antigenic portion of corticotropin. Although the short cosyntropin test is recognized as a valid screening test to assess adrenocortical insufficiency, the overnight metyrapone test or insulin hypoglycemia test may prove more sensitive.

Metyrapone
Mechanism of Action

Metyrapone (*Metopirone*) produces its primary pharmacological effect by inhibiting 11-β-hydroxylase, thereby causing diminished production and release of cortisol. The resulting reduction in the negative feedback of cortisol on the hypothalamus and pituitary causes an increase in corticotrophin release and in the secretion of precursor 11-deoxysteroids.

Clinical Uses

Metyrapone is used in the differential diagnosis of both adrenocortical insufficiency and Cushing's syndrome (hypercortisolism). The drug tests the functional competence of the hypothalamic–pituitary axis when the adrenals are able to respond to corticotrophin; that is, when primary adrenal insufficiency has been ruled out.

After metyrapone administration, a patient with a disease of pituitary origin cannot achieve a compensatory increase in the urinary excretion of 17-hydroxycorticosteroids or 11-deoxysteroids. Moreover, if pituitary corticotrophin is suppressed by an autonomously secreting adrenal carcinoma, there will be no increase in response to metyrapone. On the other hand, if pituitary corticotrophin secretion is maintained, as occurs in adrenal hyperplasia, the inhibition of corticoid synthesis produced by metyrapone will stimulate corticotrophin secretion and the release of metabolites of precursor urinary steroids, which can be measured as 17-hydroxycorticosteroids. Metyrapone is now used less frequently in the differential diagnosis of Cushing's syndrome because of the ability to measure plasma corticotrophin directly.

The steroid-inhibiting properties of metyrapone have also been used in the treatment of Cushing's syndrome, and it remains one of the more effective drugs used to treat this syndrome. However, the compensatory rise in corticotrophin levels in response to falling cortisol levels tends to maintain adrenal activity. This requires that glucocorticoids be administered concomitantly to suppress hypothalamic–pituitary activity. Although metyrapone interferes with 11β- and 18-hydroxylation reactions and thereby inhibits aldosterone synthesis, it may not cause mineralocorticoid deficiency because of the compensatory increased production of 11-desoxycorticosterone.

Adverse Effects

Side effects associated with the use of metyrapone include gastrointestinal distress, dizziness, headache, sedation, and allergic rash. The drug should not be used in cases of adrenocortical insufficiency or when hypersensitivity reactions can be expected. When administered to pregnant women during the second or third trimesters, the drug may impair steroid biosynthesis in the fetus. Because metyrapone is relatively nontoxic, it is used in combination therapy with the more toxic aminoglutethimide to reduce its dosage.

Aminoglutethimide

Aminoglutethimide (*Cytadren*) is a competitive inhibitor of desmolase, the enzyme that catalyzes the conversion of cholesterol to pregnenolone; it also inhibits 11-hydroxylase activity. This drug also reduces estrogen production by inhibiting the aromatase enzyme complex in peripheral (skin, muscle, fat) and steroid target tissues.

Such a medical adrenalectomy is an efficacious treatment for metastatic breast and prostate cancer, since it diminishes the levels of circulating sex hormones. Glucocorticoids are administered concomitantly to suppress enhanced corticotrophin release. Cortisol is preferable to dexamethasone in this situation because aminoglutethimide markedly enhances the hepatic microsomal metabolism of dexamethasone. Hepatic enzyme induction may be responsible for the development of tolerance to the side effects of aminoglutethimide, such as ataxia, lethargy, dizziness, and rashes.

Aminoglutethimide is suitable for use in Cushing's syndrome that results from adrenal carcinoma and in congenital adrenal hyperplasia, in which it protects the patient from excessive secretion of endogenous androgens. The drug is not curative, and relapse occurs when treatment is terminated. Since aminoglutethimide therapy is frequently associated with mineralocorticoid deficiency, mineralocorticoid supplements may be needed. Aminoglutethimide and metyrapone are frequently used in combination at lower doses of both drugs as an adjunct to radiation or surgical therapy.

Mitotane

Mitotane *(Lysodren)* produces selective atrophy of the zona fasciculata and zona reticularis, which results in a decrease in the secretion of 17-hydroxycorticosteroids. Direct inhibition of cholesterol side-chain cleavage and 11β/18-hydroxylase activities has also been demonstrated. Mitotane is capable of inducing remission of Cushing's disease, but only after several weeks of therapy and at the price of severe gastrointestinal distress. Moreover, more than half of patients relapse following cessation of therapy. Other side effects include lethargy,

mental confusion, skin rashes, and altered hepatic function. Being a lipid-soluble substance, mitotane remains stored in body tissues for extended periods. This may account for the marked patient-to-patient variability in its therapeutic and/or toxic effects.

Mitotane is the drug of choice for the treatment of primary adrenal carcinoma when surgery or radiation therapy is not feasible (see Chapter 56). Its effectiveness in curtailing adrenal activity is due to an action on adrenocortical mitochondria to impair cytochrome P450 steps in steroid biosynthesis. Mitotane requires metabolic transformation to exert its therapeutic action, and the differential ability of tumors to metabolize the drug may determine its clinical effectiveness. It is advised to measure serum mitotane levels and urinary free cortisol excretion to ensure adequate therapeutic concentrations. Mitotane increases circulating cholesterol by inhibiting cytochrome P450–mediated reactions and therefore contributes to the cardiovascular events that are a significant cause of mortality in untreated Cushing's syndrome.

Mitotane, being closely related to the organochlorine insecticides, shares its inductive effects on the liver microsomal drug-metabolizing enzyme system, and its use may therefore alter the requirement for concomitantly administered drugs that are also metabolized by this pathway.

Ketoconazole

Ketoconazole *(Nizoral)*, an orally effective broad-spectrum antifungal agent (see Chapter 52), blocks hydroxylating enzyme systems by interacting with cytochrome P450 at the heme iron site to inhibit steroid and/or androgen synthesis in adrenals, gonads, liver, and kidney. The most sensitive site of action appears to be the C17-20 lyase reaction involved in the formation of sex steroids. This explains the greater suppressibility of testosterone production than with cortisol. Cholesterol side-chain cleavage and 11β/18-hydroxylase are secondary sites of inhibition.

Ketoconazole can be used as palliative treatment for Cushing's syndrome in patients undergoing surgery or receiving pituitary radiation and in those for whom more definitive treatment is still contemplated. Because surgical treatment is not always well tolerated by elderly patients, ketoconazole 200 to 1,000 mg/day can be a valuable alternative for the control of hypercortisolism. Common side effects include pruritus, liver dysfunction, and gastrointestinal symptoms.

Because of its effectiveness in blocking C17-20 lyase activities, ketoconazole does not enhance existing hirsutism associated with metyrapone. On the other hand, the antiandrogenic effects of ketoconazole may prove disconcerting to male patients.

Mifepristone (RU 486)

Mifepristone is a progesterone receptor antagonist that has a high affinity for glucocorticoid receptors and little agonist effect. This drug has recently been approved for use in the United States for the treatment of hypercortisolism. At high doses, mifepristone blocks negative feedback of the hypothalamic–pituitary axis, thereby increasing endogenous corticotrophin and cortisol levels. Because mifepristone exerts its effects at the receptor level and not by altering glucocorticoid production, elevated serum cortisol and corticotrophin levels may not accurately reflect the effectiveness of the therapeutic regimen. Mifepristone does not inhibit cortisol binding to the mineralocorticoid receptor, so that the resulting corticotrophin disinhibition may cause potassium depletion. Thus, administration of a mineralocorticoid receptor antagonist such as spironolactone may be indicated with mifepristone. Hypoadrenalism, nausea, and drowsiness have been reported during prolonged administration of mifepristone.

Dexamethasone

Cushing's disease is defined as hypercortisolism due to chronic overproduction of corticotrophin by a corticotroph adenoma. Cortisol's lack of suppressibility during the administration of low doses of dexamethasone but suppressibility during high-dose dexamethasone is the key diagnostic finding in 99% of the patients with Cushing's disease. This contrasts with the lack of glucocorticoid suppressibility typically found in patients with corticotrophin-independent hypercortisolism (Cushing's syndrome). A judicious selection of the available tests may be necessary to obtain an accurate diagnosis in patients with Cushing's syndrome.

Study QUESTIONS

1. During the period of withdrawal from extended glucocorticoid therapy
(A) Prompt recovery of the hypothalamic–pituitary–adrenal axis results in restoration of endogenous corticotrophin release.
(B) The patient may be eager to further reduce the dose of glucocorticoid.
(C) The physician should rapidly reduce glucocorticoid therapy to physiological doses.
(D) Patients should not require an increment in steroid therapy during increased stress (e.g., severe infection).
(E) The appearance of fever and malaise attributed to steroid withdrawal may be difficult to distinguish from reactivation of rheumatic disease.

2. Which one of the following enzymes is required for cortisol biosynthesis?
(A) 21-hydroxylase
(B) 17,20 lyase
(C) Cyclooxygenase
(D) 11-β-hydroxysteroid dehydrogenase-2
(E) 18-hydroxylase

3. The primary goal of glucocorticoid treatment in rheumatic arthritis is
(A) Suppression of inflammation and improvement in functional capacity
(B) Eradication of all symptoms
(C) Reversal of the degenerative process
(D) Development of a sense of well-being in the patient
(E) Prevention of suppression of the hypothalamic–pituitary–adrenal axis

4. The addition of a fluoride group on ring C of cortisol to give 9-α-fluorocortisol
(A) Will shorten its half-life
(B) Will increase both glucocorticoid and mineralocorticoid activity
(C) Shares an advantage over cortisol in that sodium retention is not as marked at equipotent inflammatory doses
(D) Will not cause suppression of the hypothalamic–pituitary–adrenal axis when applied topically.
(E) Provides a steroid widely used in the treatment of rheumatoid arthritis

5. Dexamethasone
(A) Is adequate replacement therapy in an adrenalectomized patient
(B) Has a half-life equivalent to that of cortisol
(C) Produces salt retention in therapeutic doses
(D) Possesses most of the undesirable side effects of cortisol
(E) Has antiinflammatory potency equivalent to that of cortisol

6. Which answer is most appropriate for the action of ketoconazole?
(A) It has a single major action that is confined to the adrenal cortex.
(B) It provides long term treatment for Cushing's disease.
(C) It has an action on the adrenal cortex that is irreversible.
(D) Its action may be associated with liver dysfunction.
(E) It preferentially blocks cortisol synthesis as opposed to testosterone production.

ANSWERS

1. **E.** Recovery from prolonged steroid therapy is slow, and the withdrawal may be unpleasant. The patient may be reluctant to reduce the dose of steroid because of its salutary effects on the psyche. Tapering the dose of steroid is important in steroid withdrawal; however, the patient may temporarily require a dose increase during periods of heightened stress.

2. **A.** 17,20 lyase is required for androgen synthesis, cyclooxygenase for prostaglandin production, 11-β-hydroxysteroid dehydrogenase-2 acts as a reductase-converting cortisol to its inactive 11-keto derivative cortisone, whereas 18-hydroxylase is required for aldosterone production.

3. **A.** Glucocorticoid treatment of rheumatoid arthritis does not eradicate all symptoms, nor does it reverse the degenerative process. Suppression of the hypothalamic–pituitary–adrenal axis is an unwanted side effect of glucocorticoid therapy. While development of a sense of well-being may be attributed to the relief of symptoms, it is not the primary basis for employing the potent glucocorticoids.

4. **B.** The addition of a fluoride group to ring C of cortisol to give 9-α-fluorocortisol greatly increases and prolongs all biological activity. The result is an agent with potent glucocorticoid and mineralocorticoid activity, making it inappropriate to use in rheumatoid arthritis. Because of its potency and extended action, fluorocortisol will have a greater tendency to depress the hypothalamic–pituitary axis than cortisol, even when applied topically.

5. **D.** Dexamethasone is a fluorinated glucocorticoid that is more potent and longer acting than cortisol. While devoid of salt-retaining activity in therapeutic doses, this glucocorticoid does possess most of the adverse effects observed with cortisol. Because it lacks mineralocorticoid activity, dexamethasone is not used in replacement therapy.

6. **D.** In addition to its ability to block steroid biosynthesis, ketoconazole is frequently used as an antifungal agent. Its action is readily reversible and is used principally for interim management of Cushing's disease prior to surgery or radiotherapy. Ketoconazole preferentially blocks the C17,20 lyase reaction that is involved in the synthesis of sex steroids.

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C A S E **S t u d y**   **Diagnosis and Treatment of Cushing's Disease**

Julie Singer is a 55-year-old white woman who was admitted to the emergency department in acute distress. A previous physical examination showed hypertension and diabetes mellitus type 2. The patient's present medications include enalapril 40 mg, nifedipine 60 mg, and 100 U insulin. A physical examination revealed prominent ankle edema, a palpable spleen, and hepatomegaly. Chest radiography revealed diffuse cardiac enlargement and left ventricular hypertrophy. Based upon the history and clinical findings, what is your diagnosis and what treatment do you recommend?

ANSWER: This study describes the clinical features of Cushing's disease (pituitary-dependent hypercortisolism), the tests for its diagnosis, and its treatment. The combination of hypertension, congestive heart failure, and hyperglycemia (blood glucose 220 mg/dL) suggest hypercortisolism (Cushing's syndrome). This tentative diagnosis was supported by a low-dose (1 mg) dexamethasone overnight suppression test demonstrating unsuppressed serum cortisol (1409 nM). It was further substantiated by elevated corticotrophin (85 pM) and suppression of serum cortisol (598 nM) by high-dose (10 mg) dex-

amethasone. Inferior petrosal sinus sampling provided a final confirmation of the diagnosis. The patient was prescribed metyrapone 2 g/day and aminoglutethimide 500 mg/day. Hyponatremia and hyperkalemia required the concomitant administration of a mineralocorticoid, fludrocortisone acetate 0.1 mg/day. With this treatment regimen, the patient's overall appearance and the clinical findings began to improve slowly. Blood pressure became better controlled, congestive failure showed improvement, insulin resistance diminished, and bone density improved. Corticotrophin levels eventually fell (from 18.5 to 8 ng/L) and serum cortisol became normally responsive to exogenous corticotrophin (rising from 407 to 1089 nM). After 6 months, the combination of metyrapone and aminoglutethimide was tapered and terminated, and radiation therapy was initiated. This study illustrates the important principle that clinical acumen and judicious use of drugs in diagnosis and treatment can lead to the dramatic reversal of the metabolic and cardiovascular abnormalities in a patient with severe Cushing's syndrome.