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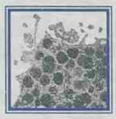
CHAPTER

46 Glucocorticosteroids



Their Mechanisms of Action and Use in Allergic Diseases

Robert P. Schleimer

HISTORY

The glucocorticoid hormones of the adrenal cortex and their synthetic analogs (hereafter referred to simply as *steroids*) represent the single most effective class of drugs for the therapy of diseases of inflammation. The modern history of these important natural hormones began in 1855 when Addison first described a wasting disease after destruction of the adrenal gland.[1] The adrenal gland was subsequently shown to be essential for life by ablation experiments and restoration with adrenal extracts. The importance of the adrenal gland in homeostatic processes is partly related to its role in the regulation of glucose metabolism and electrolyte levels. Hyperactivity of the adrenal gland was first described as a syndrome by Cushing in the 1930s.[2] This was followed by a flurry of research that revealed that the main activity found in adrenal extracts was attributable to adrenal steroids, including cortisol (hydrocortisone, the major glucocorticoid in humans), cortisone, corticosterone, and the major adrenal mineralocorticoid, aldosterone. Within just a few years of the elucidation of the stucture of the adrenal steroids, cortisone was first used to treat arthritis by Hench et al with such remarkable results that their work led to the Nobel Prize within the next year and promoted the testing of steroids in virtually all inflammatory diseases.[3] Because many of the undesired effects of steroid therapy take a substantial amount of time to develop, the impact of these side effects was not appreciated until the next few years; this revelation somewhat dampened enthusiasm for these "miracle cure" drugs. A resurgence of interest in steroids has occurred after the development of effective, topically active drugs with dramatically reduced side effects. In the last two or three decades, much work has been directed toward an understanding of the mechanism of the antiinflammatory action of these drugs. This chapter focuses on the general pharmacologic aspects of glucocorticoids,[4-6] the mechanism of their antiinflammatory actions, and their use in the therapy of allergic diseases, with an emphasis on asthma.

PHARMACOLOGY

Structure-Activity Relationships

The structures of hydrocortisone and other related natural and synthetic steroids commonly used orally or parenterally are shown in Figure 46-1. The shaded areas on the structures in Figure 46-1 emphasize structural variation from hydrocortisone, the parent molecule, in the other natural and synthetic steroids. Hydrocortisone has a four-ring, 21-carbon structure. Structural elements important for antiinflammatory action are numerous.[5-7] In the A-ring, the 4,5 double bond and the 3-ketone group are essential for glucocorticoid and antiinflammatory activity. The addition of a 1,2 double bond, such as is seen in prednisolone, prednisone, methylprednisolone, and dexamethasone (see Figure 46-1), increases the glucocorticoid activity relative to mineralocorticoid effects. In the B-ring the addition of a 9α-fluoro group, such as is seen in dexamethasone, betamethasone, and triamcinolone, increases all biologic activities, both glucocorticoid and mineralocorticoid. In the C-ring the 11-hydroxyl group is essential for antiinflammatory and glucocorticoid effects but not for mineralocorticoid effects. For example, desoxycorticosterone, which lacks the 11-hydroxyl group, has mineralocorticoid activity but lacks glucocorticoid effects. Steroids bearing an 11-ketone group (e.g., cortisone, prednisone) must be first converted to 11-hydroxy molecules for glucocorticoid activity (see below). In the D-ring, the addition of a 16-methyl group eliminates mineralocorticoid activity (as seen in the case of dexamethasone) (see Figure 46-1). Removal of the 17α substituent greatly reduces antiinflammatory activity (although not completely, as in the example of corticosterone). This fact has been exploited by the pharmaceutical industry. As illustrated in Figure 46-2, some topical steroid preparations are 16α-, 17α-acetal, or 17α-, 21α-ester derivatives (e.g., budesonide and beclomethasone dipropionate [BDP]), which are readily cleaved after absorption, dramatically reducing systemic effects.[8,9] These glucocorticoids also have high affinity for the glucocorticoid receptor, increasing their topical actions. All natural and most active synthetic glucocorticoids contain a 21-hydroxyl group. The relative potencies and pharmacologic effects of some common glucocorticoids are shown in Table 46-1.

Synthesis

Adrenal production of hydrocortisone and aldosterone results from a single branching pathway in which cholesterol is converted, via a pregnenolone intermediate, to progesterone. Progesterone is sequentially hydroxylated at the 17-, 21-, and 11-positions to form hydrocortisone.[4] The regulation of adrenal cortex production of hydrocortisone is illustrated in Figure 46-3. Glucocorticoids are primarily produced in the zona fasciculata of the adrenal cortex, as a result of stimulation with adrenocorticotropic hormone (ACTH); in the absence of this trophic hormone, this area of the adrenal cortex atrophies. ACTH is a product of the basophil cells of the anterior pituitary gland and is released as a result of stimulation by corticotropin-releasing factor (CRF), which is released from the hypothalamus. ACTH (and glucocorticoid) secretion displays a diurnal rhythm with levels reaching peak values in the early morning, declining throughout the day to reach their lowest in the early evening. Additional CRF release, and therefore subsequent ACTH production and steroid synthesis, can result from environmental stress via the input of higher centers to the hypothalamus (see Figure 46-3) or from increased circulating levels of cytokines such as interleukin-1 (IL-1), IL-2, IL-6, or tumor necrosis factor (TNF, cachectin).[10-13] These cytokines can also directly induce adrenal cortisol synthesis.[14] Amines such as histamine or serotonin, as well as prostaglandins such as prostaglandin E (PGE), have been reported to stimulate release of steroids from the adrenal gland both indirectly and directly [14-17] Circulating cortisol regulates its own production by inhibiting secretion of ACTH, as well as by inhibiting the production of cytokines that stimulate ACTH release (Figure 46-4).[4,5,10,11,18] The inhibition of ACTH secretion by acute increases in glucocorticoids is one of the most rapidly occurring steroid effects and requires only minutes; removal of steroid readily reverses the effect. However, chronic elevations of glucocorticoid in the circulation can produce a more long-lasting inhibition of ACTH secretion that can result in atrophy of the anterior pituitary and can have serious consequences when patients on chronic steroid therapy are suddenly withdrawn from treatment. The recovery of hypothalamic-pituitary-adrenal (HPA) axis function after withdrawal of glucocorticoid treatment has been reviewed.[19,20] Although recovery of the HPA axis is rapid (i.e., requires days) after brief (i.e., 1 week or less) treatment with glucocorticoids, treatment lasting for more than a few weeks should be assumed to have a long-lasting suppressive effect on the HPA axis (i.e., corresponding in duration somewhat to the dose and duration of treatment and lasting up to 12

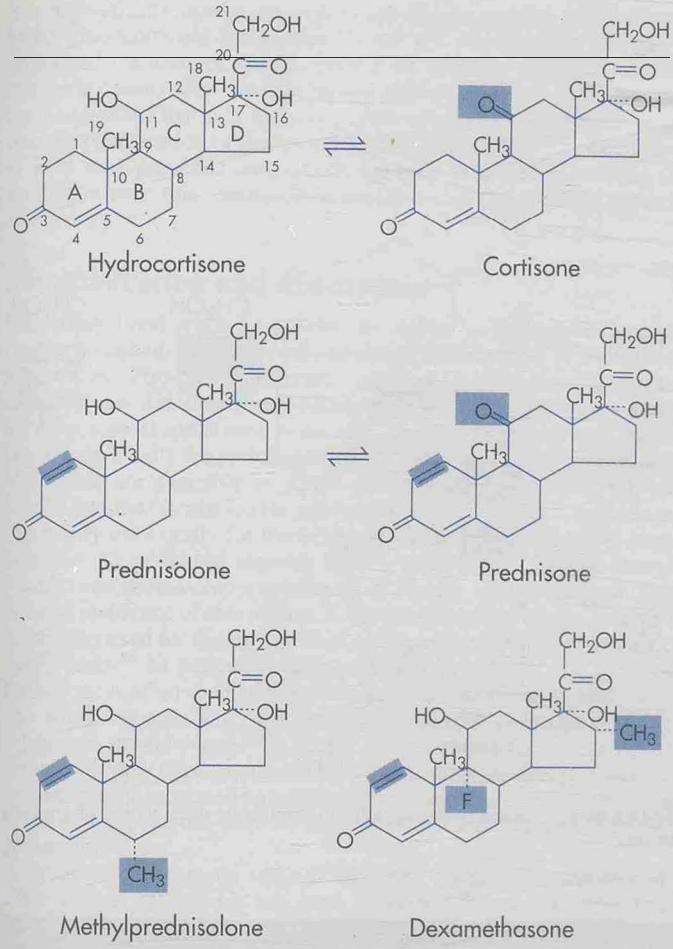


FIGURE 46-1 Chemical structure of some important oral glucocorticoids.

months) after discontinuation of treatment. Recovery of the adrenal cortex is generally slower than recovery of hypothalamic-pituitary function.[20]

Metabolism and Excretion

Greater than 90% of circulating cortisol is bound to plasma proteins.[4] There are two plasma protein binding sites of importance for steroids in the circulation. Cortisol (and some other steroids) binds to the corticosteroid-binding globulin, transcortin, with high affinity; this binding site has a relatively low capacity. Relative binding to transcortin of common glucocorticoids is prednisolone = hydrocortisone ≥ methylprednisolone (approximately 3%) ≥ dexamethasone (approximately 0.1%).[21] Additionally, steroids bind to serum albumin with low affinity; this is a high-capacity reservoir. At low concentrations of cortisol or synthetic steroids such as prednisone, the binding to transcortin is quantitatively more important in influencing free steroid levels. On the other hand, with high steroid doses, the transcortin-binding site is saturated and the albumin-binding site becomes the more influential. Many synthetic glucocorticoids such as dexamethasone exhibit little or no binding to transcortin. Because pharmacologic actions, metabolism, and excretion of steroids are all related to unbound steroid concentrations, the binding of circulating steroids to transcortin and albumin can play an important role in modifying glucocorticoid potency, half-life, and duration of action. Thus hepatic diseases that result in decreased levels of transcortin and albumin can influence steroid efficacy.

The metabolic fate of hydrocortisone is illustrated in Figure 46-4.[4,5,7] Reduction of the 4/5 double bond and 3-ketone groups yields an inactive compound that is subsequently conjugated (e.g., by the formation of a glucuronide) to produce a highly water-soluble steroid that is readily excreted (step 1 in Figure 46-4). Another common metabolic reaction (step 2) is hydroxylation at the 2-position in the

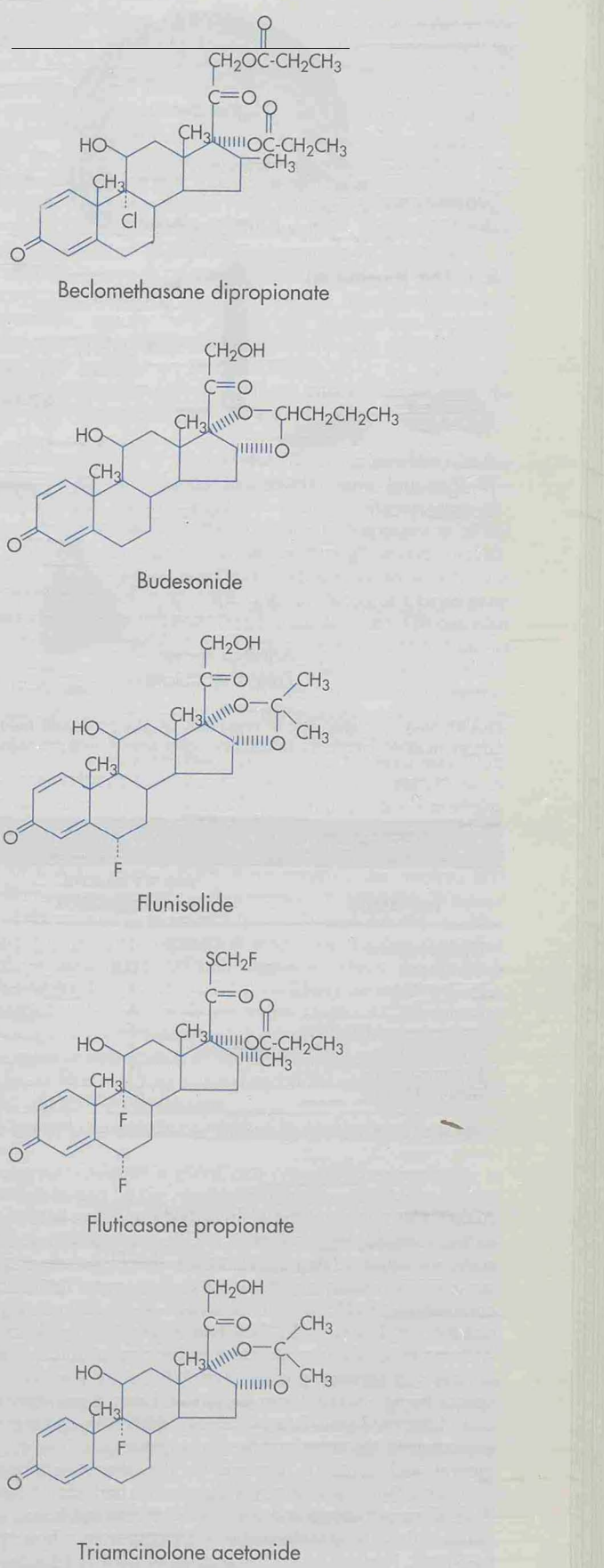


FIGURE 46-2 Some commonly used topical steroids.

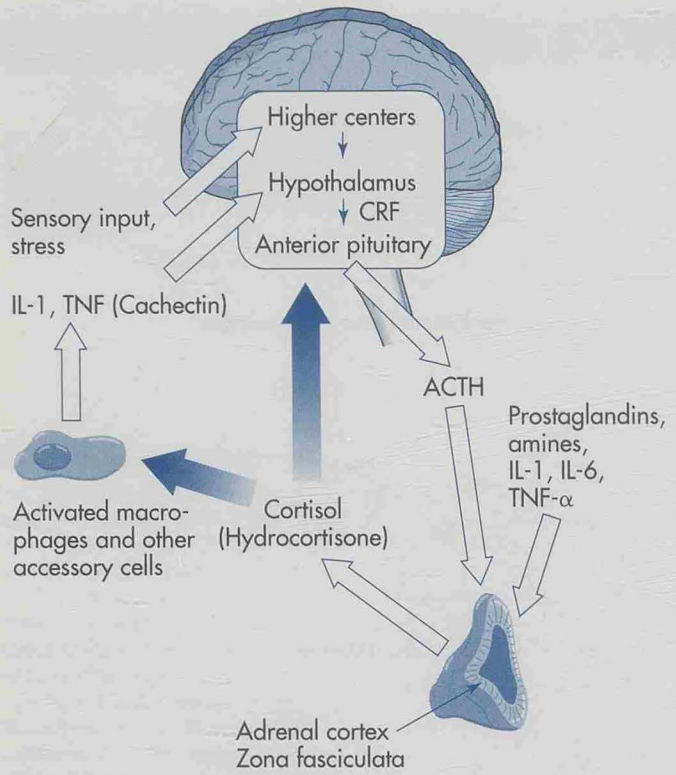


FIGURE 46-3 Schematic of regulation of glucocorticoid production. Filled arrows indicate inhibitory influences; open arrows indicate stimulation.

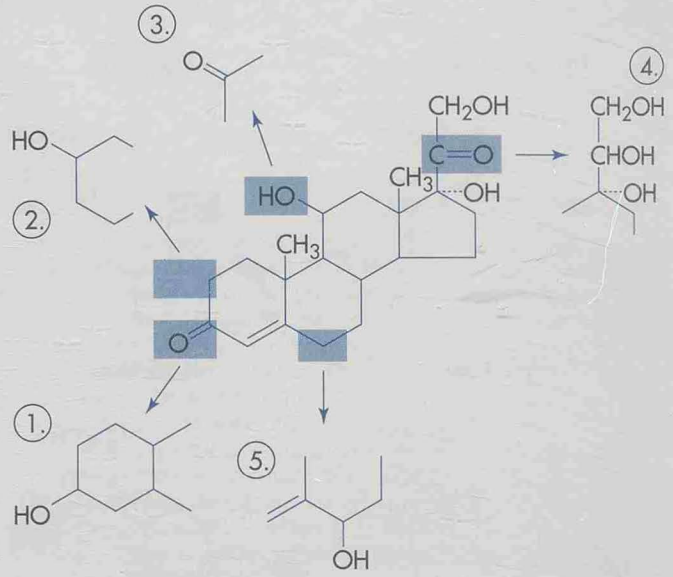


FIGURE 46-4 Some major steps for the metabolic deactivation of glucocorticoids.

Table 46-1 Relative Potencies and Pharmacologic Effects of Common Oral Glucocorticoids

PREPARATION	POTENCY RELATIVE TO HYDROCORTISONE	RELATIVE TO SODIUM-RETAINING POTENCY	APPROXIMATELY EQUIVALENT DOSE (MG)	DURATION OF ACTION*
Hydrocortisone	1	1	20	Short
Cortisone	0.8	0.8	25	Short
Prednisolone	4	0.8	5	Intermediate
Prednisone	4	0.8	5	Intermediate
6α-Methylprednisolone	5	0.5	4	Intermediate
Triamcinolone	5	0	4	Intermediate
Dexamethasone	25	0	0.75	Long
Betamethasone	25	0	0.75	Long

**Short,* 8- to 12-hour biologic half-life; *intermediate,* 12- to 36-hour biologic half-life; *long,* 36- to 72-hour biologic half life.

A-ring. Conversion of the 11-hydroxyl group to a ketone group by 11β hydroxysteroid dehydrogenase yields a compound devoid of glucocorticoid activity (step 3). However, the 11-ketone and 11-hydroxyl steroids are readily interconverted (e.g., see Figure 46-1).[22] Other common metabolic fates are reduction of the 20-ketone group (step 4) and hydroxylation of the 6-carbon in the B-ring, which is associated with removal of a fluoride atom in the case of flunisolide (step 5). In the case of cortisol, greater than 98% of the steroid is metabolized before being excreted into the urine. Liver mixed-function oxidases and glucuronyl transferases (among other conjugating enzymes) are important in the metabolism of many steroids. The susceptibility of natural and synthetic steroids to the above-mentioned metabolic transformations can influence the plasma half-life of the compounds. Thus dexamethasone and triamcinolone are much less susceptible to many of these biotransformations, a fact that contributes to their longer half-lives. Further, as a consequence of the need for hepatic metabolism of steroids, liver disease, drugs, or other chemicals that modify liver function can affect the biologic half-life of administered steroids. Compounds that induce liver mixed-function oxidases such as barbiturates, diphenylhydantoin, and ephedrine, or many agents of occupational exposure can shorten the biologic half-life of steroids by increasing the rate of their metabolism.[23-25] On the other hand, compounds that interfere with liver mixed-function oxidases, such as troleandomycin (TAO; see below), prolong the plasma half-life and metabolic action of administered methylprednisolone.[26,27] TAO, which has limited usefulness because of hepatotoxicity, enhances the antiasthmatic activity of methylprednisolone but not prednisolone, suggesting that it has little intrinsic antiasthmatic effects.[27,28] The effect of TAO in "sparing" the metabolic destruction of methylprednisolone probably explains its efficacy in the combination therapy.

Local metabolism of endogenous cortisol at tissue sites has recently been found to regulate steroid action. For example, 11β-hydroxysteroid dehydrogenase (11β HSD [step 3, Figure 46-4]) "protects" mineralocorticoid receptors in the kidney from cortisol and probably dampens the antiinflammatory effects of endogenous steroids in the skin and lungs[29-32] by quantitative conversion of hydrocortisone in those tissues to cortisone, which has no intrinsic receptor-binding activity. Inhibition of this enzyme by a compound found in licorice, glycyrrhetinic acid, produces mineralocorticoid effects in the kidney (by allowing hydrocortisone access to mineralocorticoid receptors) and antiinflammatory effects in the skin. The possibility that similar compounds will have efficacy in the lungs has been raised.[31] Local metabolism occurs with some inhaled glucocorticoids. Beclomethasone dipropionate is converted to beclomethasone 17α propionate (BMP), which

is a high-affinity, active glucocorticoid. Recent studies using the inhaled glucocorticoid budesonide in rat and human lung indicate a prolonged retention of the glucocorticoid resulting from a reversible fatty acid conjugation forming highly lipid-soluble compounds. It has been suggested that this leads to a slow release of active budesonide upon deesterification of the fatty acid conjugated drug.[33-35] Formation of fatty acid–esterified budesonide has been proposed to prolong the local activity of this compound in the airways by providing a depot of active drug.

Administration and Absorption

Both natural and synthetic steroids are lipophilic compounds that are readily absorbed after oral, subcutaneous, intravenous, or topical administration. Phosphate or hemisuccinate esters of glucocorticoids are commonly used intravenously because of their improved water solubility. After topical application to the skin, significant quantities of steroid can remain locally for prolonged periods. Similarly, depot preparations of steroids are available in which a subcutaneous injection releases steroid into the circulation for prolonged periods of time.[4] Steroids are commonly used orally for the treatment of chronic asthma.[36,37] However, the use of topical steroids for the treatment of asthma, allergic rhinitis, and dermatologic conditions is rapidly increasing because of reduced incidence of side effects.[37] Parenteral steroid administration is sometimes used for the treatment of severe exacerbations of asthma or anaphylaxis.[38] In patients who have intact liver metabolic function, prednisone is often used because it is less expensive than prednisolone. One study suggests that methylprednisolone may penetrate the lungs better than prednisolone.[38] A recent study comparing the use of oral prednisone and intravenous methylprednisolone in severe exacerbations of asthma indicated no additional benefit of intravenous glucocorticoid and substantial cost savings by using the oral glucocorticoid preparation.[39]

A subset of asthmatic subjects who are "resistant" to the antiasthmatic actions of steroids has been described.[40-44] Leukocytes from these patients have been shown to be resistant to steroids in vitro despite having apparently normal steroid receptor numbers. It is possible that this resistance is the result of insufficiencies in receptor affinity for the steroid, binding to the glucocorticoid response element (GRE), interaction of the steroid-receptor complex with transcription factors, or posttranscriptional events (see below).[44]

Factors Influencing Local and Systemic Activity of Presently Available Inhaled Glucocorticoids

Many of the important factors that influence the ability of an inhaled steroid to have specificity for actions in the lung are summarized in Figure 46-5. Values for these tables are derived from several sources.[45-47] For compounds with a low oral bioavailability, the majority of the dose that ends up in the systemic circulation is absorbed from the lungs. The volume of distribution gives some insight into tissue binding. These data and some direct evidence suggest that fluticasone propionate and budesonide bind well to lung tissue. Although inhaled steroids have a range of affinities for the glucocorticoid receptor, all inhaled steroids have a high affinity compared with most oral glucocorticoids. The plasma half-life for the steroids varies over a substantial range as well, from less than 2 hours for budesonide, flunisolide, and triamcinolone acetonide to over 5 hours for BDP/BMP and fluticasone propionate.

When steroids are inhaled using a typical metered-dose inhaler (MDI), over half of the drug is deposited in the mouth and pharynx and subsequently swallowed. A small proportion, perhaps 10% to 20% , is delivered to the lungs. Addition of a spacer device and/or mouth rinsing can increase the proportion of drug that is delivered to the lungs and reduce local side effects, such as dysphonia and thrush. Because such a large proportion of drug is swallowed, it is important that inhaled steroids have a low oral bioavailability (see Figure 46-5).

MOLECULAR BIOLOGY

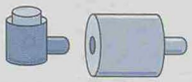
The action of steroid hormones requires the steps delineated in Figure 46-6.[48] Free hormone (i.e., that not bound to albumin or transcortin) diffuses across the plasma membrane and becomes associated with a class-specific steroid receptor (e.g., for glucocorticoids vs. sex steroids). After the association of steroid with the receptor, a molecular transformation of the steroid-receptor complex takes place, involving dissociation of heat shock proteins, phosphorylation of the receptor, dimerization of receptors, and translocation into the nucleus where it binds to a specific GRE in the chromatin. This binding is mediated through elongated zinc-associated structural elements termed *zinc fingers* specific for the GRE. Glucocorticoid-receptor complexes then dissociate from this binding site, glucocorticoid receptors are recycled to the cytoplasm, and reassociation with heat shock proteins occurs before glucocorticoid binding can again take place. Present models of how steroids modify gene transcription are shown in Figure 46-7. In the case of steroid induction of transcription, binding of the steroid-receptor complex to the GRE leads to catalysis by ribonucleic acid (RNA) polymerase, and the new transcripts undergo posttranscriptional processing and are transported to the cytoplasm where they are translated and new proteins are formed (Figure 46-7, *A*). After posttranslational processing, the new proteins are either released from the cell (in cases of proteins designed for export) or exert intracellular activity.

The suppressive effects of glucocorticoids are believed to be the most important in mediating their antiinflammatory actions.[49] The molecular mechanisms by which glucocorticoids influence gene expression are summarized in Figure 46-7, *B* and *C*. Suppression of the expression of inflammatory genes can occur through several mechanisms.[49] These include direct target gene repression, in which case binding of the GR to a "negative" GRE in the promoter of a target gene can suppress expression of the gene (see Figure 46-7, *B*). GR can also exert gene repression by indirect mechanisms. GR is able to bind to numerous activating transcription factors, including AP-1, CREB, OCT-1, NF-IL-6, and others. Binding to these transcription factors interferes with their ability to activate inflammatory gene expression by preventing their interactions with promoter sites to which they bind (see Figure 46-7, *C, top*). This interaction can be bidirectional. Thus high levels of transcription factors can theoretically suppress glucocorticoid action by neutralizing receptors (a potential mechanism of glucocorticoid resistance). Glucocorticoids can also repress gene expression by inducing inhibitors of transcription factors. A good example is IκB, a protein that prevents NF-κB from entering the nucleus and activating inflammatory genes[50,51] (Figure 46-7 *C, middle*). Whether GR activates IκB via a GRE is not firmly established. Another mechanism of indirect target gene repression hinges on the fact that most genes of inflammation have AU-rich elements. These are 3′ RNA sequences that target the messenger RNA (mRNA) for rapid degradation. Glucocorticoids have been shown to destabilize AURE-containing mRNAs by an as-yet-undefined mechanism[52] (see Figure 46-7, *C, bottom*). The relative importance of the above mechanisms in glucocorticoid action is likely to vary depending on the cell type, cytokine produced, and cell activation stimulus.

There are several consequences of these molecular mechanisms of steroid action:

1. The responsiveness of a given cell type to glucocorticoids is determined in part by the number of glucocorticoid receptors in that particular cell type.[53] Thus there are cases in which a given target cell type has reduced steroid receptor numbers and so displays reduced steroid responsiveness. This can also result from impaired access of the receptor to the GRE because of the presence of other deoxyribonucleic acid (DNA)-binding moieties or a steroid receptor with a weak steroid or GRE-binding domain.
2. Steroid receptor antagonists have been developed that bind to the receptor but do not allow either translocation or productive interaction with the GRE, preventing the action of glucocorticoids. These compounds are useful in vivo in antagonizing undesired steroid actions.[54,55]
3. The requirement of transcription and translational events for steroid action is often responsible for a significant time delay between exposure of a given cell type or tissue to steroid and the eventual steroid effect.
4. In the case of indirect repression (see Figure 46-7, *C, top*), overproduction of a transcriptional activator (e.g., AP-1) could antagonize steroid actions by binding GC receptors.
5. The requirement for transcription and translation in many steroid responses can render steroid actions sensitive to inhibitors of either transcription or protein synthesis.

Factors influencing local and systemic activity of presently available inhaled glucocorticoids

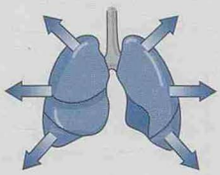


1. Delivery device/delivery method
   - Presence of a spacer and mouth rinsing can reduce the oral deposition of inhaled dose by up to 90%.

2. Oral bioavailibility
   - Drug absorbed in the stomach and intestine is immediately transported to the liver by the hepatic portal system.
   - ICS are all efficiently metabolized by the liver during this first pass. A small percentage survives this hepatic transit intact:

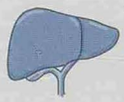
Oral Bioavailability of Inhaled Glucocorticoids

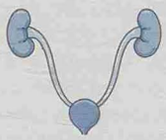
BDP	BUD	FLUN	FP	TAA
—	6-11%	21%	<1%	10%



3. Volume of distribution (V_D)
   - The V_D for ICS is determined in part by binding to lung and other tissues.
   - ICS vary in their tissue binding.
   - Tissue binding is related to water solubility and other characteristics:

	BDP/BMP	BUD	FLUN	FP	TAA
V_D (L/Kg)	NA	2.7-4.3	1.8	3.7	1.4-2.1
H_2O sol (μg/ml)	0.1/10	14	100	0.04	40





4. Plasma clearance/terminal half life
   - Persistence of plasma levels ($t_{1/2}$ or half life) of ICS reflects the balance between metabolism and flux from tissue binding sites into the circulation.
   - Systemic side effects relate to receptor binding affinity, plasma concentration, and maintenance of elevated plasma levels:

	BDP/BMP	BUD	FLUN	FP	TAA
GR binding*	0.4/13.5	9.4	1.8	18-22	2.3-3.6
Clearance (L/min)	NA	.9-1.5	1.0	0.9	0.8-1.2
$t_{1/2}$ (terminal)	15	1.5-2.8	1.6	3.1-14	1.5

* Relative to dexamethasone.

FIGURE 46-5 Factors influencing local and systemic activity of presently available inhaled glucocorticoids.

6. The half-life of steroid-receptor complexes and the proportion of steroid receptors that are bound by drug are determined by affinity of a given steroid for the receptors. The more potent, longer-lasting steroids (e.g., the 6α- and 9α-fluorinated steroids, such as most inhaled steroids) have greater affinity for the steroid receptor.

METABOLIC EFFECTS

Glucocorticoids regulate carbohydrate, lipid, and protein metabolism; water and electrolyte homeostasis; and the functions of most major organ systems, including the lung, the kidney, the cardiovascular system, and the nervous system.[4,5] The variety of glucocorticoid actions on these systems is diverse and beyond the scope of this review. The glucocorticoid namesake effect, regulation of glucose metabolism, includes stimulation of glucose formation, reduction of the peripheral usage of glucose, and promotion of glucose storage in the form of glycogen. These actions of glucocorticoids maintain glucose levels during periods of starvation—an action that may protect cerebral centers, which are restricted to glucose for metabolic energy. Glucocorticoids stimulate the gluconeogenic formation of glucose from amino acids derived from muscle and bone, one consequence of which is muscle wasting and osteoporosis during prolonged steroid usage. Glucocorticoids facilitate release of fatty acids from neutral lipids in adipose tissue with chronic use and produce rearrangements of body fat localization. Several clinically used glucocorticoids (such as hydrocortisone and prednisolone) have mineralocorticoid properties, producing salt retention by stimulating reabsorption of sodium at the renal distal tubules.

EFFECTS OF GLUCOCORTICOIDS ON THE PRODUCTION OF INFLAMMATORY CELLS

The oral or intravenous administration of glucocorticoids (e.g., 50 mg of prednisone) causes marked changes in circulating leukocyte numbers. Most striking of these changes is a fall in the number of basophils,

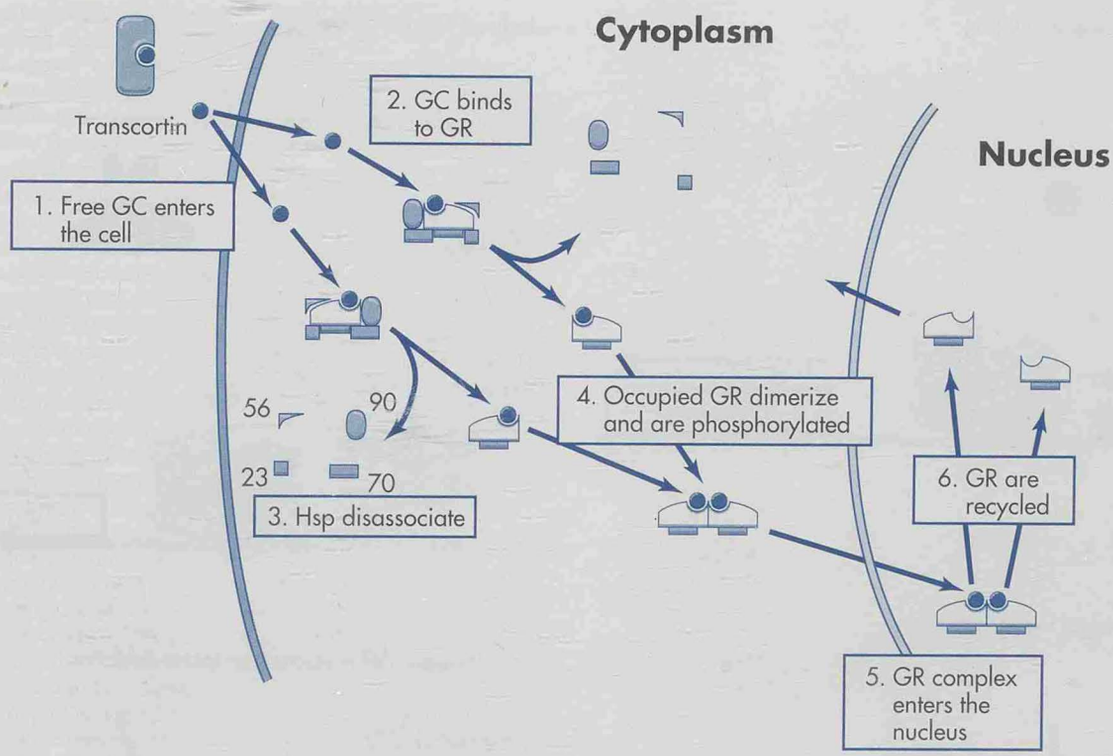


FIGURE 46-6 Molecular basis of glucocorticoid action. For explanation, see text.

eosinophils, and monocytes to approximately 20% of the normal circulating quantity of each of these cell types.[56-58] Recirculating lymphocyte numbers also fall but not as dramatically. The nonrecirculating lymphocytes, that is, those that remain in the circulation and generally do not enter the lymph, are only modestly depressed by steroid administration.[59] A greater fall in the number of T cells than B cells causes a relative enrichment of B cells.[59,60] Among T cells, steroids cause a fall in helper/inducer (CD4) but not cytotoxic/suppressor (CD8) cell numbers.[61,62] Null and natural killer (NK) cell numbers are not influenced by acute steroid administration.[63]

Changes in leukocyte number occur within 4 to 6 hours and abate by 24 to 48 hours after a single steroid dose. In contradistinction to the effects of steroids in reducing basophil, eosinophil, and monocyte numbers, steroid administration elevates the number of neutrophils in the circulation.[64,65] The increase in neutrophils that follows administration of steroid probably results from combined effects of a decreased egress of these cells from the blood, increased survival, a decrease in the size of the marginated granulocyte pool, and an increase in production of neutrophils by the bone marrow.[64-66] The increased production of neutrophils by the bone marrow may be one of the more important effects because steroid treatment in patients with impaired marrow function causes little increase in circulating neutrophil levels.[67] However, the decrease in the size of the marginated granulocyte pool must also play a substantial role because the levels of neutrophil alkaline phosphatase, a marker of neutrophil maturity, indicate that a large proportion of the additional neutrophils found in the blood after steroid administration are mature neutrophils.[65] There is a selective effect of steroids in vitro on the proliferation of eosinophils and neutrophils from human bone marrow cultures; steroid treatment inhibits formation of eosinophil colonies but enhances formation of neutrophil colonies in culture.[68,69] The decrease in eosinophils in blood after steroid treatment is probably not exclusively the result of decreased bone marrow production of eosinophils, however, because studies with radiolabelled eosinophils indicate that the eosinophil half-life and transit times are relatively long.[70] Recent studies have shown that the release of eosinophils from the bone marrow of sensitized mice challenged with allergen is inhibited by glucocorticoid treatment.[71] Thus the fall of eosinophil numbers in the circulation of steroid-treated individuals probably results from the combined influence of reversible sequestration, apoptosis, reduced production of eosinophils, and reduced release of eosinophils from the bone marrow.

Because eosinophils are now recognized to play an important role in the pathogenesis of allergic diseases such as asthma, particular interest has been paid to factors that maintain their survival in vivo and in vitro (see Chapter 19). In vitro, glucocorticoids inhibit the prolongation of eosinophil survival induced by granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5.[72,73] In addition to inhibiting the ability of these cytokines to prolong eosinophil survival and activate eosinophil function, steroids can also inhibit the production of these cytokines. This effect is readily demonstrated in vitro,[74] and stress (which increases glucocorticoid levels) and the administration of cortisone both cause an 80% decrease in the total level of colony-stimulating factors in mouse serum.[75,76] One study of a patient with hypereosinophilia demonstrated that steroid treatment reduced elevated serum cytokine levels (mostly GM-CSF) to the normal range.[77] Although the source of cytokines in vivo is unclear, recent studies have implicated lymphocytes in experimental late phase reactions to antigen challenge, as well as in chronic allergic diseases. These studies have demonstrated increased cytokine production in allergic reactions[78-80] and increased numbers of activated lymphocytes (i.e., those expressing IL-2 receptors) in bronchial biopsies of asthmatic patients and after antigen challenge in the skin.[81] These cells resemble the T helper 2 cell (Th2) subtype in rodents, which produces IL-3, IL-4, IL-5, and IL-6, along with some other cytokines but not IL-2 or interferon-γ (IFN-γ). Because lymphocyte-derived cytokines are now felt to play a role in allergic inflammation, inhibition of lymphocyte cytokine production by steroids, a well-characterized phenomenon, may thus be an extremely important steroid mechanism in the inhibition of the experimental late phase reaction and chronic allergic diseases (see below).[74,81]

The effects of steroids on basophils and mast cells have been extensively studied and this topic has been reviewed.[82,83] The reduction in circulating basophils produced by steroids occurs by an unknown mechanism. There is at present little evidence that steroids are toxic to basophils, and this mechanism seems unlikely. One explanation for the reduced basophil number after steroid treatment is a sequestration of these cells in selected vascular beds.[57,84] Alternatively, mechanisms involving cytokines (e.g., IL-3) that prolong basophil survival and increase their generation, as described previously for

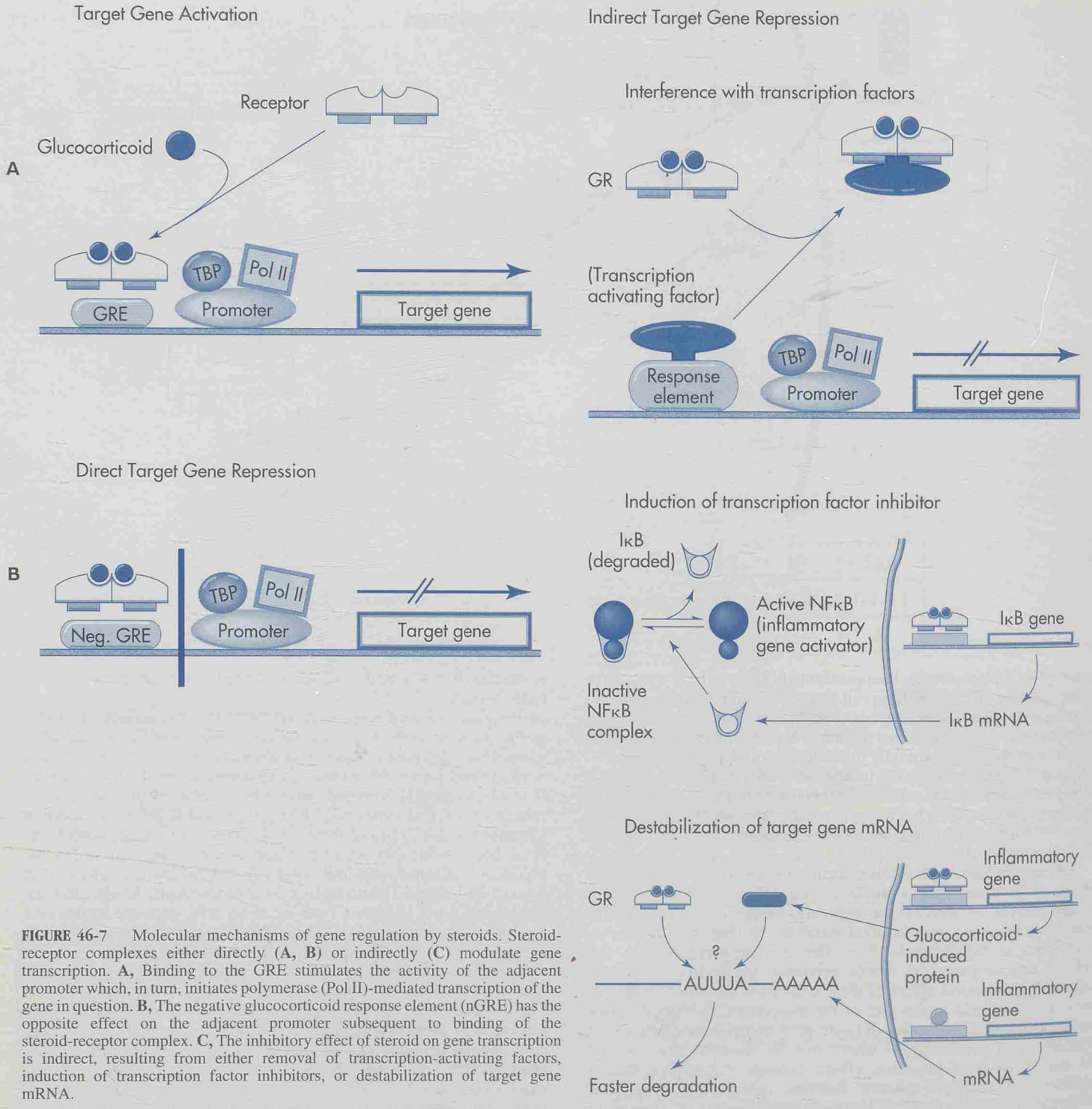


FIGURE 46-7 Molecular mechanisms of gene regulation by steroids. Steroid-receptor complexes either directly (**A, B**) or indirectly (**C**) modulate gene transcription. **A,** Binding to the GRE stimulates the activity of the adjacent promoter which, in turn, initiates polymerase (Pol II)-mediated transcription of the gene in question. **B,** The negative glucocorticoid response element (nGRE) has the opposite effect on the adjacent promoter subsequent to binding of the steroid-receptor complex. **C,** The inhibitory effect of steroid on gene transcription is indirect, resulting from either removal of transcription-activating factors, induction of transcription factor inhibitors, or destabilization of target gene mRNA.

eosinophils, may also be operative; in this case, steroids may directly and indirectly diminish basophil survival time. As is the case with the eosinophil, basophil half-life is sufficiently long to indicate that steroid treatment is not reducing circulating basophil numbers strictly by a decrease in production or release of basophils from the bone marrow. Interestingly, only a subpopulation of basophils is lost after steroid treatment, suggesting heterogeneity of basophils.[85] Long-term treatment with steroids in asthmatic subjects or patients with collagen vascular diseases does not lead to chronically reduced levels of circulating basophils.[86]

Numerous studies have analyzed the effects of steroid treatment on mast call numbers. Some early studies suggested that treatment with cortisone or ACTH reduced the number of connective tissue mast cells.[87] Subsequent studies showed that 3 to 4.5 mg per day of dexamethasone for 10 days in asthma patients reduced the number of mast cells found in formalin-fixed bronchial biopsies.[88] A reduction in synovial mast cells was observed after intraarticular steroid administration.[89] Some studies suggest no effect of oral steroid administration on skin mast cell numbers.[58,90] Several studies suggest that inhaled steroids may reduce the number of mast cells in bronchial biopsies or bronchoalveolar lavage (BAL).[91-93] In the nose, treatment for 1 to 4 weeks with topical steroids has no effect on the number of mast cells in nasal biopsies.[92,94] One week of topical budesonide reduced the amount of histamine in nasal mucosal biopsies[95]; taken together, these data were interpreted to suggest that the reduction in histamine after topical budesonide treatment did not result from reduced numbers of mast cells but rather reduced mast cell histamine content. When metachromatic cells were enumerated in nasal scrapings, which in-

cluded only the mast cells in and adjacent to the epithelium (in contrast to biopsies, which include subepithelial mast cells), topical steroid treatment was shown to reduce the number of mast cells and the histamine content of the scrapings while having no effect on the ability of the mast cells to release histamine in response to allergen challenge in vitro.[96-98] Thus it seems that topical steroid treatment causes redistribution of mast cells in the nasal tissue, having as its most pronounced effect a diminution of the most relevant mast cell population—those residing immediately adjacent to the nasal epithelium. The seasonal increase in mast cells in the nasal mucosa associated with exposure to antigen can be profound; mast cell numbers in nasal imprints or scrapings have been observed to increase by up to fiftyfold by several investigators.[98-100] This increase of mast cells is suppressed in most studies by steroid treatment before and during the allergen season.[98-100] Steroids also block an apparent migration of mast cells to the mucosal epithelium after experimental exposure to antigen in dogs.[101] Although a similar migration has been reported in human bronchial mucosa,[102] the effects of steroids on this phenomenon are unknown. Glucocorticoids may achieve reduction of mucosal mast cell numbers in part by inhibiting the local production of mast cell growth factors (including possibly c-*kit* ligand, IL-3, IL-4, IL-10, or others).[82,103] Some direct effects on mast cell proliferation, production of mast cell precursors, or migration may also occur. Mast cells from rodents have been shown to migrate in response to chemokines in vitro.[104] Glucocorticoids are effective inhibitors of the expression of chemokines by airway epithelial cells.[105] Thus it is possible that the profound ability of glucocorticoids to inhibit migration of mast cells to the epithelial surface relates in part to a suppression of epithelial chemokine production. The chemokine receptor CCR3 has been observed on human mast cells in tissue sections (C. MacKay, MD, personal communication), suggesting that CC chemokines, such as eotaxin, monocyte chemotactil protein-4 (MCP-4) and RANTES (regulated on activation, normal T cell expressed and secreted), all of which are produced by epithelial cells in a glucocorticoid-inhibited fashion, may be involved in mast cell localization. In rats, the loss of mucosal mast cells (during a parasite infestation) induced by steroids appears to involve engulfment of the mast cells by macrophages.[106] It is not known whether this phenomenon occurs in humans.

The effect of relatively long-term cutaneous treatment with the topical steroids clobetasol-17-propionate and fluocinonide on mast cell numbers in the skin were analyzed.[107] Whereas up to 3 weeks' treatment with topical steroid had little effect on the histamine levels in skin biopsies, a 6-week treatment with either steroid caused a significant reduction in both histamine and mast cell numbers. Discontinuation of the steroid resulted in the slow reappearance of histamine and mast cells in the skin, which required up to 4 months to reach near-normal levels. It was suggested that reduced mast cell numbers and histamine in the skin were the result of a toxic effect of steroids on the mast cells. This effect of high-dose, high-potency steroids on the skin has been exploited, with good results, as a "pulse" therapy for cutaneous diseases, such as urticaria pigmentosa, associated with mast cell dysfunction.[108] Several studies have shown that oral steroid therapy, even over an extended period of time, does not inhibit the allergen skin test response.

STRESS, GLUCOCORTICOIDS, AND THE GENERAL ADAPTATIONAL SYNDROME

The earliest recognized actions of glucocorticoids were those relating to maintenance of homeostasis in glucose metabolism and electrolyte balance. Subsequently, the decreased resistance of an adrenalectomized animal to the stress of surgery or infection led early workers to suggest that glucocorticoids and the elevation of glucocorticoids that is seen after stress serve to protect the organism from the harmful effects of stress.[109] In addition to the other beneficial effects of steroids, it is felt that increased levels of steroids that occur during infection-related stress may also serve to dampen what would otherwise be an overvigorous immune response.[110,111]

TOXICITY

Acute administration of glucocorticoids produces CNS effects, including changes in mood ranging from euphoria to psychosis, irritability,

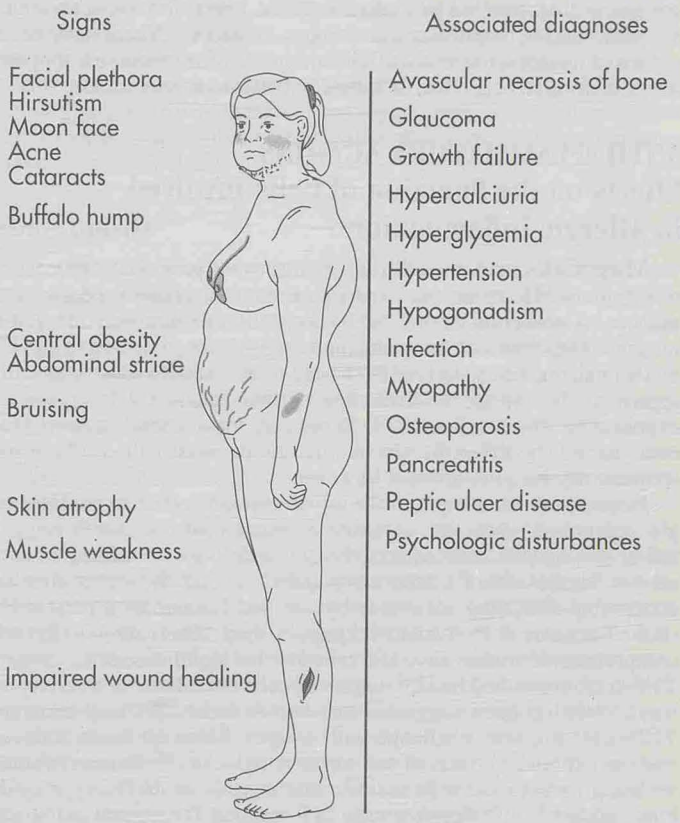


FIGURE 46-8 Signs of glucocorticoid excess and associated diagnoses.

depression, increased appetite, and suppression of the HPA axis. All of these symptoms are reversed after discontinuation of medication when they occur as a result of brief steroid administration.[112] The more problematic toxic effects of chronic steroid administration, as illustrated in Figure 46-8, include deposition of fatty tissue in the back, cheek, and abdominal area (so-called moonface, buffalo hump), increased bruisability, osteoporosis, hypertension, a thinning of the skin, striae, muscle wasting of the extremities with proximal muscular weakness (possibly the result of gluconeogenic action of steroids), and cataracts[4,5] (see Figure 46-8). Although these effects are normally associated with high-dose oral steroid usage, as higher dosages of potent inhaled steroids are used it can be anticipated that these side effects will be observed more frequently in patients on inhaled steroid only. Monitoring of patients on chronic steroid therapy for toxicity should include tests for suppression of the HPA axis, cataracts, hyperglycemia, hypertension, and attention to signs of osteoporosis. Therapy with calcium and 25-hydroxy vitamin D may be indicated in severe cases of steroid-induced osteoporosis.[113] Because steroid-induced osteoporosis appears to be irreversible, efforts should be directed toward prevention of bone loss by the combined use of vitamin D, calcium, and, if appropriate, estrogen in patients for whom long-term systemic steroid therapy is anticipated. Endogenous basal adrenal function can be monitored by early-morning plasma cortisol concentration measurements; this index is well correlated with a patient's ability to withstand surgical or hypoglycemic stress.[114,115] Because there is considerable variation in normal early-morning values of hydrocortisone, several measurements must be obtained. Such measurements must be made at least 12 hours after administration of a patient's corticosteroid dose to reduce interference of administered steroids with the hydrocorticosone assays. Measurement of 24-hour urinary steroids may be a more sensitive indicator of adrenal suppression. Several tests are utilized to assess HPA responses after stimulation with tetracosactrin, metyrapone, or insulin. Although these tests can produce some risk to the patient, they give insight to the adrenal reserve and are felt to be useful.[116] Aggressive withdrawal of systemic steroids can place some asthmatic patients at risk of sudden death.[117,118] Discontinuation of corticosteroids after administration for weeks or months produces a steroid withdrawal

syndrome characterized by general malaise, fever, arthralgia, abdominal pain, nausea, vomiting, and changes in affect.[36] There have been reports of hydrocortisone sensitivity among aspirin-sensitive asthmatic subjects. In such cases, use of a different steroid is appropriate.[119]

ANTIINFLAMMATORY ACTIONS
Effects on the Function of Cells Involved in Allergic Inflammation

Mast Cells and Basophils. As discussed previously, glucocorticoids have effects on the localization of mast cells to the airways mucosa. A reduction of mucosal mast cells can diminish the acute response to exposure to antigen. Numerous in vitro studies have shown that human mast cells derived from lung or skin are not influenced with regard to the release of histamine or leukotriene C4 by previous exposure to glucocorticoids.[120] Several in vivo studies support this conclusion. The effect of glucocorticoids on mast cell cytokine responses may be quite distinct, however.

Because of the clear sensitivity of cytokine gene expression to glucocorticoids, mast cell cytokine production, if it exists in human mast cells, may be anticipated to be glucocorticoid sensitive.[120] Early studies in the author's laboratory failed to find the generation of endothelial-activating cytokines by purified human lung mast cells (B.S. Bochner, R.P. Schleimer, unpublished observations). Recent comprehensive studies have also failed to find significant generation of TNF-α from purified human lung mast cells stimulated in a variety of ways.[121] It has been suggested that human mast cells may generate TNF-α in skin after challenge with antigen, based on tissue staining and the inhibitory effects of sodium cromoglycate.[122] Extensive studies using rodent mast cells indicate that a synthesis of Th2-type cytokines occurs.[123,124] Positive mast cell staining for several cytokines has been observed using immunohistochemistry in human tissues, and positive IL-4 protein generation has been reported in vitro from mast cell preparations.[125,126] Very small quantities of IL-5 mRNA have been detected in human lung fragments and purified human lung mast cells, stimulated with phorbol myristate acetate (PMA) and anti-immunoglobulin E (anti-IgE), and this response is inhibited by dexamethasone.[127] Numerous other laboratories have failed to find generation of IL-4 or IL-5 from purified human lung mast cells, however. This may be related in some part to technical issues, however, because human mast cells grown from cord blood progenitor cells have recently been reported to elaborate macrophage inflammatory protein-1α (MIP-1α), IL-8, and GM-CSF.[128] Several studies have shown the presence of significant numbers of IL-4 and IL-5 mRNA-positive cells by in situ hybridization in upper and lower airway tissues. These studies have further determined that a small percentage (≤15%) of the IL-4 and IL-5-positive cells were mast cells as assessed by immunohistochemical staining for mast cell markers, suggesting that some cytokine-positive mast cells may exist in the airways.[129,130] At 24 hours after local antigen provocation of allergic rhinitis subjects, double in situ hybridization/immunocytochemistry of nasal biopsy sections demonstrated that the percentage of IL-5 and IL-4 mRNA-positive cells coexpressing immunoreactivity for tryptase was 11.3% and 26%, respectively.[129,130] In asthmatic airways, however, the proportion of IL-4 and IL-5 mRNA-positive cells expressing tryptase (9.8 and 11.9%, respectively) was relatively less than in the nasal mucosa of subjects with allergic rhinitis.[131] Recent studies indicate that tryptase-positive cells in the bronchial mucosa of asthmatic subjects also express mRNA for IL-13 and IL-16 (Q. Hamid, et al, personal communication). In addition to Th2 cytokines, mast cells may produce selected chemokines. Using the human mast cell-1 (HMC-1) cell line, production of several C-C chemokines and inhibition by glucocorticoids has been observed.[132] Messenger RNA for RANTES, MIP-1α, and IL-4 has been observed in mouse mast cells.[133] Human mast cells have been reported to produce eotaxin.[134,135] Production of IL-8 and GM-CSF cord blood–derived mast cells is inhibited by glucocorticoid exposure.[128] Although it is still uncertain to what extent mast cell cytokine responses occur in asthma or allergic reactions, to the extent that they do contribute to airways inflammation it is reasonable to expect that glucocorticoids inhibit these responses. To summarize, mast cell degranulation is not inhibited by glucocorticoids in humans, explaining the relative resistance of the acute phase response to these drugs. Mast cell cytokine production is of unknown importance in humans. In those model systems in which mast cell cytokine production has been demonstrated, it is inhibited by glucocorticoids.

In contrast to the human mast cell, the human basophil is sensitive to glucocorticoids in vitro. Twenty-four-hour incubation with steroids produces a marked inhibition of histamine and leukotriene release from human basophils.[136-138] This effect of steroids is stimulus-dependent; that is, IgE-dependent mediator release is inhibited while mediator release induced by ionophore, phorbol diester, or formyl-methionyl-leucyl-phenylalanine (fMLP) is not inhibited by steroid treatment.[137] In vivo treatment of normal subjects with steroid does not reduce histamine release tested in vitro despite markedly decreasing circulating basophil numbers.[58,90] Similarly, patients on long-term steroid treatment for either allergic diseases or collagen vascular diseases have normal levels of circulating basophils (i.e., approximately 1% of total leukocytes), which release histamine normally to an IgE-dependent stimulus.[86] However, circulating basophils in patients on chronic steroid therapy are considerably less responsive to the in vitro effects of steroid on mediator release, possibly because steroid treatment removes from the circulation those basophils that are sensitive to the steroid, leaving a subpopulation that is relatively resistant to the inhibitory effects of the glucocorticoid.[86]

Lymphocytes. As discussed previously, treatment of patients with steroid causes a decrease in total circulating lymphocyte numbers. However, steroid therapy has relatively modest effects on total immunoglobulin levels.[139,140] Large doses of steroid can cause a slight decrease in the IgG and IgM levels while causing little effect or a mild enhancement of IgE levels.[139-141] Most studies have focused on total circulating immunoglobulin, and the question of the effect of steroids on antigen-specific responses, both primary and secondary, needs to be carefully addressed. This is especially clear because in vitro studies show that corticosteroids inhibit early B cell activation events (i.e., decreased proliferation with anti-T3 antibody or *Staphylococcus aureus*) but have little effect on later events (e.g., proliferation in response to B cell growth factors, and the final differentiation to become immunoglobulin producers).[142,143] Interestingly, and somewhat paradoxically, steroids enhance immunoglobulin production in vitro.[144] A modest increase of total IgE has been observed in vivo after steroid treatment.[145] Glucocorticoid treatment of patients with rhinitis has been shown to inhibit the seasonal increase of IgE levels.[146]

In vivo glucocorticoid therapy is especially effective in inhibiting delayed-type hypersensitivity reactions, such as occur with the tuberculin test. This probably results largely from inhibition of the emigration of lymphocytes to the site of antigen challenge[147,148]; inhibition of production of lymphocyte growth and activating factors, including IL-1, IL-2, and IFN-γ; and consequent inhibition of lymphocyte proliferation.[149-152] Numerous cell types play an important role in allergic reactions of the airways, including both infiltrating and structural cells. However, perhaps the single most important cell type involved in asthma is the T cell.[153] Glucocorticoids modify the expression of immunoglobulin receptors (for IgG or IgE) on lymphoid cells.[154-156] Atopic patients have substantially elevated numbers of lymphocytes and monocytes bearing the low-affinity IgE receptor, whereas normal patients have little or no Fcε receptor–positive lymphoid cells.[155] Treatment of atopic subjects with glucocorticoid reduces the number of Fcε receptor–positive cells to the normal range.[156] The impact of this effect of steroids on allergic diseases or reactions has not been established.

T cells are the primary antigen-recognizing cells that are responsible for amplification of other elements of the response (inducing IgE synthesis, mobilizing eosinophils and basophils from bone marrow, and coordinating local cellular infiltration). The conclusion that T cells play a central role in asthma is based on both animal and human studies. Animal studies have shown that depletion of T cells inhibits the late phase allergic reaction almost completely, including eosinophil infiltration and changes in airways reactivity.[157] Furthermore, adoptive transfer of sensitized T cells can reconstitute late phase reactions.[158,159] Antiinflammatory drugs, including glucocorticoids, cyclosporin, FK506, and others that target T lymphocytes, are all effective as suppressants of allergic inflammation in the airways. In situ hybridization has been used to analyze the cytokine mRNA-positive cells in a variety of allergic reactions and diseases of both the airways

and the skin. In BAL and biopsies from asthmatic subjects, as well as in late phase reactions, the primary IL-4–and IL-5–producing cell type is the T cell based on co-expression of CD2 or CD3. Several studies have shown that the T cells isolated from BAL are primarily of the Th2 phenotype (i.e., producing IL-4 and IL-5). T cells (CD3-positive cells) are the major source of IL-4 and IL-5 mRNA in BAL from asthmatic subjects.[131] Treatment with glucocorticoid, either topically or systemically, profoundly inhibits the appearance of these cytokine-producing cells. The relative importance of suppression of lymphocyte cytokine expression vs. suppression of accumulation of lymphocytes in the tissue has not yet been determined.[160] T cells isolated from asthmatic subjects express higher levels of the activation antigen CD25 (the IL-2 receptor), and biopsy tissues from asthmatic patients also have higher CD25+/CD2+ cells, suggesting an elevation of activated T cells.[161] The numbers of IL-4 and IL-5 mRNA-positive cells in BAL from asthmatic subjects correlated significantly with forced expiratory volume in 1 second (FEV_1).[162,163] More recently, it was found that the increase in FEV_1 in response to a 1-week course of oral steroids is directly correlated to the increase in IL-12 mRNA-positive cells observed within the bronchial mucosa.[164] IL-12 (and IL-18) may be expected to profoundly modify the relative balance of Th1 and Th2 cells because it is a potent and effective inducer of IFN-γ. IFN-γ in turn has previously been shown to be a major inducer of Th1 and suppressor of Th2 cell development. Cells expressing mRNA for IL-16, a cytokine that is a potent chemoattractant for lymphocytes and eosinophils, are also correlated with pulmonary function tests.[165] However, the strongest correlation observed in bronchial biopsies from asthmatic patients was the presence of IL-5 membrane-receptor mRNA-positive cells with FEV_1 ($r^2 = 0.89$; $p < 0.001$).[166] Glucocorticoids are potent and effective inhibitors of T cell activation and production of cytokines involved in allergic inflammation, including IL-2, IL-3, IL-4, IL-5, IL-13, IL-16, IFN-γ, GM-CSF, TNF-α, and several chemokines (see below).[167] In light of the central role of T cells in orchestrating allergic inflammation, these are pivotal effects of glucocorticoids.

Macrophages and Monocytes. Because macrophages are the most numerous of the inflammatory cell types found in alveolar spaces, and they produce a spectrum of inflammatory mediators, great interest has been focused on the role of macrophages and monocytes in allergic diseases such as asthma. Mononuclear cells and alveolar macrophages have been demonstrated to bear low-affinity and high-affinity receptors for IgE; cells with these receptors are increased in numbers in allergic patients, especially those with asthma.[155,156,168-172] These cells can be activated to secrete mediators upon stimulation with antigen if they are sensitized with antigen-specific IgE. Macrophages release a host of inflammatory mediators, including enzymes (e.g., plasminogen activator, lysozyme, collagenase, elastase), metabolites of arachidonic acid (e.g., leukotriene B_4, leukotriene C_4, 5-hydroxyeicosatetraenoic acids [HETEs]), platelet activating factor (PAF) and growth factors for fibroblasts and other cell types, and a mucous secretagogue.[173] Steroids inhibit the production of arachidonic acid metabolites by alveolar macrophages, depending on the stimulus and other conditions.[174-176] Macrophage-derived IL-1 and TNF are capable of elevating body temperature through an activity on hypothalamic centers and stimulate synthesis of acute phase proteins (mostly in the liver).[177] IL-1 and TNF are also necessary for lymphocyte growth, stimulate fibroblast activation and proliferation, and activate vascular endothelium to express procoagulant activity (so-called tissue factor), as well as adhesion molecules that are responsible for binding and recruitment of circulating leukocytes.[173,177-181]

Macrophages and monocytes are exquisitely sensitive to antiinflammatory steroids.[173] In vivo treatment with steroids reduces circulating monocyte numbers and reduces the percentage of FcεRII-bearing monocytes.[155] Steroid treatment has no effect on bronchoalveolar macrophage numbers. Treatment with glucocorticoids causes a profound reduction in the MHC class II (Ia)-positive cells residing in airway tissues.[182] In vitro incubation of macrophages with glucocorticoid for 24 hours inhibits the release of enzymes, such as plasminogen activator, elastase, and collagenase, but does not inhibit the release of lysozyme.[183,184] These enzymes differ in that lysozyme is constitutively released by macrophages, whereas the other enzymes require cell activation for release, suggesting that steroids prevent the cell activation process. Although macrophage phagocytic activity appears to be resistant to steroid treatment, the intracellular killing of, for example, *Nocardia, Listeria,* or *Salmonella,* is impaired by steroids in vitro.[185] Treatment with steroids either in vivo (in animals) or in vitro causes inhibition of the release of IL-1 and TNF.[186-190] This activity of steroids may be critical to their antipyrogenic effects, as well as in their activity in preventing the recruitment of leukocytes to a local inflammatory site (see below).

Eosinophils

Eosinophils are prominent in allergic diseases, and eosinophila is exquisitely sensitive to glucocorticoid suppression. Thus they are likely to be an important target of the beneficial action of steroid treatment. (See Chapter 19 for details of eosinophil biology.)

Eosinophils develop under the hematopoietic action of IL-3, IL-5, and GM-CSF, from progenitor cells that arise in the bone marrow, and IL-5 induces their release into the circulation. Treatment with glucocorticoid or anti–IL-5 profoundly inhibits this release but not the number of eosinophils in the marrow. Although eosinophil progenitors themselves may directly respond to glucocorticoids, in vitro studies suggest this is not the case.[191] More probably, steroids cause a decreased production of IL-5 or other trigger factors either locally in the marrow or elsewhere, for example, the lung.[192] Inhaled glucocorticoids can prevent eosinophil migration into the lung and can prevent the appearance of increased eosinophil precursors in the circulation, suggesting that the effects of steroid on the bone marrow response may, in some part, be mediated in the lung.[178] The mechanism by which eosinophils are bound in the marrow and subsequently released are poorly understood. An IL-5–induced decrease in β_1 integrin affinity for very late antigen-4 (VLA-4) could be one factor.[193] Chemokines may also be involved because eotaxin knockout mice have diminished circulating eosinophil numbers but normal numbers in the bone marrow.[194] Both of these mechanisms would be expected to be glucocorticoid sensitive because production of IL-5 or eotaxin would be inhibited by glucocorticoids.

Once mature eosinophils are in the circulation, numerous events mediated by adhesion molecules occur by which they migrate into an affected tissue (see Chapters 9 and 19).

In vitro studies with glucocorticoids have shown that endothelial adhesion molecule expression on human umbilical vein–derived cells is not inhibited by glucocorticoid treatment.[195] On a theoretic basis, however, one would anticipate, and the author and colleagues have previously hypothesized,[196] that endothelial adhesion molecule expression in vivo should be inhibited by glucocorticoids because synthesis of the major endothelial-activating cytokines, IL-1, TNF-α, IL-4, and IL-13, is inhibited by glucocorticoids in vitro.[167] The influence of glucocorticoid treatment on expression of adhesion molecules on endothelium after antigen challenge in human airways has not been firmly established. However, several studies have been performed on this subject. Steroid treatment had no effect on adhesion molecule expression after cutaneous challenge with tuberculin.[197] Similarly, 3-day treatment with oral glucocorticoids had no effect on expression of E-selectin, on levels of IL-1β, or on neutrophil influx after intracutaneous challenge with endotoxin.[198] In contrast, a profound decrease in soluble E-selectin levels in BAL fluid was observed 20 hours after antigen challenge in subjects treated for 3 days with prednisone compared with controls.[199] It is not established that this E-selectin directly reflects the level of endothelial activation in the lungs, however. Prednisone treatment was associated with at least a 90% reduction in eosinophils and approximately 50% reduction in neutrophils found in BAL fluids. In rats, indirect evidence suggests that dexamethasone inhibits the expression of P-selectin, and perhaps other selectin molecules, in an endotoxin model in the mesentery.[200] Studies on the expression of vascular cell adhesion molecule-1 (VCAM-1) after antigen challenge in the airways of steroid-treated and control individuals are sorely needed. Several groups have shown that glucocorticoid treatment leads to a decrease in IL-4 and IL-13 mRNA or protein levels, suggesting that VCAM-1 expression may be diminished.[160,201] In contrast, little information is available on the nonspecific endothelial activators IL-1 and TNF-α in antigen challenge systems. Eosinophil transendothelial migration has been studied extensively in vitro.[202-204] No significant inhibition of eosinophil transendothelial migration by glucocorticoids was found, suggesting that, if it occurs in vivo, it may

be indirect, by inhibition of the release of cytokines that induce the event in vivo (M Ebisawa, BS Bochner, RP Schleimer, et al, unpublished observations).

Associated with the interaction between leukocytes and endothelial cells may be an activation of expression of inflammatory genes in the leukocyte. Engagement of PAF receptors and P-selectin counterligand simultaneously on the surface of monocytes leads to an activation of the expression of chemokine and inflammatory cytokine genes.[205] Similar activation of eosinophils by seven spanner receptor agonists (e.g., chemokines) along with selectins may be speculated to activate gene expression. Indeed, liganding of VLA-4 on eosinophils is known to induce cytokine gene expression (see below). Thus, during the process of transendothelial migration, eosinophils and other inflammatory cells being recruited to the airways may be activated to express cytokine genes involved in the inflammatory response. Although it is reasonable to speculate that adhesion-dependent activation of cytokine gene expression is inhibited by glucocorticoids, more information is needed in this area.

Eosinophils have been found to migrate toward selected structures within the airways; they are found concentrated in and around epithelium, blood vessels, and nerves. Although the precise mechanism(s) by which this occurs are unknown, several lines of evidence point toward eosinophil-directed chemokines. To date, six C-C chemokines have been shown to induce eosinophil migration (RANTES, MCP-3, MCP-4, MIP-1α, eotaxin-1, and eotaxin-2). In vitro studies with human eosinophils indicate that the most potent of these are MCP-4, RANTES, eotaxin-1 and eotaxin-2.[206] The localization of eosinophils to epithelium and endothelium could be explained by the observation that these cell types produce these chemokines after activation. Several other cell types produce chemokines in airway inflammation, including lymphocytes, smooth muscle, and, perhaps, mast cells. Glucocorticoids are potent inhibitors of epithelial chemokine production, suggesting a mechanism for inhibition of epithelial localization of eosinophils.[105,207] Chemokine production by cultured umbilical vein endothelial cells is not inhibited by glucocorticoids in vitro, however.[208] Whether the failure of cultured endothelial cells to respond to glucocorticoids reflects the in vivo situation is unknown. Also unknown is the relative importance of epithelial- and endothelial-derived chemokines in inducing eosinophil transendothelial migration. These gaps in our knowledge must be filled to better understand the importance of suppression of local chemokine production as a glucocorticoid mechanism.

As discussed previously, several cytokines are able to induce a prolongation of eosinophil survival in vitro. Synthesis of these cytokines is inhibited by glucocorticoids. Considerable evidence has accumulated suggesting that prolonged survival and priming of eosinophils occur in vivo in asthmatic subjects. IL-5, IL-3, and GM-CSF are found to be elevated in asthmatic airways.[80,209-211] Glucocorticoids, by reducing the production of eosinophil-priming cytokines, reduce the availability of the factors necessary for eosinophil survival in the airways. In the absence of these cytokines, eosinophils undergo apoptosis. Glucocorticoids may also trigger eosinophil apoptosis as a direct effect on the eosinophil. Recent studies indicate that eosinophils themselves produce survival-promoting cytokines (autocrine production) and that this autocrine production is inhibited by glucocorticoids. It is therefore not yet clear whether the direct effects of glucocorticoids on eosinophil survival are secondary to suppression of eosinophil cytokine production or via a distinct mechanism.

Blood Vessels

Increased blood flow and increased permeability of the microvasculature are both important elements of the inflammatory response because they aid in the transport of inflammatory cells and plasma proteins to a local tissue inflammatory site. Many mediators, such as histamine and bradykinin, can directly stimulate increases in blood vessel diameter and permeability.[212] Prostaglandins, such as PGE_2 or prostacyclin, synergize with such mediators by further increasing vascular diameter.[213] A second class of mediators, including chemotactic factors such as leukotriene B_4 (LTB_4), C5a, and f-Met-peptide, can increase vascular permeability through a mechanism that requires the presence of neutrophils and cyclooxygenase metabolites of arachidonic acid.[213-215] In the case of chemotactic factor–induced edema, the adherence of leukocytes to vascular endothelium may be an important step in the reaction. The endothelial-activating cytokines IL-1, TNF-α, and IFN-γ have been demonstrated to increase endothelial permeability.[216] The effects of steroids on vascular permeability have been reviewed.[217] The topical application of steroids produces marked blanching of the skin. This is the basis of a widely used in vivo assay of topical steroid activity (the so-called McKenzie test).[218] Although the mechanism of this effect of steroids is unknown, one possibility is that steroids inhibit the release of cyclooxygenase metabolites that constitutively maintain patent vascular beds.[219] Alternatively, steroids may inhibit the release of endothelial-derived relaxing factor, now thought to be nitric oxide (NO).[220,221] Steroid-induced skin blanching is greatly reduced in steroid-resistant asthmatic subjects.[222]

Several studies have demonstrated inhibition by steroids of vascular permeability in animals induced by histamine, LTC_4, PAF, and other stimuli.[223-226] There is little information, however, on the mechanism by which steroids decrease vascular permeability in response to these inflammatory stimuli. This effect could result from decreased contractility of endothelial cells, decreased production of vasodilating prostaglandins in the local tissue site, decreased adherence of leukocytes, in cases where the inflammatory stimulus indirectly produces a leukocyte-dependent increase in vasopermeability, or other mechanisms. Recent studies have shown that steroids can reduce neurogenic edema in some, but not all, cases.[227-229] This is associated with steroid induction of neutral endopeptidase, an enzyme that degrades neuropeptides and presumably lowers endogenous concentrations of the neuropeptides (e.g., substance P) responsible for causing the vascular leak. That steroids reduce vascular permeability in vivo in the lungs of asthmatic subjects is indicated by studies using macromolecular markers of permeability.[230]

Epithelium

Airway epithelial cells have classically been thought of as barrier cells that are involved in homeostasis and respond to a variety of environmental stimuli resulting in the alteration of their cellular functions, including ion transport and movement of airway secretions. Recent evidence suggests that airway epithelial cells may also act as effector cells in response to noxious endogenous or exogenous stimuli. Airway epithelium produces and secretes several inflammatory mediators, including lipid mediators, oxygen radicals, and a number of different cytokines.[231] Through the production of such agents, which can mediate the chemotaxis, activation, and survival of inflammatory cell types within the airway, the epithelium is now thought to be important in the initiation and exacerbation of airway inflammation associated with asthma.

Human epithelial cells metabolize arachidonic acid via the cyclooxygenase pathway, resulting in the production of prostaglandins, including PGE_2 and $PGF_{2\alpha}$. PGE_2 appears to relax smooth muscle, thereby attenuating bronchoconstriction, whereas $PGF_{2\alpha}$ functions as a bronchoconstrictor.[232] Airway epithelial cells secrete endothelin-1, a bronchoconstrictor, in response to several cytokines, including IL-1α, IL-1β, IL-2, IL-6, and TNF-α.[233] Airway epithelial cells also produce the inducible form of cyclooxygenase (COX2) and the inducible nitric oxide synthase (iNOS) in response to TNF-α.[231] TNF-α may indirectly activate the transcription factor NF-κB, which appears to have a role in the up-regulation of COX2 and iNOS gene expression.[231] Increased nitric oxide production may cause bronchodilation and epithelial cell damage via increased airway blood flow and plasma exudation, as well as enhanced Th2 proliferation, which may mediate eosinophilic inflammation of the airways[234]; however, it should be noted that normal NO levels may serve to protect the host from microbial infection at the air/surface interface.[235] Glucocorticoids inhibit the synthesis of endothelin-1, COX2, and iNOS[231]; such inhibition may be mediated by the interaction of GR with the transcription factors AP-1 and NF-κB.

The bronchial epithelium produces a wide variety of cytokines, including chemotactic factors and colony-stimulating factors. Chemokine production may play an important role in the chemotaxis of leukocytes into the bronchial mucosa and their subsequent activation during an inflammatory response. The chemokine superfamily includes the C-X-C subfamily, in which the first two of four conserved cysteines are separated by one amino acid, and the C-C subfamily, which contains two adjacent cysteines. These subfamilies exhibit cell selectivity

with respect to chemoattraction; the C-X-C subfamily primarily targets neutrophils, whereas various members of the C-C subfamily target basophils, eosinophils, monocytes, and T lymphocytes.[236] The bronchial epithelium produces chemokines in both of these subfamilies, including IL-8, GROα, and GROγ of the C-X-C subfamily and MCP-1, MCP-4, eotaxin, and RANTES of the C-C subfamily.[237] IL-8, GROα, and GROγ mediate neutrophil chemotaxis and activation.[236] In addition, IL-8 has been reported to induce chemotaxis of T cells, cytokine-primed eosinophils, and cytokine-primed basophils, as well as stimulate the release of histamine and sulfidopeptide leukotrienes from primed basophils.[236] MCP-1 mediates monocyte and basophil chemotaxis and activation,[236] whereas RANTES induces chemotaxis of T cells, monocytes, and eosinophils.[237] Enhanced immunostaining of MCP-1 and RANTES has been detected in bronchial biopsies from patients with atopic asthma.[238]

Airway epithelial cells also produce several fibrogenic growth factors, including TGF-β,[236] platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF),[239] and cytokines that may exert pro-inflammatory effects, including IL-1, IL-6, and TNF-α.[236] TGF-β appears to regulate bronchial epithelial cell growth and differentiation, as well as modulate leukocyte recruitment and activation.[236] PDGF, bFGF, and IGF have been postulated to be involved in the remodelling of the airways in chronic asthma.[239] IL-6 promotes B cell immunoglobulin production, T lymphocyte proliferation, and the differentiation of cytotoxic T cells, macrophages, and neuronal cells.[236] Moreover, it has recently been shown that overexpression of IL-6 in transgenic mice results in a CD4+, MHC class II+, B220+ lymphocytic infiltrate surrounding large and midsized airways that does not alter basal respiratory resistance but does diminish airway reactivity to methacholine.[240] Interestingly, IL-1 and TNF-α appear to amplify the inflammatory cascade in that IL-1β and/or TNF-α increase airway epithelial production of IL-6, IL-8, GROα, MCP-1, RANTES, GM-CSF, and granulocyte colony-stimulating factor (G-CSF).[231]

Glucocorticoids inhibit the production by epithelial cells of many of the cytokines and factors described above, including IL-1, IL-6, IL-8, IL-11, TNF-α, GM-CSF, and RANTES[231,237]; the inhibition of epithelial cytokine production may ultimately decrease inflammatory cell activation and recruitment and the associated generation of inflammatory mediators.

Glucocorticoids appear to increase the mRNA level and expression of neutral endopeptidase in cultured airway epithelial cells while decreasing the expression of the NK_1 receptor.[231] It has been reported that neutral endopeptidase (NEP) and the angiotensin-converting enzyme (ACE) mediate glucocorticoid inhibition of neurogenic inflammation in rat trachea.[241] The suppressive effects of dexamethasone on substance P–induced extravasation were completely reversed by simultaneously inhibiting NEP and ACE activities.[241] However, others have reported no effect of glucocorticoids on NEP expression,[242] suggesting that the inhibitory effects of glucocorticoids on neurogenic inflammation may, in part, be due to the inhibition of the expression of NK_1 receptors. The NK_1 receptor has an AP-1 response element in its promoter, indicating that an activated GR may interact with AP-1 to down-regulate transcription of this gene.[231]

The expression of adhesion molecules on airway epithelial cells facilitates their interaction with the underlying substratum and adjacent cells, thereby forming functional permeability barriers. To this end, epithelial cells express various types of integrin receptors, including $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_6\beta_1$ collagen-laminin receptors and $\alpha_v\beta_1$ fibronectin-fibrinogen receptors.[243] In addition, the epithelium may also interact with inflammatory cells through adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and VCAM-1. TNF-α and IL-1β up-regulate ICAM-1 and VCAM-1 expression, which may be important in the migration of neutrophils and eosinophils into the lumen of the airway.[243] Expression of VCAM-1 by airway epithelial cells is inhibited by exposure of the cells to glucocorticoids.[244,245] As described above, TNF-α and IL-1β activate the transcription factor NF-κB in airway epithelial cells.[246] Recent evidence indicates that the glucocorticoid-mediated repression of the ICAM-1 promoter is due to the interaction of GR with the NF-κB family member RelA.[48]

Although the mechanisms by which steroids improve bronchial hyperresponsiveness are incompletely understood (see below), airway epithelial activation is now implicated. The increased awareness of the proinflammatory effects of epithelial cells and the accessibility of epithelial cells to inhaled steroids make the airway epithelium a prominent candidate among potential steroid targets. Glucocorticoids either directly or indirectly modulate the production, release, and/or actions of epithelial-derived inflammatory factors, which may, in part, explain the great efficacy of these drugs in the treatment of asthma.

TISSUE REPAIR PROCESSES

Prolonged administration of glucocorticoids in the perioperative period leads to a delay in wound healing and an increase in local wound complications, whereas short-term steroid treatment has little impact on these events.[247] Possible sites of steroid action include: (1) the exudation and cell recruitment phase, (2) activation and proliferation of recruited cells, (3) angiogenesis, and (4) fibroplasia and repair processes. The effects of steroids on cell recruitment and proliferation have already been discussed. Because many of the stimuli that are responsible for tissue repair and new blood vessel growth arise from macrophages (including macrophage angiogenesis factor, macrophage-derived growth factor, epidermal growth factor, and fibroblast growth factor), a blunting of angiogenesis by steroids may be related to the inhibition of growth factor production.[173,247] Both angiogenic and angiostatic chemokines have been described.[248] The effects of steroids on these chemokines may ultimately influence new blood vessel growth. Further, angiostatic effects of some glucocorticoids have been shown to occur via a receptor distinct from the glucocorticoid receptor.[249,250] Effects of steroids on fibroblast growth and fibroblast- dependent repair processes are controversial, although steroids appear to inhibit these events.[247,251,252] Fibroblast generation of the cytokines GM-CSF, IL-8, and IL-6, which may participate in tissue repair processes, is inhibited by steroids.[253] Interestingly, the synthesis of hyaluronic acid is inhibited by steroids at much lower concentrations in skin fibroblasts than in lung fibroblasts, perhaps explaining why steroids do not seem to cause tissue atrophy in airways as is observed in the skin.[254]

ADRENERGIC SYSTEM

It has long been known that adrenalectomized animals have reduced or absent responses to epinephrine or norepinephrine (e.g., vascular responses or effects on glucose metabolism and circulating eosinophil numbers). Such adrenergic responses are restored in adrenalectomized animals by the administration of steroids.[255,256] Many patients with asthma also display significantly reduced responsiveness to adrenergic agents when measured in vitro (e.g., lymphocyte or neutrophil cyclic adenosine monophosphate [cAMP] responses to isoproterenol) or when measured in vivo (e.g., bronchodilating effects of inhaled β agonist or increased pulse pressure with injected catecholamine).[257-261] Reduced β-adrenergic responses are most often seen in severe asthmatic patients, who are often receiving treatment with inhaled catecholamines. Because the administration of catecholamines produces tachyphylaxis (desensitization) to catecholamine responses, it has been somewhat problematic to distinguish between inhaled catecholamine-induced desensitization and a disease-related decrease in adrenergic responses independent of therapeutic administration of catecholamines.[262-265] In either case it is clear that steroid administration reverses the reduced β-adrenergic responsiveness in asthmatic patients.[260,262-264] In vivo administration of steroids restores the cAMP response in lymphocytes or neutrophils from asthmatic subjects by increasing β-receptor numbers and by increasing the efficiency of coupling of β receptors to the adenylate cyclase.[263,264] Treatment with steroids in vivo also dramatically improves the response to inhaled β-adrenergic agents in patients who are resistant to inhaled β-adrenergic bronchodilators.[260,262] Finally, other systemic effects of catecholamines, including glucose mobilization and increased pulse pressure, are restored to normal levels by administration of steroids.[264] In vitro, steroids increase β-adrenergic receptor mRNA twofold to a new steady-state level, associated with a fourfold increase in transcription rate. Several investigators have reported that glucocorticoids up- regulate the expression of β_2-adrenoreceptors by increasing the rate of β_2-adrenoreceptor gene transcription and possibly by binding to multiple GRE sequences found within the β_2-adrenoreceptor promoter.[231] This action of glucocorticoids may counteract the down-regulation of

β_2-adrenoreceptors in response to prolonged β_2-agonist treatment. Desensitization with isoproterenol decreases the half-life of receptor mRNA from 12 hours to 5 hours.[266,267] Desensitization of β-adrenergic responses is dependent on the genotype of β_2 receptors a given individual expresses.[268] Adrenalectomy is associated with a decrease in G protein β subunits, and this effect is reversed by steroids.[269] In human lung mast cells, steroids antagonize β-adrenergic agonist-induced desensitization.[270]

ARACHIDONIC ACID METABOLISM

Arachidonic acid is a 20-carbon unsaturated fatty acid with four double bonds that is stored in membrane phospholipids and neutral lipids. It is a precursor for both leukotrienes and cyclooxygenase metabolites, which are important inflammatory mediators. Arachidonic acid is liberated from the sn-2 position of both 1-acyl and 1-alkyl phospholipids by the action of the enzyme phospholipase A_2.[271,272] In some cell types, arachidonic acid may also be liberated by the combined action of a phospholipase C and a diglyceride lipase.[273] Once liberated, arachidonic acid is metabolized by cyclooxygenase enzymes to produce a variety of prostaglandins, thromboxane, and prostacyclin, or by the combined action of 5-lipoxygenase activating protein (FLAP) and the 5-lipoxygenase to produce LTA_4, the precursor to LTB_4, and the sulfidopeptide leukotrienes, LTC_4, LTD_4, and LTE_4.[274] Other lipoxygenase products of arachidonic acid include mono- and diHETEs and lipoxins. Phospholipase A_2 also produces the lysolipid precursor of PAF (1-alkyl glyceryl phosphocholine), which is converted to PAF by the action of an acetyltransferase enzyme.[275] Activities of arachidonic acid metabolites relevant to inflammatory responses include chemotaxis, stimulation of mucous secretion, constriction of smooth muscle in airways, regulation of vascular tone and permeability, activation of leukocyte secretion, regulation of neuronal activity, and regulation of cell proliferative events.[212,274,276] Antiinflammatory steroids inhibit the formation of arachidonic acid metabolites (and the PAF precursor, lysoPAF) in vitro in many tissues by blocking the release of arachidonic acid from phospholipid stores.[219,277-280] In some cell systems the apparent decrease in arachidonic acid release caused by steroids may result from effects on protein synthesis or increased reacylation of arachidonic acid rather than decreased release through phospholipase inhibition.[281,282] In some cases, steroids can inhibit prostanoid release by decreasing the expression or induction of the cyclooxygenase enzyme.[283] Not all cell and tissue types respond to steroid treatment in this manner. Further, in a given cell type, this effect of steroids may be stimulus-dependent. Inhibition of the release of arachidonic acid metabolites is likely to be important in the antiinflammatory actions of steroids. Systemic steroid treatment does not consistently reduce the levels of arachidonic acid metabolites in vivo, suggesting that inhibition of arachidonic acid release is not a universal effect of steroids.[284]

MECHANISMS OF STEROID ACTION IN ALLERGIC DISEASES

Rhinitis

Allergic rhinitis represents one of the most common allergic diseases and is readily amenable to experimental study. Many double-blind crossover studies have been performed to establish the efficacy of treatment with topical or systemic corticosteroids. The mechanisms of rhinitis are rapidly being elucidated because of the accessibility of the target organ, the nose. Insofar as rhinitis and asthma are related, such studies yield useful information relating to mechanisms of asthma. (It has been suggested that in fact the nose is "that part of the lung accessible to the finger.") Because the nose represents a mucosal surface, it is relatively easy to study mucosal cell types, as well as cell types that enter the lumen of the nasal cavity. Furthermore, nasal lavage allows analysis of inflammatory mediators that are released during nasal allergen challenge.[285] Nasal mucosal tissue from allergic subjects contains substantially higher numbers of mucosal mast cells than in nonallergic controls.[92,94-98] This is probably related to a higher number of mast cell precursors found in the circulation of allergic subjects, and also to local production of mast cell growth factors and chemotactic factors in the nasal mucosal tissue.[286,287] Allergic individuals also have elevated basophils in nasal secretions.[96]

Experimental antigen challenge in the nose produces symptoms of rhinitis, including sneezing, rhinorrhea, and edema. In approximately 50% of allergic subjects challenged with 1000 PNU of an antigen to which they are sensitive (e.g., grass or ragweed), a late phase reaction occurs from 4 to 12 hours after the antigen challenge.[288,289] During the late phase reaction, rhinorrhea, nasal stuffiness, and sneezing reoccur, accompanied by an influx of inflammatory cells.[322,323] Further, a priming phenomenon, in which the amount of antigen required for the response is reduced by tenfold to 100-fold, is observed.[290] The relationship of this experimental priming to the priming (or increased antigen responsiveness) seen during the later part of the allergen season in rhinitis patients is at present unknown.[291,292]

Lavage of the nasal cavity after experimental allergen challenge in allergic subjects reveals elevated levels of mucous glycoproteins, histamine, prostaglandin D_2, leukotriene C_4, kinin, mast cell tryptase, and tosyl arginine methyl ester (TAME) esterase, a nonspecific protease activity.[285] Nonallergic subjects challenged with the same antigen show none of the mediators and fail to display symptoms. In challenged allergic subjects, a second wave of mediator release occurs during the late phase in which all of the above mediators, with the exception of tryptase and prostaglandin D_2, are elevated in nasal secretions.[288] Large numbers of eosinophils and neutrophils and significant numbers of basophils infiltrate the nasal cavity during the late phase reaction.[293] The renewed onset of symptoms and mediators is probably related to the cellular infiltrate that occurs. Stimuli that activate the infiltrating cells are as yet unknown. Histamine-releasing factors have been detected in nasal lavages, as well as late phase skin blister fluids, suggesting that release of histamine and other mediators may be initiated during the late phase by these factors.[294]

Oral steroids are extremely effective as a treatment of rhinitis.[295] Brief oral steroid treatment is sometimes used when severe nasal obstruction is present in rhinitis to rapidly alleviate symptoms.[37] However, the symptoms of rhinitis are seldom severe enough to justify the sustained use of oral steroids with their concomitant systemic side effects. Early studies demonstrated efficacy of topical treatment with hydrocortisone or dexamethasone. However, effective treatment with these steroids required the use of doses that produced systemic side effects, including HPA suppression.[296,297] The safety and efficacy of topically active synthetic steroid treatment in rhinitis has clearly been established.[296,298-300] Topical steroid treatment is useful in reducing symptoms and recurrence of nasal polyposis.[301] Although the efficacy of topical nasal steroids in vasomotor rhinitis is controversial, in any given case a trial is warranted. Medical observations indicate no inhibition of HPA axis function or other systemic toxicity when these latest-generation topical nasal steroids are used in recommended dosages.[302] Although *Candida* colonization is a significant problem with inhaled steroids, it is not with topical nasal steroids.[303,304]

The question of the mechanism of action of glucocorticoids in rhinitis has been addressed experimentally, revealing differences between topical and oral administration of drug.[305,306] Two-day treatment with oral steroids preceding experimental challenge with antigen demonstrates no inhibition of the acute phase response after challenge and nearly complete inhibition of the late phase.[305] The oral steroid treatment failed to inhibit the appearance of mediators, especially mast cell mediators, such as histamine and prostaglandin D_2, during the acute phase response, whereas it completely inhibited the late phase appearance of mediators and reduced the priming response as measured by mediator release and symptoms.[305] Treatment with topical steroids (1 week or longer) inhibits the acute phase response as measured by symptoms and the appearance of mediators.[306] Like oral steroid treatment, topical steroids also inhibit the late phase symptoms, appearance of mediators, and priming. Pretreatment time as brief as 48 hours before challenge is adequate for inhibition of these parameters.[307]

In contrast to antigen-induced reactions, cold dry air–induced nasal histamine release was inhibited, whereas neither TAME esterase release nor symptoms was affected.[308] Studies in which tissue was taken from topical steroid–treated patients have demonstrated a reduction in the number of mucosal mast cells on or near the surface of the nasal mucosa, whereas the number of mast cells in biopsies (which include mostly submucosal tissues) were unaltered (see above).[94-98] Whether the ability to release histamine of mast cells remaining in biopsies or mucosal scrapings is impaired after topical

steroid treatment is controversial. The reduced appearance of mast cell mediators in nasal lavage after antigen challenge in topical steroid–treated subjects probably results from reduced numbers of mast cells in the mucosa rather than reduced release of mediators from those mast cells present.[82,97,309-311] These studies further suggest that the critical mast cell type in the acute antigen response in experimental rhinitis is the mast cell that resides in the mucosa, that is, the mast cell type elevated in allergic subjects.

With regard to the cellular infiltrate, and, as discussed above, both topical and oral steroids reduce the influx of leukocytes into the nasal cavity.[293] The appearance of cytokine mRNA-positive T cells and other cells expressing proinflammatory cytokines is inhibited by glucocorticoid treatment before antigen challenge. Analysis of cytokine mRNA-positive cells by in situ hybridization revealed modest elevations of IL-4–positive and IL-5–positive cells in the nasal mucosa of grass pollen–sensitive subjects outside of the allergen season compared with normal controls. Experimental challenge with allergen produced typical acute responses and late phase responses characterized by a significant (approximately threefold to fourfold) increase in IL-4– and IL-5–positive cells. Prior treatment for 6 weeks with fluticasone propionate had a modest inhibitory effect on the increase of IL-5–positive cells and substantially reduced the IL-4–positive cells, associated with a decrease of CD25-positive cells in the nasal mucosa. The decrease in IL-4–positive cells correlated with a decrease in eosinophils that was also observed.[312]

Asthma

Asthma is a serious, sometimes fatal, and often debilitating disease that affects over 10 million Americans.[313,314] There are many drugs that are effective in the therapy of asthma but none so effective as the glucocorticoids. In fact, were it not for their undesired side effects, the steroids would be the only therapy used for the treatment of this disease. In the lungs of patients who have died of asthma, there is epithelial shedding, the normal columnar epithelium being replaced by stratified epithelium, copious quantities of mucus, smooth muscle hyperplasia, and dead and dying eosinophils and eosinophil proteins at areas of epithelial destruction and in the lumen of the airway.[315] The thickened basement membrane observed in asthma may represent subepithelial fibrosis.[316] These changes are also seen in biopsies of the airways of asthmatic subjects.[317] One hallmark of asthma is nonspecific hyperreactivity of the airways to inhalation (or, in some cases, intravenous) challenge with histamine, methacholine, adenosine, $PGF_{2\alpha}$, leukotrienes, and a host of other stimuli.[318] Lavage of the airways of asthmatic patients reveals increased numbers of mast cells in the BAL fluid; the numbers of mast cells and eosinophils and the levels of eosinophil proteins and histamine in lavage correlate with the severity of asthma, as indicated by either FEV_1 or the hyperreactivity of the airways to inhaled histamine or methacholine.[318-324] The correlation of mast cells in lavage and bronchial hyperreactivity is also seen in basenji greyhounds, a natural animal model of allergic asthma.[319] The correlation of asthma severity and quantities of eosinophils in lavage and in blood suggests that hyperreactivity of the airways is related to inflammation and the local appearance (and presumably activation) of eosinophils, mast cells, and other leukocytes.[320-328] The destruction of epithelium and shedding of epithelial cells into the lumen of the airways result in large part from eosinophil deposition of major basic protein in the epithelial region.[327] Treatment with the inhaled steroid budesonide had no effect on resting eosinophil levels in lavage fluid but did decrease the eosinophil-derived protein eosinophil chemotactic protein (ECP).[91] Mucous secretions result from stimulation of mucous glands and goblet cells by arachidonic acid metabolites (both pathways), cytokines, C3a, macrophage-derived mucous secretagogue, and other mediators, in addition to possible neuronal pathways.[329-332]

Several studies have addressed the immunologic basis of asthma. Increases of bronchial hyperreactivity are associated with an increased frequency of eosinophil and basophil progenitors in the blood 24 hours after antigen challenge of the airways.[192] In one study, asthmatic subjects had elevations in circulating CD4 cells expressing the IL-2 receptor, human leukocyte antigen-DR (HLA-DR) and VLA-1 compared with controls.[161] These subjects also had elevations of circulating IFN-γ and soluble IL-2R. Interestingly, after several days of treatment with steroids (combined with other medications), all of the above parameters returned toward normal in association with an improvement of FEV_1. In a similar study, oral steroid treatment was found to reduce T cells expressing CD45, HLA-DR, and CD45RO and decreased plasma IL-5 levels in association with a fall in peripheral blood eosinophil counts.[333] Biopsy, combined with immunohistochemical or in situ hybridization techniques, has also been very useful in describing the immunologic characteristics of asthma. Although earlier studies had suggested elevations of mucosal mast cells in asthma,[317,334,335] subsequent studies have not; however, evidence of increased mast cell degranulation has been presented.[336,337] Several groups have reported elevated numbers of activated eosinophils in biopsies of asthmatic subjects.[162,336-338] Inhalation of budesonide for 4 weeks has been shown to decrease biopsy mast cell and eosinophil numbers and decrease free eosinophil granules in asthmatic subjects.[212] Increased numbers of activated lymphocytes have been observed in bronchial biopsies of asthmatic patients; these cells are activated to a higher degree than in normals, based on expression of the IL-2 receptor, CD25.[337-339] Correlations between lymphocytes, eosinophils, and bronchial reactivity have been observed in biopsy studies.[337,338] Evidence has been obtained that airway lymphocytes produce mRNA for several proinflammatory cytokines, including IL-4, GM-CSF, IL-5, and IL-13 in asthmatic subjects, and for GM-CSF after antigen challenge.[78,80,162,211]

The effects of glucocorticoids on the appearance of cytokine mRNA and protein in the airways has been examined. An immunohistochemical study showed that inhaled BDP inhibits the expression of GM-CSF and IL-8 in airway epithelium.[340] Another study found that 6 weeks' treatment with prednisolone significantly attenuated bronchial hyperreactivity and reduced BAL eosinophil counts. The steroid treatment was found to decrease the number of cells positive for mRNA for IL-4 and IL-5, as determined by in situ hybridization.[160] Interestingly, IFN-γ–positive cells increased after steroid treatment. In a followup study, the effect of glucocorticoid treatment on the presence of mRNA-positive cells expressing IL-12 and IL-13 was determined.[164] Asthmatic subjects had increased basal IL-13–positive cells and decreased basal IL-12–positive cells compared with normal subjects. Treatment with glucocorticoids normalized both IL-13– and IL-12–positive cells. That is to say, the number of IL-12–positive cells increased in subjects being treated with glucocorticoids. This is notable because IL-12 has been found to be a regulatory cytokine that turns down Th2 responses, probably via its ability to induce expression of IFN-γ. This finding agrees nicely with the steroid-induced increase in IFN-γ–positive cells.[160] Whether the increase in IL-12–positive cells by glucocorticoid treatment is a direct stimulation of IL-12 expression by the steroid, or is indirect, resulting from a down-regulation of other cytokines that suppress Th1 responses, such as IL-4 or IL-13, is unknown.

In vitro studies indicate that glucocorticoids inhibit the release of most chemokines, including those that attract eosinophils, such as MCP-3, MCP-4, eotaxin, and RANTES.[237] The effects of glucocorticoids on eotaxin-2 are still unknown. Several studies have shown expression of some of these chemokines in asthmatic patients or after allergen challenge in the lungs, nose, or skin.[375-379] Intranasal BDP was found to inhibit the appearance of several cytokines, including MIP-1α and RANTES, in allergen-challenged subjects.[345]

Those patients with the most hyperreactive airways are generally the patients that require treatment with corticosteroids, as a result of having the most severe asthma symptoms. Although an individual subject's responsiveness to inhalation challenge testing is relatively stable over time, in allergic asthmatic subjects such reactivity can increase during the pollen season.[346] The mechanism of bronchial hyperreactivity in asthma is as yet undetermined; however, a substantial amount of experimental clinical work has been done to address this issue[347] (see Chapter 60).

Because bronchial hyperreactivity is correlated with the severity of asthma, and because those patients who require steroid therapy tend to be those with the most hyperreactive airways, there is the general impression that steroids must work by reducing the reactivity of the airways to nonspecific stimuli.[348] Although some studies report no effect of steroid treatment on bronchial reactivity,[349-353] most studies report a reduction in bronchial hyperreactivity, albeit a modest one.[354-363] Prolonged, aggressive treatment with inhaled steroids has been reported to produce a profound improvement in airways hyperre-

activity.[364] These experiments have usually been performed using patients that do not require steroid treatment for management of their asthma and therefore do not have the most severe asthma or bronchial hyperreactivity. In many of these studies, great efforts were made to control experimentally for other effects of the steroid, such as an increase in basal lung volume and resting FEV_1. Although a twofold to fourfold improvement in bronchial reactivity is usual with inhaled steroid, the question of whether a decrease of airways reactivity is a major effect of steroids has yet to be resolved. It is possible that the combination of a relatively small change in airways reactivity with reduced appearance of bronchospastic mediators can synergize and contribute to the profound improvement of lung function after steroid therapy.

The efficacy of steroids or ACTH in the therapy of asthma was recognized in the first studies.[365-370] Improvement of pulmonary function in asthmatic patients by treatment with corticosteroids occurs within hours or, in some cases, days of initiation of treatment; this delay results from the requirement for protein synthesis (see above) and the need to reverse ongoing inflammation.[371,372] As in the skin and the upper airways (i.e., in the nose), experimental allergen challenge by inhalation produces a biphasic response in allergen-sensitive subjects.[289,373] The mast cell, presumably by release of bronchoconstrictors such as histamine and leukotrienes, is likely to be a key effector cell in the acute narrowing of the airways in response to antigen inhalation.[374] The relative roles of alveolar, intraepithelial, and subepithelial mast cells in producing the acute response are unclear. Many, but not all, studies have demonstrated that treatment with oral steroids for days to weeks produces no effect on the acute response to antigen inhalation challenge, while blunting or entirely eradicating the late phase pulmonary response.[306,375-381] In contrast, treatment for 2 to 4 weeks with a topical steroid such as budesonide or beclomethasone dipropionate blunts both the acute and late responses.[382,383] Shorter treatment times with topical steroid (i.e., less than a day) have no effect on the acute response but still block the late phase response.[384]

Because inflammation of the airways contributes heavily to the symptomatology of asthma, the antiinflammatory effects of steroids are key.[385] With regard to asthma, these effects can be classified into distinct activities that include the following:

1. *Inhibition of the secretion of growth factors and other mediators.* Glucocorticoids inhibit the release of factors responsible for the proliferation and activation of cells that play a role in asthma including lymphocytes, eosinophils, mast cells, basophils, and fibroblasts.* Factors for which inhibitory effects of steroids on synthesis have been demonstrated include IL-1 through IL-6, IL-8, IL-13, and IL-16; GM-CSF, TGF-α, and FGF. Steroids also inhibit the release of preformed mediators from macrophages (enzymes, including elastase, collagenase, and plasminogen activator) and basophils (histamine).[136,184] They do not inhibit the release of mediators from human neutrophils, eosinophils, or mast cells.[310,387,388] The effects of steroids on platelet function are presumed to be nonexistent because these cells do not contain a nucleus and are theoretically incapable of exhibiting a glucocorticoid effect. Finally, glucocorticoids inhibit secretion of mucus in the airways.[389] This occurs both directly and by reducing the amount of mucous secretagogues present in the airways.
2. *Enhancement of the production of regulatory molecules.* Steroids induce two cytokines in vivo that down-regulate Th2 cells: IFN-γ and IL-12. They also induce expression of the "decoy" IL-1 receptor, IL-1RII, which can act as a "sink" for IL-1. Steroid treatment increases the ratio between IL-1Ra, an antagonist of IL-1, and IL-1β in the airways. Steroids also induce secretory leukocyte protease inhibitor (SLPI) and PDGF, a cytokine involved in wound healing.[45,390,391]
3. *Inhibition of the release of arachidonic acid metabolites and PAF.* In addition to producing hyperreactivity, many of these stimuli directly constrict the airways.[382,392,393] Thus inhibition by steroids of the production of leukotrienes and bronchoconstricting prostaglandins can help relax the airways. Because these mediators also produce edema, cause mucous secretion, are active chemoattractants, and contribute to accumulation of leukocytes, and so on, inhibition by steroids of production of arachidonate metabolites and PAF may contribute to their antiasthmatic action.[274-276,394] Insofar as PAF and arachidonic acid metabolites are important in producing bronchial hyperreactivity, inhibition of their release will prevent further increases in hyperreactivity and possibly blunt ongoing hyperreactivity.
4. *Inhibition of the accumulation of leukocytes in lung tissue.* As discussed at some length above, steroids inhibit leukocyte accumulation, probably largely by reducing the release of factors that recruit leukocytes, including IL-1, IL-4, IL-13, TNF, and chemoattractants such as arachidonate metabolites, eosinophil-active chemokines (RANTES, MCP-3, MCP-4, eotaxin), IL-8, and PAF.
5. *Synergism or permissive effects on adrenergic responses.* The reversal of catecholamine hyporesponsiveness by treatment with steroids is probably of importance in the therapy of asthma when such therapy uses β agonists and may also be important in the efficacy of steroids alone, to the extent that endogenous catecholamines regulate airway function.
6. *Decreased vascular permeability.* Reduction of the edema associated with inflammation of the airways results from direct effects on vascular permeability responses, reduced vasopermeability-inducing factors, and reduced leukocyte accumulation.[395]
7. *Inhibition of neuropeptide-mediated responses.* Steroids inhibit vascular and other responses to neuropeptides, possibly by increasing the catabolism of these peptides via induction of neutral endopeptidase, as well as by direct antagonism of end organ responses.[227-229]
8. *Alteration in the secretion of glycoconjugates and surfactants.* Steroids can improve lung function by inhibiting mucus glycoprotein secretion[396,397] and stimulating the production of major surfactant-associated proteins.[398-400] This latter effect may partially explain the efficacy of steroids in the respiratory distress syndrome associated with premature delivery.

The main goal of therapy with steroids is to restore lung functions maximally at the cost of a minimal amount of undesired side effects.[401-403] Many strategies have been developed toward this goal.

Initial attempts to treat asthma with topical steroids used hydrocortisone or dexamethasone. The use of these steroids topically presents little advantage over their oral use because they are not catabolized quickly after swallowing, resulting in the majority of bioavailable steroid entering through the gastrointestinal tract anyway. Because these steroids are also well absorbed from the lungs, inhalation does not present advantages over oral administration and does not avoid undesired systemic effects. With the advent of high-affinity topical corticosteroid preparations (see Figure 46-2), which are extensively metabolized after absorption from the gastrointestinal tract, this treatment modality has become feasible as a means of reducing systemic side effects while still maintaining adequate asthma control. The use of topical (i.e., inhaled) steroids for asthma was initially confined to the treatment of mild-to-moderate asthma. This was largely because of the low doses that were delivered by the formulations available. Higher-dose inhaled steroid regimens are now being used with good success in more severe asthma cases or during exacerbations in some cases.[402,404] It has been demonstrated that for a given amount of antiasthmatic efficacy, the development of systemic side effects (e.g., HPA suppression) is greater with oral steroids (approximately fourfold).[37,402,405,406] High-dose preparations of inhaled steroids have become more widely available, and it is expected that this trend will continue because of reduced side effects for comparable efficacy. Two potent inhaled glucocorticoids, fluticasone propionate and budesonide, are now available in the United States and have been successfully used to treat moderate and severe unstable chronic asthma.[402,406-408]

Although inhaled steroids, even at high doses, are superior to oral steroids with respect to efficacy vs. side effects, the trend toward use of higher-dose regimens has revealed that these inhaled steroids can produce similar side effects as caused by oral steroids. Side effects reported for inhaled steroids include HPA suppression, suppression of bone turnover, growth retardation, cataracts, dysphonia, and alterations in lipid and glucose metabolism.[403-405,409-413] In adults, 1 mg/day of BDP in four divided doses has been determined to be the threshold dose above which systemic effects on HPA function or leukocyte counts occur.[37] The threshold for systemic side effects may fall as low as 500

* References 75, 186-190, 196, and 386.

μg/day for fluticasone propionate (FP), a particularly potent steroid with a plasma half-life longer than average.[414] A large proportion of patients that previously required oral steroids can be successfully controlled on inhaled steroid treatment alone.[408,415] Effectiveness of inhaled steroids is related to the effectiveness of delivery (see Chapter 40). With many delivery systems, up to 80% of the steroid is deposited in the oropharynx. Slow inspiratory rates during administration of inhaled steroids and spacer units can aid in production of smaller particles and better penetration of drug to the distal airways. Such techniques also reduce the incidence of side effects in the oropharynx, such as candidiasis and dysphonia.[37,416-419] Oral steroids may be necessary in patients in whom inhaled steroids have proven to be inadequate in controlling asthma and in patients in whom practical considerations influence the decision (i.e., cost of the drug, ability to use the inhaler, compliance).[37]

It is not clear that the mechanism by which inhaled steroids function in asthma is the same as the mechanism of oral steroids. To be sure, the above listed steroid actions all must play a role in the action of topical steroids. It is possible that by maintaining or prolonging receptor-saturating concentrations of steroids in the airways that topical steroids have effects on local cell types that are not attained by oral steroid treatments. Thus topical steroids may reduce local synthesis of IgE or have a much greater effect in reducing numbers of mast cells and blood-derived leukocytes in the mucosa and in the airways. Because the mechanism by which steroids inhibit cellular accumulation appears to be local inhibition of the release of factors that recruit cells, topical steroids may be more effective in reducing cellular recruitment. In the final analysis, however, it must be acknowledged that topical steroids, even at high doses, may not be as effective as oral steroids in controlling the most severe cases of asthma, possibly because the aerosol cannot penetrate behind occluded airways, so delivery of the drug through the circulation is required. Also, there may be actions of steroids that are exerted systemically rather than locally that have relevance to their action in the lung. Such effects might include modification of bone marrow production of the formed and proteinaceous constituents of the blood, steroid modification of reflex actions involved in control of airway tone or secretions, and effects of steroids on the release of proinflammatory hormones or other mediators from sites distant from the lung. In some patients, oral steroids alone or in some combination with inhaled steroid are required for adequate control of symptoms. In such patients, combined oral and inhaled steroid treatment is more effective in controlling asthma than alternate-morning prednisone for a given amount of systemic effects on endogenous cortisol production.[420] The addition of inhaled steroid treatment confers a major reduction in the frequency of symptoms, disability, and risk of iatrogenic disease such as hypertension.[37]

In some cases, use of oral steroids is unavoidable. Oral corticosteroids should be administered to all asthmatic patients with symptoms of sufficient severity to require hospitalization.[36] Patients receiving inhaled steroid therapy must be immediately administered systemic steroid treatment when acute exacerbations of asthma appear. Multiple daily oral administrations of steroids are more likely to produce systemic side effects and are to be avoided if possible, in preference of single morning doses.[36,37] Asthmatic subjects with nasal polyps, hyperplastic sinusitis, or associated chronic bronchitis have higher dosage requirements of steroids than uncomplicated asthmatic subjects.[421] When daily or alternate-day oral steroid is not effective in controlling asthma, the physician can choose among several therapeutic options that include: (1) increasing the dose of steroid (e.g., prednisone) and rescheduling to a multidose daily regimen to gain control of the asthma, followed by a reduction in the dosing frequency to determine the minimal frequency required to control the asthma satisfactorily; (2) substituting a steroid such as dexamethasone, which is slowly metabolized and given once or twice daily; and (3) substituting methylprednisolone for prednisone to aid in identifying whether the individual patient is unable to adequately convert prednisone.

Exercise or hyperventilation can induce an acute narrowing of the airways in many asthmatic subjects. Exercise-induced bronchoconstriction represents a subset of asthma because many or most individuals who experience it have airway hyperreactivity and are asthmatic.[422] Some evidence suggests that exercise-induced bronchospasm may be the result of increased osmolarity of airway secretions, resulting in mast cell degranulation in the airways.[423,424] There may be a contribution of airway cooling to the response, and the relative influence of these two factors has not yet been resolved.[425] Exercise-induced bronchospasm is relatively recalcitrant to treatment with steroids, and this may reflect a major mast cell component in the response.[426,427]

Although status asthmaticus, the most severe and potentially lethal presentation of asthma, is not immediately improved by steroid treatment (because the delay in steroid effects occurs during a critical period), the prompt use of systemic steroids for treatment of acute asthma is recommended with the following rationale:

1. Failure to do so has been correlated with sudden death during severe asthma, and it is not possible to predict which patients presenting with asthma may suddenly die.
2. The risks of an acute treatment with a high dose of steroids are negligible.
3. Steroids increase arterial pulmonary oxygen tension.
4. Steroids augment the bronchodilator action of β-adrenergic drugs, which are clearly more important in the acute treatment of asthma.
5. Longer-term (i.e., hours to days) effects of steroid administration in reducing inflammation can aid in normalizing pulmonary function in patients experiencing acute asthma.[36,37]

Although a steroid of choice for such treatments has been parenteral methylprednisolone or hydrocortisone (e.g., hydrocortisone 500 mg/24 hours followed by 250 mg by injection or continuous drip every 6 hours for 24 hours),[371,428] recent studies indicate that oral prednisone or prednisolone may be equally effective and less costly.[39] The risk of sudden severe asthma relapse is increased by premature discontinuation of steroid treatment in the hospital or after discharge, or inadequate treatment at discharge.[429] Significantly lower relapse rates have been observed in patients who receive steroid (plus bronchodilator) treatment during an acute asthma attack than in patients treated with bronchodilators alone.[430,431] Intravenous methylprednisolone or hydrocortisone every 4 to 6 hours has been used to treat the asthma or laryngeal edema and prolonged hypotension that is associated with anaphylaxis.[432] Premedication with steroids has been used to lower incidence of radiocontrast dye reactions.[433,434]

It is clear that asthma and other allergic diseases result from the combined influence of a panoply of mediators, inflammatory cells, and pathogenetic mechanisms. As new information is obtained regarding these mechanisms, their relative importance will be determined in part by the influence that steroid treatment has on them. Once these mechanisms have been sorted out, it is hoped a rational strategy can be evolved to develop drugs that exert steroidlike effects on specific cellular/mediator targets in the absence of the side effects that result from the global glucocorticoid actions in homeostatic processes.

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Effects of Glucocorticoids on the Production of Inflammatory Cells

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Stress, Glucocorticoids, and the General Adaptational Syndrome

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Arachidonic Acid Metabolism

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Mechanisms of Steroid Action in Allergic Diseases

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