Glucocorticoid Therapy for Immune-mediated Diseases: Basic and Clinical Correlates

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Glucocorticoids are pleiotropic hormones that at the molecular level, glucocorticoids form complexes with specific receptors that migrate to the nucleus; this results in positive and negative modulation of several genes involved in inflammatory and immune responses. At the cellular level, glucocorticoids inhibit the access of leukocytes to inflammatory sites; interfere with the functions of leukocytes, endothelial cells, and fibroblasts; and suppress the production and the effects of humoral factors involved in the inflammatory response. Clinically, several modes of glucocorticoid administration are used, depending on the disease process, the organ involved, and the extent of involvement. High doses of daily glucocorticoids are usually required in patients with severe diseases involving major organs, whereas alternate-day regimens may be used in patients with less aggressive diseases. Intravenous glucocorticoids (pulse therapy) are frequently used to initiate therapy in patients with rapidly progressive, immunologically mediated diseases. The benefits of glucocorticoid therapy can easily be offset by severe side effects; even with the greatest care, side effects may occur. Moreover, for certain complications (for example, infection diathesis, peptic ulcer, osteoporosis, avascular necrosis, and atherosclerosis), other drug toxicities and pathogenic factors overlap with glucocorticoid effects. Minimizing the incidence and severity of glucocorticoid-related side effects requires carefully decreasing the dose; using adjunctive disease-modifying immunosuppressive and anti-inflammatory agents; and taking general preventive measures.


Dr. Dimitrios T. Boumpas (Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], National Institutes of Health [NIH], Bethesda, Maryland): Since 1949, when Hench and colleagues first introduced cortisone for the treatment of rheumatoid arthritis, glucocorticoids have revolutionized the treatment of immunologically mediated diseases. Although substantial complications associated with glucocorticoids have tempered enthusiasm for their use, they have remained the cornerstone of therapy for virtually all immunologically mediated diseases. In recent years, an explosion of new information has occurred relevant to both basic and clinical aspects of glucocorticoid therapy.

We describe the molecular mechanisms, sites of action, and effects of glucocorticoids on various cells involved in inflammatory and immunologically mediated reactions. Treatment principles are also provided with examples of specific glucocorticoid regimens in prototypical conditions. We also review selective complications of glucocorticoid therapy and discuss recent information about their pathogenesis and management.

Mechanisms of Action

Dr. George P. Chrousos (Chief, Pediatric Endocrinology Section, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, NIH, Bethesda, Maryland): Glucocorticoids exert most of their effects through specific, ubiquitously distributed intracellular receptors (1). The classic model of glucocorticoid action was described more than two decades ago and is briefly updated here (Figure 1, panel A). Glucocorticoids circulate in blood, is either in the free form or in association with cortisol-binding globulin. The free form of the steroid can readily diffuse through the plasma membrane and can bind with high affinity to cytoplasmic glucocorticoid receptors (the role of receptors primarily residing in the nucleus is controversial). The formation of the ligand-receptor complex is followed by its “activation” (that is, translocation into the nucleus and binding to what are called “receptor sites”). The bound complex modulates transcription of specific genes that encode proteins responsible for the action of glucocorticoids.

Glucocorticoid Receptors

In 1985, the complementary DNA of the human glucocorticoid receptor was cloned (2); it contains three main functional domains (Figure 1, panel B): first, the DNA-binding domain in the center of the molecule that recognizes specific sequences of the DNA called hormone-responsive elements; second, the ligand-binding domain in the carboxyl terminal region that interacts...
Figure 1. Mechanisms of glucocorticoid action. Panel A. Steroid hormone (S) circulates as a free molecule or as a complex with plasma-binding protein. After the steroid enters the cell, it binds to receptors (R) that reside in the cytosol complexed to heat-shock protein (HSP) and immunophilin (IP). Binding of the ligand to the complex causes dissociation of HSP and IP. The receptor-ligand translocates into the nucleus where it binds at or near the 5'-flanking DNA sequences of certain genes (glucocorticoid-responsive elements [GRE]). Receptor binding to the regulatory sequences of the responsive genes increases or decreases their expression. In the first instance (ON), glucocorticoids increase the transcription or stability or both of messenger RNA, which is translated on ribosomes to the designated protein. In the second instance (OFF), glucocorticoids repress (cross-hatched arrows) certain genes at the transcriptional level by interacting with and preventing the binding of nuclear factors required for activation of the gene (for example, activator protein (AP)-1 nuclear factor). In other instances, glucocorticoids exert their effects post-transcriptionally by either increasing the degradation of messenger RNA or by inhibiting the synthesis or secretion of the protein. Panel B. The three main domains (immunogenic, DNA-binding, and ligand-binding) of the glucocorticoid receptor represented in a linear model. At left are the indicated domains and amino acid sequences of the receptor (see text for details). HSP 90 = heat-shock protein 90; NLS\(_1\) and NLS\(_2\) = nuclear localization sequences 1 and 2; \(\tau_1\) and \(\tau_2\) = transactivation domains 1 and 2.
with the specific steroid; and third, the "immunogenic" domain in the amino terminal region.

The nonactivated glucocorticoid receptor resides in the cytosol in the form of a hetero-oligomer with other highly conserved proteins (3). This molecular complex comprises receptor, heat-shock proteins, and immunophilin (Appendix Table 1) (4). The binding of the receptor to the heat-shock protein 90 facilitates its interaction with the ligand (5). When the ligand binds, the receptor dissociates from the rest of the hetero-oligomer and translocates into the nucleus. Before or after the translocation, the receptor forms homodimers through sequences present in the DNA and ligand-binding domains (6).

Gene Regulation

After specific interaction with pore-associated proteins, the hormone-receptor complexes enter the nucleus through the nuclear pores (7). The interaction is facilitated by two nuclear localization sequences in the receptor, both in the ligand-binding domain. Inside the nucleus, the hormone-receptor complexes bind to specific glucocorticoid responsive elements within DNA (8). The complexes modulate the transcription rates of the corresponding glucocorticoid-responsive genes (9), apparently by stabilizing the initiation complex, composed of RNA polymerase II and its ancillary factors A through F. The hormone-receptor complex may interact directly with factor IIB (10), but it also interacts with other nuclear proteins to produce the conditions necessary for effective transcription (11). These proteins may be able to relax the DNA away from the nucleosome and thus make it easier for the polymerase to exert its effects. In addition, glucocorticoid receptors may interact with DNA-binding proteins that are associated with different regulatory elements of the DNA (12, 13). At least two such proteins have been described: One is the glucocorticoid modulatory element-binding protein and the other is the CACCC-box-binding protein. Both of these transcription factors potentiate the modulatory effects of glucocorticoids after transcription of specific genes.

Transcription appears to be important in the regulation of genes involved in growth and inflammation. Glucocorticoid response elements can act both positively and negatively on transcription, depending on the gene on which the complex acts (14, 15). One major way by which glucocorticoids exert down-modulatory effects on transcription is through noncovalent interaction of the activated hormone-receptor complex with the c-Jun/c-Fos heterodimer (16-18), which binds to the activator protein (AP)-1 site of genes of several growth factors and cytokines. The glucocorticoid-receptor complex prevents the c-Jun/c-Fos heterodimer from stimulating the transcription of these genes. Another mechanism by which glucocorticoids may suppress gene transcription is by an interaction between the hormone-receptor complex and glucocorticoid response elements that are in close proximity to responsive elements for other transcription factors (19). Thus, the promoter region of the glycoprotein hormone-α subunit, which is stimulated by cyclic AMP through the cyclic AMP-responsive element, contains a glucocorticoid response element in close proximity, so that when the receptor dimer binds to its own element, it hinders the cyclic AMP-binding protein from exerting its stimulatory effect on that gene.

Post-Transcriptional Effects

In addition to modulating transcription, glucocorticoids also have effects on later cellular events, including RNA translation, protein synthesis, and secretion. They can alter the stability of specific messenger RNAs of several cytokines and other proteins, thereby altering the intracellular steady-state levels of these molecules (20, 21). This may occur through modulation of transcription of still unknown proteins that bind RNA and alter its translation and degradation rates. Also, glucocorticoids influence the secretion rates of specific proteins through mechanisms that have not yet been defined. Finally, the receptor itself has guanylate cyclase activity, and glucocorticoids can rapidly alter the electrical potential of some cells (22, 23).

Anti-inflammatory and Immunosuppressive Effects

Dr. Dimitrios T. Boumpas: Although the cause and pathogenesis of many immunologically mediated diseases are not completely understood, it is known that the localization of leukocytes at sites of inflammation, their subsequent activation, and the generation of secretory products contribute to tissue damage, as shown in Figures 2 and 3 (24-26). Glucocorticoids inhibit the access of leukocytes to inflammatory sites, interfere with their function and the function of fibroblasts and endothelial cells at those sites, and suppress the production and the effects of humoral factors. In general, leukocyte traffic is more susceptible to alteration by glucocorticoids than is cellular function; in turn, cellular immunity is more susceptible than humoral immunity to these agents.

Even though the effects of glucocorticoids on the different types of inflammatory cells will be discussed separately, each cell type is actually involved in complex interactions with other cells. Glucocorticoids affect many, if not all, the cells and tissues of the body, thus provoking a wide range of changes that involve several cell types concurrently.

Effects on Nonlymphoid Inflammatory Cells

Dr. Ronald L. Wilder (Chief, Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland): Glucocorticoids are among the most potent anti-inflammatory agents available in clinical medicine. Pharmacologic doses of glucocorticoids dramatically inhibit eduction of plasma and accumulation of leukocytes at sites of inflammation. Several factors influence the magnitude of these effects, including the dose and route of administration of the glucocorticoids used, as well as the type and differentiation state of the target cell population (27). Several host variables also modify the anti-inflammatory response to glucocorticoids. For example, some persons (those with active systemic lupus erythemato-
sus) appear to have an accelerated rate of glucocorticoid catabolism (28). Various levels of target tissue resistance may exist in some patients with systemic lupus erythematosus and rheumatoid arthritis (29). These factors, alone or in combination, may explain the observation that different patients and diseases have variable therapeutic responses to glucocorticoids (30, 31).

**Macrophages**

Glucocorticoids antagonize macrophage differentiation and inhibit many of their functions (27). These agents 1) depress myelopoiesis and inhibit expression of class II major histocompatibility complex antigens induced by interferon-γ; 2) block the release of numerous cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α; 3) depress production and release of proinflammatory prostaglandins and leukotrienes; and 4) depress tumoricidal and microbicidal activities of activated macrophages.

**Neutrophils**

The major effect of glucocorticoids on neutrophils appears to be the inhibition of neutrophil adhesion to endothelial cells. This effect diminishes trapping of neutrophils in the inflamed site and probably is responsible for the characteristic neutrophilia. At pharmacologic doses, glucocorticoids only modestly impair important neutrophil functions, such as lysosomal enzyme release, the respiratory burst, and chemotaxis to the inflamed site. Lower doses do not affect these neutrophil functions (27, 30).

**Eosinophils, Basophils, and Mast Cells**

Just as they affect macrophages, glucocorticoids decrease circulating eosinophil and basophil counts. They also decrease the accumulation of eosinophils and mast cells at sites of allergic reactions. Functionally, glucocorticoids inhibit IgE-dependent release of histamine and leukotriene C4 from basophils, and they also inhibit degranulation of mast cells (27).

**Endothelial Cells**

These cells form the barrier between the blood and the tissues and are critical regulators of the inflammatory cascade. They affect hemosis, vascular permeability, trapping, and exudation of leukocytes into inflammatory sites. Glucocorticoids have profound effects on the activation and subsequent function of these cells (27) and clearly inhibit vascular permeability. Moreover, they inhibit numerous molecular events associated with activation. For example, they inhibit up-regulation of the expression of class II major histocompatibility complex antigens, as well as endotoxin-induced up-regulated expression of the adhesion molecules (endothelial leukocyte adhesion molecule-1 [ELAM-1] and intercellular cell adhesion molecule-1 [ICAM-1]), which are cell surface molecules critical to leukocyte localization (24–26, 32) (see Figure 3). Further, glucocorticoids in-
Figure 3. Cellular adhesion molecules. Several adhesion molecules participate in the binding of leukocytes to endothelial cells (25, 26). These molecules belong to at least three groups of glycoproteins: immunoglobulin supergene families, integrins, and selectins. Members of the immunoglobulin supergene family (intercellular cell adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]) are found exclusively on the endothelial cells. Their counter-receptors on leukocytes belong to the integrin group of adhesion molecules (lymphocyte (leukocyte) function-associated antigen-1 [LFA-1], very late antigen-4 [VLA-4]). Members of the selectin group (endothelial leukocyte adhesion molecule-1 [ELAM-1], sialyl Lewis X) group can be found in both cell types. These adhesion molecules mediate the initial tethering and subsequent shear-resistant attachment of leukocytes to the endothelium as well as their penetration into the inflamed tissue. The cytokines interleukin-1, tumor necrosis factor-α, and interferon-γ are also involved in this process through the activation of endothelial cells and the induction of adhesion molecules on their surface. Activated endothelial cells secrete interleukin-8 and other chemotactic cytokines that further stimulate the extravasation of leukocytes bound to endothelial cells.

hbit the secretion of the complement pathway proteins C3 and factor B; they also inhibit the formation of interleukin-1 and arachidonic acid metabolites and are potent inhibitors of the expression of cyclooxygenase type 2.

**Fibroblasts**

These cells contribute to the inflammatory process and are major targets of glucocorticoids (27). At supraphysiologic concentrations, glucocorticoids suppress proliferation and suppress growth factor-induced DNA synthesis and protein synthesis, including synthesis of collagens. They induce fibronectin messenger RNA transcription, inhibit interleukin-1, inhibit tumor necrosis factor-α-induced metalloproteinase synthesis, and inhibit arachidonic acid metabolite synthesis. They are also potent inhibitors of the up-regulated expression of cyclooxygenase type 2 (Crofford L, Wilder R, Hla T. Unpublished observations). These observations suggest that glucocorticoids might retard bone and cartilage destruction in diseases such as rheumatoid arthritis.

**Prostaglandins**

The cellular actions of glucocorticoids may be affected by prostaglandins. Prostaglandins are metabolites of arachidonic acid, which is released from phospholipids by the action of phospholipase A₂. Previously, it was assumed that glucocorticoids directly inhibited the enzymatic activity of this enzyme. New evidence, however, indicates that suppression of phospholipase A₂ activity is mediated by the activation of inhibitors of the enzyme itself or by inhibition of enzyme synthesis. The primary mediators of the inhibition of enzyme activity appear to be members of the “annexin” family of proteins, which includes proteins such as lipocortin-1 (33). This topic, however, remains controversial (34–36).

A second step in prostaglandin synthesis is the formation of prostaglandin H₂ from arachidonic acid by enzymes called cyclooxygenases. Recent data have shown the existence of at least two cyclooxygenase (COX) genes, COX-1 and COX-2; the proteins have 61% amino acid identity. The COX-2 gene and protein, but not COX-1, are strongly up-regulated in macrophages, endothelial cells, and fibroblasts by mediators such as endotoxin and interleukin-1, although they are inhibited by glucocorticoids. In contrast, COX-1 is constitutively expressed and relatively unaffected by glucocorticoids.

The role of the differential expression of COX-1 and COX-2 in inflammation and their dramatically different responses to glucocorticoids is unclear, but the available data suggest that glucocorticoids affect the production of proinflammatory arachidonic metabolites (37–40; Crofford L, Wilder R, Hla T. Unpublished observations).

**Effects on Lymphocytes**

Dr. Dimitrios T. Boumpas: The immunosuppressive effects of glucocorticoids are also directed at the traffic and function of lymphocytes.

**T Lymphocytes**

In humans, a single dose of glucocorticoids produces a marked but transient lymphopenia involving all lymphocyte subpopulations (41). The mechanism of the lymphopenia involves the redistribution of circulating lymphocytes to other lymphoid compartments, particularly the bone marrow (42). Changes in the expression of adhesion molecules (see Figure 3) may be responsible for that redistribution of lymphocytes (32). In contrast to other species (such as the mouse, rat, or rabbit), glucocorticoid-induced lymphopenia in humans is not due primarily to cell death. Mature, resting human lymphocytes are not lysed even by suprapharmacologic doses of glucocorticoids. However, immature human T cells (thymocytes and transformed lymphocytes) and, in some instances, activated T cells may be susceptible to lysis (43, 44) by programmed cell death (apoptosis).

In addition to their effects on cell distribution, glucocorticoids also affect the initiation and the progression of the T-cell cycle. During the initiation phase (activation), antigen binds to the T-cell receptor and initiates a cascade of events that leads to production of interleukin-2 (and other cytokines) and induction of high-affinity interleukin-2 receptors. Binding of interleukin-2 to its receptor promotes T-cell proliferation and generation of effector, suppressor, and cytotoxic functions. As shown in Figure 4, glucocorticoids inhibit, through various mechanisms, several events associated with T-cell activation (45–48). In addition to depressing interleukin-2 production, they interfere with the action of interleu-

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**Studypool's Note:**

The text above is a detailed explanation of the cellular actions and effects of glucocorticoids on various cellular and molecular processes, including the suppression of proinflammatory arachidonic metabolites, the redistribution of circulating lymphocytes, and the effects on the T-cell cycle. The document highlights the role of glucocorticoids in the immune system, with emphasis on their effects on lymphocytes and the mechanisms by which they exert their immunosuppressive properties. The text is rich with references to further studies and observations, suggesting a comprehensive understanding of the field.
Figure 4. Nuclear factors involved in regulation of interleukin-2 gene expression. Binding of antigen to the T-cell antigen receptor (TCR)-CD3 complex stimulates the tyrosine phosphorylation of several intracellular proteins. This is followed by activation of protein kinase C (PKC) and an increase in intracellular calcium (Ca^2+) concentration, which then activates calcium-calmodulin-dependent kinases and phosphatases. The combination of these two signals (PKC and calcium) mediates the binding of nuclear proteins (transcription factors) to the interleukin (IL-2) gene promoter and initiates the transcription of the interleukin-2 gene. The newly synthesized interleukin-2 messenger RNA transcripts are transferred into the cytoplasm where they either are translated into the polyribosomes to the interleukin-2 protein product (which is subsequently excreted) or are degraded by the RNAases. Glucocorticoids inhibit several steps during T-cell activation (indicated by the circled numbers). Thus, glucocorticoids inhibit the tyrosine phosphorylation (#7) but not the activation of PKC or the calcium influx (49). However, more distal sites in the calcium pathway (#2), such as the calcium-calmodulin kinase II, are inhibited (96). Binding of nuclear proteins (transcription factors) to the activated T cell (AT) (#3) and activator protein (AP)-1 (#4) sites of the human interleukin-2 promoter and its transcription activity are also inhibited by glucocorticoids (46, 47). This results in decreased production of interleukin-2 messenger RNA. Glucocorticoids also increase messenger RNA degradation (#5) (probably through the induction of RNAases), resulting in a profound decrease in interleukin-2 messenger RNA accumulation in ribosomes (#6) and a decrease in translation into protein product (#7) (45). Inhibition of interleukin-2 production requires low doses of glucocorticoids, whereas higher doses are required to inhibit interleukin-2 gene transcription suggesting that post-transcriptional mechanisms are also important for the inhibition of interleukin-2 by glucocorticoids.

B Lymphocytes

In contrast to T cells, B cells are relatively resistant to the immunosuppressive effects of glucocorticoids. These agents inhibit the proliferation of B cells, provided that they are present in culture during the first 24 hours after stimulation. Once B cells are activated, they differentiate into immunoglobulin-secreting plasma cells; glucocorticoids have only minimal effects on this process (53).

From a clinical standpoint, the most important effect of glucocorticoids on B cells relates to antibody production. Low doses of glucocorticoids do not affect serum immunoglobulin levels or antibody synthesis in vivo after inoculation with various antigens, but a brief course of daily high-dose prednisone will decrease serum immunoglobulin levels with maximal suppression observed 2 to 4 weeks after treatment (54). This suppression is the result of an initial increase in immunoglobulin catabolism, which is followed by decreased synthesis. The mechanisms for this decrease have not been defined. Because glucocorticoids inhibit the production of several cytokines involved in immunoglobulin synthesis (interleukins-1 through 6 and interferon-γ), decreased immunoglobulin production could result from decreased accessory or helper T-cell activities. Whether glucocorticoids inhibit immunoglobulin gene expression is not known.

In summary, whereas inhibition of leukocyte traffic and cellular immune responses require lower doses of...
glucocorticoids, higher doses of these agents are needed to suppress the functions of leukocytes and the humoral immune response. This heterogeneity of response is also apparent among different persons and diseases (as described above).

**Therapeutic Use**

Dr. Thomas R. Cupps (Department of Medicine, Georgetown University Medical Center, Washington, D.C.): Glucocorticoid use should be based on an evaluation of therapeutic goals and benefits compared with potential drug-associated morbidity. Knowledge of the clinical pharmacology and treatment protocols of glucocorticoids is critical; several excellent reviews have been published (55-60).

In general, topical or compartmental (for example, intra-articular) use of glucocorticoids results in less toxicity than does systemic administration. Among systemic treatments involving the same total dose of glucocorticoids, split-dose regimens are more toxic than single daily-dose protocols, which are themselves more toxic than alternate-day treatment schedules (42, 59). When administered on a daily basis, glucocorticoid analogs with prolonged biologic half-lives (for example, dexamethasone) have a greater potential for side effects than do analogs with intermediate biologic half-lives (for example, prednisone). Higher doses of systemic glucocorticoids can be given for less than a week with relative safety, although the same dose of drug administered for a more extended period will result in predictable, clinically significant morbidity.

Patient education is an important factor in optimal glucocorticoid therapy. The patient should be made aware of the potential clinical consequences from hypothalamic-pituitary-adrenal (HPA) axis insufficiency that may result from systemic glucocorticoid therapy. Thus, the patient must be cautioned never to stop or rapidly taper glucocorticoids without medical advice. The HPA-axis response to stress may be decreased even after a week of daily glucocorticoid therapy (61). If regular oral glucocorticoid treatment is interrupted for a period of more than 24 hours, patients may be susceptible to circulatory collapse in response to physiologic stress, trauma, infection, or surgery, and parenteral administration of glucocorticoids may be required. Even though HPA-axis insufficiency is more common with higher cumulative doses of glucocorticoids, it cannot be reliably predicted from the dose of glucocorticoids, the duration of therapy, or the basal plasma cortisol levels. Testing with corticotrophin-releasing hormone may be useful in assessing pituitary-adrenal functions in patients who may have HPA-axis insufficiency (62).

The patient should be warned that glucocorticoid therapy usually stimulates the appetite and causes weight gain; thus, the importance of diet should be emphasized when therapy is begun. The symptoms and signs of diabetes and steroid myopathy, as well as nephropathic and infectious complications associated with glucocorticoid therapy, should also be described to the patient (63).

The choice of a particular glucocorticoid analog for systemic therapy depends, in part, on clinical variables. Hydrocortisone is generally used for physiologic replacement and "stress" coverage if patients have HPA suppression (64). Because of its short biologic half-life and sodium- and potassium-retaining effects, this agent is not commonly used for systemic immunosuppressive or anti-inflammatory treatment. Fluorinated analogs, such as dexamethasone, have a long biologic half-life and little sodium-retaining potency (65, 66). This long biologic half-life, however, may be associated with a greater potential for morbidity, so this group of glucocorticoid analogs is not commonly used in prolonged daily treatment regimens.

The appropriate starting dose of glucocorticoids should be adequate to rapidly suppress disease activity and tissue damage. High daily or split-dose therapy (for example, 0.6 to 1.0 mg/kg per day of prednisone) is indicated in the early phases of particularly aggressive diseases. Within 1 to 2 weeks, therapy should be consolidated into a single morning dose. Subsequent tapering to the minimal effective maintenance dose (preferably alternate-day) is dictated by clinical variables. Tapering too gradually may be associated with greater glucocorticoid-induced morbidity, although tapering too rapidly predisposes patients to disease exacerbations.

The use of adjunctive anti-inflammatory and immunosuppressive drug therapy (so called "steroid-sparing" agents) as a means to decrease glucocorticoid dose requirements should be considered. The ideal would be to achieve a similar level of disease suppression with lower doses of glucocorticoids and an overall decrease in glucocorticoid-associated morbidity. Several agents, including azathioprine, methotrexate, antimarial agents, cyclosporin A, cyclophosphamide, and others, have been used. Alternate-day therapy is another option that may help to decrease glucocorticoid-related morbidity (67). Tapering to an alternate-day protocol is also useful to allow HPA-axis recovery before stopping glucocorticoid therapy. If a dose level, for instance, of 30 mg of prednisone per day effectively suppresses disease activity, switching to an alternate-day regimen should be considered (42). The dose can be simultaneously increased on the "high" day as the dose is decreased on the "low" day, or simply gradually decreased on the "low" day until a strictly alternate-day regimen is achieved.

The choice of a specific glucocorticoid treatment plan is frequently influenced by the physician's experience in treating the underlying disease. In some instances, alternate-day glucocorticoids can be used from the beginning of treatment, as in membranous glomerulonephritis (68). More often, tapering to alternate-day therapy is planned as a way to minimize the potential risks for complications from intense glucocorticoid induction therapy, as in systemic vasculitis (69).

Conventional high-dose glucocorticoid therapy may be disappointing because of incomplete responses or severe complications or both. Accordingly, regimens have been modified to improve the therapeutic index of glucocorticoids. One approach is the use of intravenous pulse therapy. Infusions of large doses of glucocorticoids (for example, methylprednisolone in doses up to 1.0 g/m² body surface area for 1 to 5 days) have become widely used in selected clinical situations (70-74). Pulse
therapy is commonly used to initiate therapy in patients with rapidly progressive, immunologically mediated diseases, such as acute transplant rejection, Goodpasture disease, necrotizing glomerulonephritis, and severe lupus nephritis. Unfortunately, no formal studies have compared conventional high-dose and pulse glucocorticoid therapies. The utility of pulse therapy for extended maintenance treatment appears to be limited (72, 74).

Complications of Therapy

Dr. James E. Balow (Chief, Kidney Disease Section, NIDDK, NIH, Bethesda, Maryland): Given the diversity of mechanisms and sites of action, it is not surprising that glucocorticoids cause different types of toxicity. In the early years of aggressive glucocorticoid therapy, iatrogenic Cushing syndrome was common. The consequences of extended high doses of glucocorticoid therapy were catastrophic, including death from infection and cardiovascular complications. Although such extreme complications are less frequent today, side effects are still commonplace and usually cannot be completely avoided (75). Indeed, some risk for complications is inherent in the attempt to obtain the therapeutic benefits of glucocorticoids.

The medical complications of glucocorticoid therapy are listed in Table 1. The risks for all of these complications are theoretically dose- and time-dependent. These complications range from minor to severe, early to late, flagrant to insidious, expected to rare, and tolerable to intolerable. An attempt has been made to group them in order of their practical importance. Of necessity, this review of glucocorticoid side effects is not comprehensive; it focuses on changing concepts and recent information about the pathogenesis of certain complications.

Infections

The propensity of glucocorticoids to cause an infection diathesis is controversial. Clearly, the risk for infection is dependent on the dose and duration of glucocorticoid therapy (76). The relative risk for infection across a number of clinical settings was approximately two times that of controls in a meta-analysis of 71 trials involving more than 2000 glucocorticoid-treated patients (77). The risk varied according to the type of disease being treated with glucocorticoids: Although relative risk did not increase in renal-limited diseases, it increased almost three times for patients with neurologic diseases (presumably representing attendant deficits in local host-defense mechanisms).

Peptic Ulcer Disease

Ulcers have been long considered a complication of glucocorticoid therapy; however, this side effect has recently been reexamined by also accounting for concurrent drug therapy. A prospective study (78) of 1400 patients receiving steroid therapy showed an overall twofold increased risk for peptic ulcer disease. However, multivariate analysis showed that concomitant use of nonsteroidal anti-inflammatory drugs was the variable that explained the increased risk for peptic ulcer disease in patients taking glucocorticoids.

Atherosclerosis

Accelerated atherosclerosis seems to be associated with glucocorticoid treatment (79). However, other processes operating in the systemic diseases for which glucocorticoids are used are also atherogenic. For example, in systemic lupus erythematosus, the long-term use of prednisone was found to be an independent contributor to the risk for coronary disease (80), but glucocorticoids may simply be a surrogate for the true risk factor.

Evidence of atherosclerotic risk in steroid-treated patients without complicated systemic diseases is not definitive. For example, in one study of normal volunteers, glucocorticoids did not induce lipoprotein abnormalities associated with cardiovascular risk (81); 2 weeks of glucocorticoid therapy did not substantially affect total cholesterol or low-density lipoproteins. Very low-density lipoproteins were the most adversely affected, but glucocorticoids increased high-density lipoproteins as well. If glucocorticoids themselves are indeed atherogenic, the process probably involves mechanisms other than a change in lipoprotein profiles.

Skeletal Complications

The bony complications of glucocorticoids are insidious and perplexing. Osteoporosis is predominantly associated with loss of trabecular bone, and its pathogen-
Appendix Table 1. Glossary of Genetic Terms

<table>
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<tr>
<th>Genetic Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Activation (cellular)</td>
<td>The sequence of biochemical events triggered by antigens or other molecules that enable cells to exert their functions.</td>
</tr>
<tr>
<td>Box</td>
<td>A conserved part of DNA where specific proteins bind during gene transcription.</td>
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<tr>
<td>Heat shock proteins</td>
<td>A family of proteins produced by cells in response to various insults (including heat). Members of the family may act as chaperones to prevent premature and senseless interaction between steroid receptors and DNA.</td>
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<tr>
<td>Immunophilin (cyclophilin)</td>
<td>A family of proteins expressed in most tissues that play a role in the folding of proteins in vivo; they mediate the immunosuppressive effects of cyclosporin, FK-506, and rapamycin.</td>
</tr>
<tr>
<td>Nucleosome</td>
<td>The basic structural subunit of chromatin; contains short fragments of DNA (around 200 base-pairs) and histone proteins.</td>
</tr>
<tr>
<td>RNA polymerase II</td>
<td>An enzyme that mediates the synthesis of messenger RNA from a DNA template.</td>
</tr>
<tr>
<td>Transcription</td>
<td>The synthesis of RNA on a DNA template.</td>
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Bisphosphonates, which are resistant to hydrolysis and bind to hydroxyapatite crystals in bone, also reverse the unfavorable balance of bone resorption and mineralization. Ingestion of the bisphosphonate-crystal complexes inhibits osteoclast function. Two preparations of bisphosphonates are available in the United States: etidronate (Didronel; Procter & Gamble Pharmaceuticals, Inc., Norwich, New York) and pamidronate (Aredia; Ciba Pharmaceutical Co., Summit, New Jersey). These agents have been approved primarily for use in management of malignancy-associated hypercalcemia. An oral preparation of pamidronate had a salutary effect on bone mineral density in steroid-induced osteoporosis (90), but more data on the effects of these drugs in steroid-induced osteoporosis are clearly needed. Because some concern still exists about adverse long-term toxicity, neither calcitonin nor bisphosphonates are yet considered standard therapy. If they are used at all, they should be used intermittently, perhaps on a rotating cycle.

Osteonecrosis of hips, knees, and occasionally shoulders is a known risk of receiving glucocorticoids. Its pathogenesis and treatment are both controversial (91), but compromised vascular supply to trabecular bone or the cumulative effects of multiple fatigue fractures in osteoporotic bone are theorized. Although short-term, high-dose glucocorticoids have been associated with osteonecrosis, steady long-term doses seem to pose the highest risk. Unfortunately, joint replacement is usually required to control pain and restore function (92).

Novel Pharmacologic Approaches

Alterations of the glucocorticoid molecule could decrease steroid complications. Delfazacort is a synthetic glucocorticoid (not currently available in the United States) that is nearly as efficacious as prednisone and seems to have fewer side effects (93, 94). Compared with prednisone or betamethasone, delfazacort causes a smaller decrease in intestinal calcium absorption (86) and causes less renal calcium excretion (95). Preliminary studies on bone mineral density also support the benefit of delfazacort compared with prednisone, but more clinical trials are necessary to define whether or
not deflazacort has a higher overall therapeutic index than do standard glucocorticoids.

Addendum

Recently, Sambrook and colleagues (97) conducted a prospective study involving randomization of patients treated with long-term glucocorticoids to three groups: 1) calcium plus calcitriol plus calcitonin; 2) calcium plus calcitriol; or 3) calcium alone for 1 year. The combination of calcium, calcitriol, and calcitonin was associated with the best maintenance of lumbar spine bone density during and 1 year after experimental therapy. No differences were observed among the treatment groups in femoral head bone density. Hypercalcemia occurred in one quarter of patients receiving calcitriol. As stated in the accompanying editorial by Meunier (98), the optimal regimen for prevention of glucocorticoid-induced osteoporosis has not been found.

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