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CLINICAL PHARMACOLOGY OF SYSTEMIC CORTICOSTEROIDS

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It is more than a quarter of a century since Hench showed the prompt and dramatic reversal of the inflammatory manifestations of rheumatoid arthritis after the administration of cortisone. In 1971, Christy (1) estimated that more than 5 million patients were treated with corticosteroids yearly. From this enormous experience and from a massive literature, concepts have evolved regarding the safe and effective use of these agents. An obvious generalization is that corticosteroid therapy is most often *temporary* and adjunctive. The corticosteroids allow the host to recover in self-limited conditions and to suppress some manifestations
reappear when corticosteroids are withdrawn. It is predominantly in patients with chronic diseases that the deleterious effects of the corticosteroids are most prominent.

In the discussion to follow, the clinical pharmacology of systemic corticosteroid administration and concepts of systemic corticosteroid therapy are examined. The special problem of suppression of the hypothalamic-pituitary-adrenal system is emphasized.

ACTIONS OF THE CORTICOSTEROIDS

Cortisol and its synthetic analogues—prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, and paramethasone—are known to exhibit many important physiological and biochemical effects. The multiplicity of activities that have been observed are so disparate that no unitary hypothesis of corticosteroid hormone action has been possible. It is often difficult to relate the cellular actions of the corticosteroids to their effects on physiology generally. Most interesting to the clinician are studies of the anti-inflammatory and antiallergic actions of the corticosteroids. Of almost equal importance, however, is the knowledge of biochemical actions of the corticosteroids, particularly in excessive concentrations that ac-

count for the undesirable side effects in the course of anti-inflammatory corticosteroid therapy.

Biochemical and Metabolic Effects of the Corticosteroids

Cortisol and certain of its synthetic analogues are also referred to as "glucocorticoids" because of action of the corticosteroids increasing hepatic glucose output by stimulating hepatic gluconeogenesis while depressing protein synthesis or stimulating protein catabolism in muscle. It is highly likely that one of the most primal and important events in corticosteroid biochemical action is the inhibition of amino acid incorporation into protein in peripheral tissues. After the administration of glucocorticoids, alanine is released from muscle, massively, leading to a transient rise in plasma alanine concentration. The alanine derived from muscle and other peripheral tissues released in response to acute doses of corticosteroids is derived from glucose and muscle glycogen, and the nitrogen from the catabolism of amino acids within the muscle cell. Hyperalaninemia not only provides a marked increment in substrate for hepatic gluconeogenesis, but also is implicated in the increased secretion of glucagon by the pancreatic α cells (2). Hyperglucagonemia has been shown after corticosteroid administration; the increment in plasma glucagon levels may exceed 50% of the basal level, and responsiveness to amino acid infusions (alanine) may quadruple. Whether or not hyperaminoaciduria is the proximate stimulus for glucagon elaboration by the pancreatic α cell is not known, but it is likely that the hyperglucagonemia accounts, in part, for the marked increment in hepatic glucose output after the administration of corticosteroids.

A number of hepatic enzymes concerned with gluconeogenesis exhibit marked increases in activity after the administration of glucocorticoids. Among these enzymes are glucose-6-phosphatase, fructose-6-diphosphatase, and phosphoenolpyruvate carboxykinase. The increased activities of these enzymes apparently are caused by an actual increase in the amount of enzyme protein. It has long been argued that the increase in the gluconeogenic enzymes in the liver results from induction by excessive substrate or amino acids derived from peripheral tissues. Since the corticosteroids had been shown to diminish the peripheral use of glucose and amino acid uptake, there seemed little need to posit a hepatic enzyme as a primary action of the glucocorticoid; however, corticosteroids now have been shown to increase hepatic gluconeogenesis in vitro and to increase the activities of tyrosine aminotransferase and tryptophan pyrrolase (3). The induction of these specific proteins results from the corticosteroids' promoting the transcription of messenger RNA for the two enzymes, tyrosine aminotransferase and tryptophan pyrrolase. Hepatic enzyme induction is believed to be a model for the mechanism of action of the glucocorticoids (4). The glucocorticoid enters the cell and binds to a specific cytoplasmic receptor protein. The steroid-protein receptor complex after alteration enters the nucleus of the cell, either associated with a cytoplasmic receptor or after interchange with a nuclear receptor, as described by Baxter & Tomkins in 1971 (5). A unitary hypothesis cannot explain the diverse effects of corticosteroids. Corticosteroid inhibition of amino acid incorporation into protein of peripheral tissues may be the dominant expression of glucocorticoid action.

The effects of corticosteroids on the metabolism of fat are even less clear than those for protein and carbohydrate metabolism. Glucocorticoids, independently, seem to have no effect on basal lipolysis as measured by glycerol production; but, lipolysis induced by epinephrine or any of the catecholamines is markedly potentiated by the administration of glucocorticoids. In isolated epididymal fat cells treated with dexamethasone, it was found that a small cAMP-dependent protein kinase was stimulated, as demonstrated by Lamberts et al in 1975 (6). Corticosteroids seem to have opposite effects in specific tissues. For example, the corticosteroids seem to sensitize the subcutaneous fat cells of the tissues of the arms and legs to the fat-mobilizing action of the catecholamines, and lipogenesis is inhibited, because glucose entry into fat cells is prevented by corticosteroids. On the other hand, the subcutaneous fat tissue of the abdomen and the dorsal fat pad manifest predominantly lipogenesis in response to corticosteroid administration (7).

The corticosteroids also have been shown to induce negative calcium balance, oppose the action of vitamin D on the intestine, and produce both osteoporosis and osteomalacia.

The principal biochemical actions of the glucocorticoids or the corticosteroids are the stimulation of hepatic gluconeogenesis, inhibition of peripheral tissue protein synthesis, and stimulation and induction of protein synthesis in the liver. These actions could explain many of the manifestations of Cushing's syndrome, either spontaneously or exogenously induced, with glucocorticoid or corticosteroid excess.

Anti-Inflammatory and Antiallergic Actions of the Corticosteroids

The anti-inflammatory and antiallergic activities of the corticosteroids are the most important reason for their clinical application in disease states. Suppression of the inflammatory response by corticosteroids has long been investigated without yielding a unifying concept of how the corticosteroids modify reaction. Although the precise mechanism of corticosteroid protection against cellular damage of inflammation is not understood, certain characteristics of this action can be enumerated.

1. Corticosteroid protection against cellular damage and suppression of the inflammatory response is nonspecific with regard to the kind of noxious stimulus, such as bacterial products, histamine and other by-products of the antigen-antibody union, metallic ions such as calcium, hypoglycemia, and snake venom. Pretreatment of several species of experimental animals with sufficient doses of corticosteroids will inhibit the inflammatory reaction to nearly any type of injury (8).

2. Corticosteroid action is local in that unaltered hormone must be present at the site of inflammation. It is not known whether cortisol must enter the nucleus of the cell to exert its anti-inflammatory effect. When cortisol is linked to agarose beads as cortisol hemisuccinyl sepharose, it remains outside the cell or in approximation to the cell wall. This preparation of cortisol can inhibit entry of glucose into adipose tissue; therefore, one of its biochemical actions can occur without penetration.

3. The degree of suppression of the inflammatory response and subsequent cellular injury is proportionate to the concentration of corticosteroids in a given volume of inflammatory tissue. The possibility of interference with the inflammatory re-

sponse by a remote effect of the corticosteroids cannot be excluded with certainty and could involve the lymphocytopenia and eosinopenia observed with corticosteroids (8).

Many corticosteroid effects on the inflammatory response have been described. The relative importance of each and the mechanism of action have not been explained. A few of these features of corticosteroid suppression of the inflammatory response are listed below.

MAINTENANCE OF INTEGRITY OF THE MICROCIRCULATION Corticosteroids block the increased permeability of endothelium of capillaries induced by acute inflammation. There is a reduction both in the leakage of edematous fluid and in the transport of proteins into the areas of injury. Thus, tissue swelling is minimized, if not prevented. Exudation of inflammatory cells, including white cells and mast cells, is markedly inhibited.

MAINTENANCE OF CELL MEMBRANE OR PLASMA MEMBRANE INTEGRITY Corticosteroids prevent the sequestration of water intracellularly and swelling and destruction of cells. In patients with Addison's disease, water intoxication may lead to death. In the local inflammatory response, intracellular transfer of water occurs with the swelling of the cytoplasmic organelles. Direct cellular injury by toxins, proteolytic enzymes, and mechanical factors may be inhibited by the presence of high concentrations of corticosteroids.

STABILIZATION OF LYSOSOMES Lysosomes are small, bag-like organelles of the cell, usually spherical, contained in the cytoplasm. They contain a variety of enzymes that are hydrolytic for protein, carbohydrate, and fat and are known collectively as acid hydrolases. Enzymes are stored in the organelle by a single lipoprotein membrane. With cellular injury, the lysosomal membrane ruptures, and there is a release of the acid hydrolases that digest the cell contents and enlarge and perpetuate the inflammatory response by attacking extracellular protein substituents. Secondary tissue damage from the rupture of the lysosomes after cellular injury and attendant inflammatory response can be modified or eliminated in the presence of high concentrations of corticosteroids. The corticosteroids stabilize the lysosomal membrane and protect it from rupture in cellular injury. Whether the corticosteroids are attached to the lysosomal membrane or whether they exert some more remote effect is unknown. The action of the corticosteroids, then, is to interrupt the progressive cycle of inflammatory response by inhibiting the progressive digestion and disruption of the connective tissue and cells. The lysosomal participation in the inflammatory response has been likened to the "domino" theory. Corticosteroids interfere at some point with the "domino" of inflammation.

INHIBITION OF NEUTROPHILIC CHEMOTAXIS Pharmacologic doses of the corticosteroids induce neutrophilic leukocytosis associated with eosinopenia, monocytopenia, and lymphocytopenia. This matter has been reviewed recently by Fauci et al (9). In studies on suppression of inflammation by corticosteroids, one of

the most important mechanisms appears to be corticosteroid impedance of neutrophils and monocytes when arriving at the inflammatory site. Suppression of the acute inflammatory response involves inhibition of in vivo chemotaxis, including a reduction of the volume of inflammatory fluid, lysosomal and lactic dehydrogenase enzymes, as well as neutrophils (10). The mechanism by which corticosteroids inhibit in vivo chemotaxis is not understood and cannot be explained by steroid genome interaction.

Regulation of the Circulation by Corticosteroids

In acute adrenal insufficiency, glucocorticoids are most effective in restoring circulatory competence when shock has supervened. Mineralocorticoids such as aldosterone do not have this activity. Corticosteroids in high doses may restore circulatory function in shock associated with hemorrhage, endotoxin, snake venom, anaphylaxis, and trauma. The mechanism of the corticosteroid-induced improvement in the major circulation is not completely known. Corticosteroids exhibit an inotropic effect on the myocardium. In myocardial tissue, there exist receptors with high affinity for glucocorticoids. Glucocorticoid receptors have been demonstrated in the cytosol in a number of species by Ballard & Ballard in 1974 (11). Cytoplasmic receptors for mineralocorticoids (aldosterone) have not been demonstrated in the myocardium. Glucocorticoids incubated in vitro with myocardial cells improve utilization of fatty acids for energy metabolism. The administration of dexamethasone to dogs with severe low cardiac output syndrome resulted in a 50% decrement in mortality and improvement in cardiac function. Improvement in cardiac function in the low output syndrome in animals treated with dexamethasone was attributed to an increase in myocardial linolenic acid content and a decrease in prostaglandin content (12). It is possible that the corticosteroids in various shock states, such as in acute adrenal insufficiency, may restore cardiac
output. It is possible that the therapeutic effect of corticosteroids in certain shock states may be related to improvement of cardiac function.

Antiallergic and Anti-Immunologic Effects of Corticosteroids

It is both surprising and intriguing that the corticosteroids exert a suppressive effect at each stage of the immune response (13). Corticosteroids seem to interfere with the phagocytosis of antigens and their subsequent intracellular digestion or processing. Corticosteroids also inhibit the migration of cells to areas of inflammation. The corticosteroids in large doses suppress cell-mediated hypersensitivity reaction.

It should be recalled that cell-mediated immunity is derived from the lymphocyte population that is thymus-processed or -dependent, and these lymphocytes are referred to as T cells. These T cells transform to lymphoblasts that incorporate antibody into their surface membrane but do not secrete humoral or free antibody. It is the thymus-dependent cell system that subserves the function of cell-mediated immunity. The thymus system is necessary for the development of specialized cells that are chiefly small lymphocytes which play the vital part in contact sensitivity, homograft rejection, and delayed hypersensitivity. The small lymphocytes and the thymocytes are most vulnerable to the action of corticosteroids and, in some species,

permit modification of the immune cell-mediated immune response (14). The small lymphocytes of man are much less sensitive to the effects of corticosteroids. There is ample evidence that corticosteroids are taken up by lymphoid cells and bound to specific receptors.

There are steroid-sensitive and steroid-resistant species of lymphocytes. Some of the lymphocytic steroid receptors, when occupied by a corticosteroid, undergo cytolosis; others exhibit an inhibition of metabolism of the cell. In man, thymus-derived lymphocytes are more susceptible to the effects of corticosteroids than the bursa-derived lymphocytes that elaborate humoral antibody. Thus antibody reproduction is rarely reduced significantly, except with very large doses of corticosteroids, whereas cell-mediated immunity is modified at lower corticosteroid concentrations.

In recent years the importance of cell-mediated immunity has been amplified by organ transplantation. Corticosteroids are most effective in promoting homograft acceptance and survival. There is no evidence that the union of antigen and antibody is prevented, but the inflammatory response to this union is suppressed by corticosteroid therapy. Certainly the effects of corticosteroids in the reversal of an acute rejection episode is probably related to suppression of the inflammatory response and not so much to the cell-mediated immune mechanism.

The corticosteroids inhibit antigen processing by macrophages, cell-mediated immunity, and the inflammatory response after antigen-antibody union. Only in enormous doses do corticosteroids alter gamma globulin production by plasma cells in circulation. These properties of the corticosteroids resulted in their application to a variety of disorders in which alterations of the immune response are paramount, and it is in these disorders that corticosteroid therapy is probably most appropriate.

PHARMACOLOGY OF NATURAL AND SYNTHETIC CORTICOSTEROIDS

Structural alterations of cortisol have resulted in increased biological potency of its synthetic derivatives. It is generally agreed that prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, and paramethasone share an advantage over cortisol in that sodium retention is not as marked at equipotent anti-inflammatory doses, although all of the other undesirable side effects of cortisol overdosage have been observed with the synthetic analogues.

Prednisolone, triamcinolone, methylprednisolone, betamethasone, and dexamethasone possess certain theoretical advantages over cortisol in relation to their availability to the tissues. Cortisol, the major corticosteroid product of the normal human adrenal cortex, circulates in the blood at a concentration from 5 to 25 μg per 100 ml of plasma. Eighty percent of the circulating cortisol is bound to an α-globulin, transcortin (corticosteroid-binding globulin), which represents an inactive transport complex. A smaller moiety is bound to albumin, and it is only this albumin-bound portion that may diffuse into the extravascular fluid that bathes tissue cells at any given moment. The synthetic analogues of cortisol do not compete

for the binding sites of cortisol on the protein storage complex, transcortin. The synthetic analogues of cortisol are less extensively bound to plasma albumin and diffuse more completely into the tissue than does cortisol. It is possible that they exert their biological effect at the tissue receptor site earlier than does cortisol.

All of the synthetic analogues of cortisol are metabolized more slowly than cortisol by the liver because of the alterations of the steroid molecule in each instance and the rapid equilibration in blood with peripheral tissues.

The relative biological potency of the synthetic analogues of cortisol is compared with cortisol in Table 1, as are the plasma half-life and biological half-life of action for each of the corticosteroids (8). The plasma biological half-life of the corticosteroid represents the time elapsed before one half of the concentration of the given steroid disappears at any given point. It is generally accepted that the biological half-life in plasma of the corticosteroid reflects roughly the rate of degradation of the steroid by liver enzymes and hence is probably related in some way to the duration of activity and the metabolic stability of the corticosteroid at the receptor site. Thus, dexamethasone and betamethasone, with the longest biological half-lives, exhibit the longest duration of measurable biological activity in man, and cortisol, the shortest. In addition, relative anti-inflammatory potencies are also approximately correlated with the plasma half-times.

The duration of anti-inflammatory activity of cortisol and its synthetic analogues when administered orally approximates the duration of hypothalamic-pituitary-adrenal suppression. No synthetic or natural glucocorticoid has been found in which the anti-inflammatory potency and the hypothalamic-pituitary-adrenal suppressibility do not approximately parallel each other in terms of degree and duration. Apparently, the substituents of the glucocorticoid molecule necessary for attachment to the receptors in the hypothalamus are the same as those required for attachment to the receptors in the peripheral tissues. It has been possible to estimate the duration of therapeutic effects of cortisol and its analogues by examining the hypothalamic pituitary-adrenal suppressive activity that can be quantitated readily.

Table 1 Relative anti-inflammatory potencies and plasma and biological half-lives of cortisol and its synthetic analogues

	Anti-inflammatory potency	Plasma half-life (min)	Biological half-life (hr)
Cortisol	1	90	8-12
Prednisolone	3-5	200 or greater	12-36
Methylprednisolone	3-5	200 or greater	12-36
Triamcinolone	3-5	200 or greater	12-36
Paramethasone	10		
Betamethasone	20-30	300 or greater	36-54
Dexamethasone	20-30	300 or greater	36-54

In Table 1, biological half-lives of cortisol and its synthetic analogues are compared. These biological half-lives have been determined by the duration of suppression of hypothalamic-pituitary-adrenocortical secretory activity. Except for replacement therapy, cortisol is generally not used as a therapeutic agent for nonendocrine disorders because of its propensity for sodium retention in susceptible individuals. The sodium-retaining ability of cortisol, however, is but a tiny fraction of that of aldosterone (less than one one-hundredth). The most commonly administered corticosteroids are those with intermediate and prolonged biological half-lives. Prednisolone, methylprednisolone, and triamcinolone exhibit unusually variable biological half-lives. This group of steroids is used in alternate-day dosage regimens, although it is apparent that biological activity could persist well into the alternate off-day of the regimen. Nevertheless, a single dose of any of this group of steroids, administered in the early morning, generally will not induce hypothalamic-pituitary suppression on the day in which no steroid is given. Alternate-day steroid therapy is the preferred schedule in chronic conditions requiring pharmacologic doses of steroids. Betamethasone and dexamethasone exhibit prolonged anti-inflammatory and hypothalamic-pituitary-adrenal suppressibility and are ideally suited for the treatment of disorders requiring inhibition of the pituitary ACTH secretion but are not suitable for alternate-day schedules. If intermittent therapy or periodic steroid therapy is desirable, betamethasone or dexamethasone can be given once every 3 or 4 days.

MODALITIES OF CORTICOSTEROID THERAPY

The emphasis in this discussion is on the modalities of corticosteroid therapy and not specific indications. On assessing each modality of corticosteroid therapy, I attempt to suggest regimens that will provide sufficient therapeutic benefits with minimum complicating side effects.

Replacement

The treatment of primary (Addison's disease) and secondary adrenocortical insufficiency in the chronic state requires little comment. In primary adrenocortical insufficiency, one should administer enough cortisol by mouth daily to diminish hyperpigmentation and to abolish postural hypotension, the hallmark of adrenal insufficiency even in the chronic state. The mean amount of cortisol for this task is 20 mg/day, and aldosterone replacement must be in the form of 9α-fluorocortisol (Florinef ®) at 0.1 mg/day.

Secondary adrenocortical insufficiency occurs in hypopituitarism and in patients receiving corticosteroid therapy for nonendocrine diseases. There are approximately 5 million persons in the United States receiving doses of corticosteroid sufficient to produce hypothalamic-pituitary-adrenocortical insufficiency. It is unfortunate, but true, that patients with secondary adrenocortical insufficiency are not ordinarily severely symptomatic until an acute precipitating event results in the development of the adrenocortical insufficiency. The only manifestation is that of arterial hypotension and low cardiac output. Abnormalities in potassium metabolism and hyper-

pigmentation are not present to identify the patient as having adrenocortical insufficiency. It is often necessary to treat the patient without a confirmed diagnosis. A bolus of 100 mg of cortisol, as cortisol phosphate or succinate esters, should be given intravenously, and an infusion of cortisol phosphate or succinate at a rate of 15 mg/hr for the first 24 hr with saline as a vehicle should be used. Restoration of the blood pressure may be apparent within minutes and should be apparent by 1 hr.

We have studied many patients with Gram-negative septic shock and disseminated intravascular coagulation and a few patients who died with what seemed to be replacement of the adrenal glands by intra-adrenal hemorrhage (8, 15). These patients met the criteria of the Waterhouse-Friderichsen syndrome, yet in every instance their plasma cortisol levels were elevated, with a mean of 73 μg/100 ml, and their plasma cortisol levels were further increased to between 100 and 120 μg/100 ml with injections of ACTH. Isolated reports of actual adrenal failure with hemorrhagic replacement of the adrenals do exist, but only one or two have documentation of cortisol deficiency. Acute adrenal insufficiency is not a usual feature of the Waterhouse-Friderichsen syndrome.

Intensive Short-Term Therapy

Prompt, intensive corticosteroid therapy may reduce morbidity and mortality of potentially lethal conditions in which the inflammatory response itself has imperiled the host. Such may be true for certain allergic emergencies, infectious shock, necrotizing vasculitis, and the metabolic upheaval accompanying water intoxication, central hyperthermia, hypoglycemic coma, and acute hypercalcemia associated with vitamin D intoxication and hormone therapy for metastatic cancer of the breast.

The use of corticosteroids in septic shock is controversial. If the pathophysiology of septic shock is related to endotoxin shock in animals, then corticosteroid therapy must be pushed to its ultimate. There is little doubt that restoration of cardiac output may result after a massive infusion of corticosteroids in some patients with septic shock. Hardly anyone would dispute the value of intensive corticosteroid therapy in acute allergic emergencies, but the rejoinder should be made that β-adrenergic stimulators and bronchodilators must be used as needed with corticosteroid therapy. Intensive short-term corticosteroid therapy in severe exacerbations of bronchial asthma does not induce an earlier remission than more conventional dosage forms. McFadden et al in 1976 (16) failed to demonstrate any objective improvement in pulmonary function with massive doses of cortisol succinate when compared to the administration of isoproterenol alone during the first 6 hr of treatment. In those situations in which circulatory failure is prominent, one can usually observe the restoration of blood pressure after a single dose, which may not need to be repeated. The advantage of the longer-acting corticosteroid esters, bethamethasone and dexamethasone, is that a single dose is usually all that is required.

The complications of brief, intensive corticosteroid therapy, which should be limited to a maximum 48-hr period, include burning and itching at mucocutaneous junctions and rarely, multifocal premature ventricular contractions (17), precipitation of diabetic ketoacidosis (in a genetic diabetic), and superficial punctate ulcera-

tions of the gastric mucosa with hemorrhage. One need *not* taper the dosage of steroid at all, and it may be withdrawn abruptly if the underlying disease is not exacerbated as a result. It is the activity of the underlying or precipitating condition that determines whether or not any tapering is required. It is best to withdraw the steroids as abruptly as they were begun.

Prolonged, High Dose, Suppressive Therapy

Because of the duration of therapy and the doses of corticosteroids used, complications with prolonged, high dose, suppressive corticosteroid therapy are more frequently encountered. This modality of corticosteroid therapy is indicated and efficacious to treat asthma, ulcerative colitis, subacute hepatic necrosis, chronic active hepatitis, severe alcoholic hepatitis, gluten-sensitive enteropathy, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, acute lymphocytic leukemia, disseminated Hodgkin's disease, nephrotic syndrome, acute rejection after tissue homotransplantation; central nervous system involvement, nephritis, hemolytic anemia, and thrombocytopenic purpura accompanying disseminated lupus erythematosus, polymyositis, atypical dermatomyositis, and temporal arteritis (giant cell).

In these disorders erratic coricosteroid dosage is hazardous, and rapid withdrawal of corticosteroids is often associated with an exacerbation of the underlying disease. Nearly all patients on prolonged, high dose steroid therapy (more than 15 mg of prednisolone daily) require gradual tapering of dosage when therapy is to be withdrawn. It is emphasized that although these patients are vulnerable to acute secondary adrenal insufficiency, abrupt withdrawal of steroid therapy produces secondary adrenal insufficiency only indirectly, by exacerbating the underlying disease. Prednisolone dosage varies in these disorders from 15 to 120 mg/day, and this amount of corticosteroid when given for more than two weeks may result in prolonged suppression of the hypothalamic-pituitary-adrenal axis and one or more undesirable side effects of corticosteroid therapy (see below). To avoid these complications, alternate-day steroid therapy is recommended whenever possible, and if alternate-day therapy is not effective, then the total daily dose should be given in the morning.

Low Dose, Chronic, Palliative Therapy

Low dose, chronic, palliative therapy involves ingestion, each morning, of 2–10 mg of prednisolone as an adjuvant to other therapy (such as salicylates in rheumatoid arthritis and lupus erythematosus).

This form of therapy may be used in a few patients with rheumatoid arthritis, when excruciating, unrelenting pain that is unresponsive to salicylate therapy occurs, or if systemic vasculitis and fever are predominant. Salicylate therapy remains central, and corticosteroids should not be given as a first form of therapy. The same constraints apply to the treatment of lupus erythematosus in which arthritis is the principal manifestation. Regional enteritis may respond to modest doses of corticosteroid as adjunctive therapy. Corticosteroid-treated patients with rheumatoid arthritis are particularly vulnerable to the complication of peptic ulcer (18). Erratic corticosteroid dosage or withdrawal may precipitate a panmesenchymal reaction—

"steroid pseudorheumatism" (19). Withdrawal of corticosteroids is tedious, and to avoid rheumatoid exacerbation reduction in dosage should not exceed 1 mg of prednisolone each one to two months.

It is of interest that corticosteroids apparently increase the metabolic disposition of the salicylates as the steroids enhance salicylate clearance by the kidneys (20). Toxic blood levels of salicylates have occurred in patients whose corticosteroid dosage has been reduced.

Chronic Inhibition of Pituitary ACTH Secretion

Betamethasone and dexamethasone are ideally suited for the treatment of patients with disorders of cortisol biosynthesis or idiopathic hirsutism, because the suppression of hypothalamic-pituitary-adrenocortical secretion is desired. This can best be accomplished by the administration of between 0.5 and 0.75 mg of betamethasone or dexamethasone at bedtime each night. Very few side effects are observed at the lower dose, and a good control of urinary 17-ketosteroid excretion is achieved.

COMPLICATIONS OF CORTICOSTEROID THERAPY

Prolonged, high dose, suppressive, daily corticosteroid therapy may be associated with a host of complications and side effects. Some of the more important complications are listed in Table 2, and the nonendocrine complications of corticosteroid therapy are detailed elsewhere (1, 20).

Not included in the complications listed in Table 2 is the peculiar steroid-associated entity, "steroid pseudorheumatism" or steroid-induced panmesenchymal reaction, or the steroid withdrawal syndrome. This term is used to describe musculoskeletal aching, fever, malaise, emotional lability, lupus-like syndrome, hypertension, and general debility that occurs in patients, particularly with rheumatoid arthritis, in whom erratic steroid dosage has been used or for that in which high doses of steroids have been used in the treatment of rheumatoid arthritis and then are rapidly tapered, as described by Slocumb in 1953 (21). This steroid-induced disorder frequently complicated the high dose therapy that was used in the early years of corticosteroid treatment for both lupus erythematosus and rheumatoid arthritis. Hardin (22) has described a few patients in which these manifestations have occurred quite recently. It is noteworthy that patients who have so-called steroid pseudorheumatism may have positive serological tests for lupus erythematosus. This syndrome is avoided by gradual tapering of dosage and by avoiding excessive dosage of corticosteroids in the first place.

Conn & Blitzer (23) recently have challenged the long-held clinical notion that peptic ulceration of the upper gastrointestinal tract could occur following all corticosteroid therapy. The incidence of proved peptic ulceration was 1.0% in a control population of nearly 1500 patients but 1.4% in a population of 2000 steroid-treated patients. The incidence of upper gastrointestinal hemorrhage and symptoms of ulcer, however, was significant in the combined data presented. It would seem that peptic ulceration is not the hazard it was once considered.

Table 2 Complications of corticosteroid therapy

Musculoskeletal	Metabolic
Myopathy	Precipitation of clinical manifestations, including ketoacidosis, of genetic diabetes mellitus
Osteoporosis–vertebral compression fractures	Hyperosmolar nonketotic coma
Aseptic necrosis of bone	Hyperlipidemia
Gastrointestinal	Induction of centripetal obesity
Peptic ulceration (often gastric)	Endocrine
Gastric hemorrhage	Growth failure
Intestinal perforation	Secondary amenorrhea
Pancreatitis	Suppression of hypothalamic-pituitary-adrenal system
Central Nervous System	Inhibition of fibroplasia
Psychiatric disorders	Impaired wound healing
Pseudocerebral tumor	Subcutaneous tissue atrophy
Ophthalmologic	Suppression of the immune response
Glaucoma	Superimposition of a variety of bacterial, fungous, viral, and parasitic infections in steroid-treated patients
Posterior subcapsular cataracts	
Cardiovascular and renal	
Hypertension	
Sodium and water retention–edema hypokalemic alkalosis	

Corticosteroids given to laboratory animals early in the course of pregnancy have been found to induce a high incidence of cleft palate in the offspring. No such relationship has been noted in human pregnancy and Schatz et al (24) did not observe maternal, fetal, or neonatal mortality in 70 pregnancies and 55 asthmatic patients treated with pharmacologic doses of corticosteroid. Acute adrenal insufficiency did not supervene in the infant nor was there an increased incidence of toxemia of pregnancy in the mother. A slightly increased rate of prematurity occurred in infants born of corticosteroid-treated mothers. On the other hand, fetal mortality has been significantly reduced and previously untreated mothers were given large doses of corticosteroids if they entered premature labor (25). Neonatal experimental animals exhibit marked growth retardation, when given substantial doses of corticosteroids. Loeb (26) demonstrated that low doses of glucocorticoid induced a marked suppression of cell proliferation in growing tissues with stable cell populations, such as the liver of weanling rats. Steroid-induced suppression of somatic growth may involve the suppression of cell proliferation in stable parenchymal tissue. Infants of steroid-treated mothers do not exhibit obvious inhibition in somatic growth. Inhibition of cell proliferation by steroids appears to be a postnatal event. Pharmacologic doses of the corticosteroids inhibit pituitary discharge of certain tropic hormones—the glycoprotein hormones. Re et al (27) demonstrated that dexamethasone inhibits thyroid-stimulating hormone (TSH) secretion and responsiveness to thyrotropin-releasing hormone (TRH), whereas prolactin secretion continues to be stimulated normally by TRH during dexamethasone administration. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are re-

duced in the postmenopausal woman given large doses of corticosteroids. It is likely that dexamethasone-induced suppression of pituitary secretion of TSH, LH, and FSH (the glycoprotein hormones) is a direct pituitary effect and not mediated through hypothalamic-releasing factors.

Suppression of the Hypothalamic-Pituitary-Adrenal System During Administration of Corticosteroids

Suppression of the hypothalamic-pituitary-adrenal system is among the most prevalent and potentially hazardous derangements induced by corticosteroids. Regulation of ACTH-dependent steroidogenesis is accomplished by long or external loop negative feedback. Corticotropin-releasing factor from the hypothalamus activates ACTH release by the anterior pituitary, and ACTH stimulates the conversion of cholesterol to cortisol in the adrenal cortex. As cortisol levels rise in blood, binding sites in the hypothalamus are occupied, and corticotropin-releasing factor is no longer elaborated, until concentrations of cortisol in the extracellular fluid decline. Levels of corticosteroids equipotent to or greater than physiological concentrations of cortisol, when maintained, activate the inhibitory feedback pathway. ACTH and cortisol secretion are negligible while supraphysiologic, constant levels of exogenous corticosteroids are continued. In 1953, Salassa, Bennett & Keating (28), in a series of postmortem examinations, showed that in a man receiving high dose steroid therapy, there is a significant reduction in adrenal weight within 5 to 10 days after the beginning of corticosteroid therapy. It is generally acknowledged that adrenal atrophy is apparent in nearly all species tested after 10 days of high dose corticosteroid therapy.

Adrenocortical atrophy appears to be completely reversible when caused by deprivation of ACTH and reduced ACTH-secretory activities, which are caused by deprivation of corticotropin-releasing factor. Hypothalamic corticoptropin-releasing factor production is variably suppressed during the first 1 to 2 weeks of steroid therapy, but, as the duration of therapy is extended, responsiveness of the hypothalamic-pituitary-adrenal system is progressively diminished and continues after steroid therapy is withdrawn. In a number of studies, inhibition of the feedback response persists up to 12 months if corticosteroid levels are maintained in the supraphysiologic range for only two weeks.

The responsiveness to stress, however, may be recovered much earlier than 12 months. We have examined many patients in this laboratory with respect to stress responsiveness and the relations between duration of therapy, dose, and length of time after cessation of therapy (29). These studies are described here and involve the use of the pyrogen test (30). Purified lipopolysaccharide (0.25 μg), derived from salmonella abortus-equi, was injected intravenously into healthy subjects, and activation of the hypothalamic-pituitary-adrenal system was apparent within 2 hr, since the plasma cortisol level increased 200%.

The results of studies in patients as compared with those of healthy controls appear in Table 3. Two of the test groups of patients were subjected to the intravenous pyrogen test, 24 hours after the last dose of corticosteroid. The duration of corticosteroid therapy in both groups varied from one month to eight years. The

high dose group received 50 mg or more of cortisol or equipotent doses of its synthetic analogues daily. The low dose group received 20 mg or less of cortisol or equipotent doses of its synthetic analogues daily. High dose corticosteroid therapy abolished the hypothalamic-pituitary-adrenal response to pyrogen stress, whereas low doses of steroids produced only insignificant alterations to the response to pyrogen stress. Other studies involving testing of the negative feedback response (metyrapone test) may be abnormal even at rather modest doses of corticosteroids. Patients receiving high dose corticosteroid therapy whose corticosteroid regimen was discontinued one month before the pyrogen test was undertaken showed somewhat more variable responses, yet the 4-hr response was clearly attenuated. In patients whose corticosteroid therapy was discontinued five months before the pyrogen test was given, responsiveness to this type of stress was completely restored. Patients who had been receiving alternate-day high dose corticosteroid therapy were tested on the day they received no steroid, and no interference with pyrogen stress responsiveness was demonstrated. Apparently, prolonged negative feedback inhibition is not of clinical significance, but response to pyrogen stress more nearly relates to the problem of stress responsiveness in general.

Single, daily doses of less than 20 mg of cortisol or equipotent doses of its analogue and cessation of corticosteroid therapy for a period of 5 months are associated with normal pyrogen stress responsiveness, and acute adrenocortical insufficiency in these patients is unlikely to supervene. Similarly, patients receiving alternate-day steroid therapy have little or no attenuation of pyrogen stress response. It would seem that low dose and alternate-day steroid therapy are the most desirable modalities of therapy, since they obviate concern over diminished stress responsiveness—the most hazardous complication of corticosteroid therapy.

The question of whether or not intermittent stimulation of the adrenal cortex with corticotropin in patients treated with pharmacologic doses of corticosteroids will preserve the functional integrity of the hypothalamic-pituitary-adrenocortical axis remains unsolved. In dexamethasone-suppressed normal subjects, intermittent corticotropin administration in the form of the synthetic 1-18 corticotropin maintains a hyperresponsive secretory adrenal cortex, as indicated by the studies reported by Kolanowski et al in 1975 (31). Several studies have suggested that chronic corticotropin stimulation induces less suppression of the hypothalamic-pituitary-adrenocortical axis, but it is emphasized that in order to obtain less suppression it is necessary to stimulate repeatedly with corticotropin throughout the entire period of treatment, which is not practical. Administration of corticotropin at the end of

Table 3 Results of the pyrogen response test in steroid treated patients (34)

	Control	Low dose (≤ 20 mg)	High dose (> 50 mg)			Alternate day
Time since last dose of corticosteroid		24 hr	24 hr	1 month	5 months	24 hr
Plasma cortisol (μg/dl) 4 hr after pyrogen	34 ± 4.2	28±5.9	5±3.5	13.4±7.6	37±4.8	35.6±3.8
P value test vs control	–	NS	< 0.001	< 0.02	NS	NS

prolonged corticosteroid therapy is ineffective in restoring hypothalamic-pituitary-adrenocortical functional integrity.

Alternate-Day Corticosteroid Therapy

Whenever possible, in patients requiring high dose, prolonged corticosteroid therapy, the alternate-day program should be attempted. One should *not* use alternate-day palliative, low dose steroid therapy in the treatment of rheumatoid arthritis and lupus erythematosus because of the danger of precipitating the peculiar panmesenchymal response. It is even recommended, for patients who seem to require consecutive, daily, high dose steroid therapy, that alternate-day therapy be attempted after the underlying disease is quiescent. With alternate-day or intermittent corticosteroid therapy, the hypothalamic-pituitary-adrenal system is not disturbed, the negative calcium balance is much less intense, the negative nitrogen balance is similarly reduced, and often only the desired therapeutic effect is retained. Alternate-day corticosteroid therapy allows for the administration of much higher total dosage. An extensive literature on the virtues of alternate-day corticosteroid therapy attests to the efficacy and safety of this program.

In Table 4 are listed the disease entities that might be expected to respond to alternate-day therapy. Both bronchial asthma and ulcerative colitis have been managed on an alternate-day basis successfully, but a significant portion of patients are unable to tolerate the omission of dosage within a 24-hr period. Also listed in Table 4 are those conditions in which alternate-day therapy may, in fact, be hazardous. Hunder et al (32) found that patients with temporal or giant cell arteritis would tolerate daily solitary dosage but that one half of the patients treated on an alternate-day basis were symptomatic.

Table 4 Indications and contraindications for alternate-day corticosteroid therapy

May be effective	Ineffective
Asthma	Complications of systemic lupus erythematosus: nephritis, thrombocytopenic purpura, CNS involvement
Ulcerative colitis	Polymyositis
Subacute hepatic necrosis	Polymyalgia rheumatica and temporal arteritis (giant cell)
Chronic active hepatitis	Severe rheumatoid arthritis
Severe alcoholic hepatitis	
Gluten-sensitive enteropathy	
Hemolytic anemia	
Idiopathic thrombocytopenic purpura	
Acute lymphocytic leukemia	
Disseminated Hodgkin's disease	
Acute rejection after tissue transplantation	
Macroglobulinemia	
Sarcoidosis	
Subacute thyroiditis	
Metastatic cancer of breast, prostate	
Cerebral metastases with brain edema	

Topical and Inhalant Corticosteroids with Local Anti-Inflammatory but Little Systemic Effect

Beclomethasone dipropionate, as an aerosol, has been demonstrated to be an effective agent in the treatment of bronchial asthma (33). This steroid ester exhibits intense topical or local activity and almost no measurable systemic activity. Aerosol dosage of beclomethasone dipropionate in an inhaled dose of less than one sixth the usual oral dosage of potent corticosteroid, such as dexamethasone or betamethasone, controls the symptoms of chronic bronchial asthma as completely or more so than the oral preparations. In trials carried out in the United Kingdom with this agent, the only complication observed was a 4% incidence of oral candidiasis. Local corticosteroid-ester therapy is to be preferred if significant systemic absorption does not occur, or if local anti-inflammatory activity is apparent in the absence of systemic metabolic effects.

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