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# MECHANISMS OF GLUCOCORTICOID ACTION ON IMMUNE PROCESSES

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## INTRODUCTION

Administration of pharmacologic dosages of glucocorticosteroids is one of the therapeutic mainstays in the treatment of a large number of inflammatory and immunologically mediated diseases. Despite their widespread use and despite a substantial amount of research regarding their mode of action, the precise mechanisms whereby glucocorticosteroids modulate the immune response still require elucidation. However, much progress has been made in recent years, and in the present article we highlight the important advances in this area.

Several pitfalls should be mentioned regarding the evaluation of the enormous literature on the effect of corticosteroids on immune responses. First, Claman (1) has emphasized the important differences between the effects that corticosteroids have in corticosteroid-sensitive species such as the mouse, rat, and rabbit and corticosteroid-resistant species such as the guinea pig, monkey, and man. Thus, many studies showing profound effects on immunological parameters in a corticosteroid-sensitive animal do not apply to man. The present article emphasizes those effects that have been shown to be operative in humans. Second, many studies have employed in vitro systems and shown effects only at concentrations of corticosteroids that are unattainable in vivo for any significant period of time (2). Furthermore, in vivo studies must deal with the fact that administration of corticosteroids causes a dramatic redistribution of cells in the circulation (see below), and only the functions of those cells remaining in the circulation



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are studied. Third, our understanding of immune processes has increased exponentially in recent years and the complexity and interrelationships of immune regulatory mechanisms have only recently been realized. Corticosteroids have effects on many stages of the immune process, and at times these effects appear antagonistic. Thus, it is difficult in some instances to conceptualize in a simple model the effects of corticosteroids on certain aspects of the immune response.

This review is divided into the following sections with the understanding that many of the immune processes discussed separately in each section have obvious overlap: (*a*) glucocorticoid receptors; (*b*) glucocorticoid effects on leukocyte movement; (*c*) glucocorticoid effects on leukocyte functions; (*d*) glucocorticoid effects on antibody production, complement, and various other humoral factors involved in the immune response; (*e*) vascular and tissue effects of corticosteroids that are germane to its action in various inflammatory and immunologic processes; (*f*) summary.



## GLUCOCORTICOID RECEPTORS

The currently accepted cellular model (3–7) for glucocorticoid action on most tissues states that corticosteroids can freely penetrate cellular membranes and bind to a specific steroid-binding protein receptor in the cytoplasm of the cell forming a steroid-receptor complex(s). This complex then binds or becomes associated with the cell nucleus (probably the DNA) and signals the production of RNA. The RNA directs the production of new proteins (many are probably enzymes) which ultimately determine the response of the cell to the hormone.

This cellular model of glucocorticoid action has been shown in several animal systems to be applicable to various stages in the immune process (4). Rat thymocytes that are inhibited or lysed by glucocorticoids contain glucocorticoid receptors (8). When inhibitors of RNA and protein synthesis in vitro are used, the earliest physiological effect of glucocorticoids on rat thymocytes, i.e. inhibition of glucose transport, has been shown to be closely associated with RNA and protein synthesis (9). In this rat thymocyte model, the glucose transport inhibition may be followed by inhibition of protein and nucleic acid metabolism, cell growth inhibition, and subsequent cell death (4). In several other animal models the presence or absence of binding to steroid receptors has correlated well with elicitation of the biological response; loss of receptors has been associated with a loss of steroid response (4).

Most of the above studies were performed in steroid-sensitive species and, as mentioned above, man is corticosteroid resistant. Studies in humans have been less definitive. Corticosteroid receptors were first demonstrated in

humans in neoplastic cells such as blastic cells from acute lymphoblastic leukemia (10) and acute myeloblastic leukemia (11). In lymphoblasts, the presence of corticosteroid receptors strongly correlated with the ability of in vitro corticosteroids to inhibit thymidine uptake into DNA. Patients with corticosteroid receptors in their lymphoblasts were clinically responsive to combination chemotherapy that included glucocorticoids (10). Recently, glucocorticoid receptors have been described in normal human lymphocytes and in lymphocytes that had been stimulated with phytohemagglutinin (12). Unlike rat or mouse thymocytes, human thymocytes or lymphocytes are not lysed even by suprapharmacologic concentrations of corticosteroid (1, 2, 13, 14), and therefore cell death cannot be used as a marker for steroid effect. In humans, the steroid-receptor interaction may mediate effects on lymphocyte traffic, activation, or functional capability (see below). However, thus far, good correlations between steroid effect and steroid-receptor binding in normal human lymphocytes are lacking. In fact, a recent study found no difference in specific glucocorticoid receptors between purified populations of human peripheral blood thymus derived (T) and non-T lymphocytes (15). However, previous work (see below) has demonstrated that T lymphocytes are more sensitive to the in vivo and in vitro suppressive effects of corticosteroids than are non-T cells. The explanation for this lack of correlation is unclear at present. It may well be due to lack of sensitivity of our current receptor assay system or due to a failure to identify subpopulations within the T- or non-T–cell populations. Another possibility is that corticosteroid receptors do trigger the drug effect on these cells but the final expression of these effects is modulated by as yet unidentified factors.

## GLUCOCORTICOID EFFECTS ON LEUKOCYTE MOVEMENT[1]

### *Lymphocytes*

In corticosteroid-sensitive species, glucocorticoid administration produces a profound lympholytic effect with depletion of lymphocytes from lymph nodes, spleen, and thymus and results in a significant circulating lymphocytopenia (1, 16–18). The major mechanism of lymphocytopenia in these sensitive species is cell death. In corticosteroid-resistant species including man, administration of glucocorticoid results in a circulating lymphocytopenia maximal at 4–6 hr after hormone administration. However, since even suprapharmacologic concentrations of corticosteroid do not produce lymphocyte death in humans (1, 2, 13, 14), the mechanism of circulat-

[1]See Table 1.

**Table 1** Glucocorticoid effects on leukocyte movement in humans

| |
|---|
| *Lymphocytes* |
| Circulating lymphocytopenia 4–6 hr following drug administration secondary to redistribution of cells to other lymphoid compartments. |
| Depletes recirculating lymphocytes. |
| Selectively depletes T lymphocytes (especially $T_M$ subset) more than B lymphocytes. |
| *Monocyte-Macrophages* |
| Circulating monocytopenia 4–6 hr following drug administration probably secondary to redistribution. |
| Inhibits accumulation of monocyte-macrophages at inflammatory sites. |
| *Neutrophils* |
| Circulating neutrophilia. |
| Accelerated release of neutrophils from the bone marrow. |
| Blocks accumulation of neutrophils at inflammatory sites probably secondary to reduced adherence. |
| *Eosinophils* |
| Circulating eosinopenia probably secondary to redistribution. |
| Decreased migration of eosinophils into immediate hypersensitivity skin test sites. |



ing lymphocytopenia is quite different from that of steroid-sensitive species and involves the redistribution of lymphocytes out of the circulation into other body compartments (2, 19–23). In the corticosteroid-resistant guinea pig, labeling studies have demonstrated corticosteroid-induced redistribution of circulating lymphocytes to the bone marrow (23).

The characteristics of the lymphocytes that are and are not depleted from the circulation provide information regarding the specificity of corticosteroids. One method of defining lymphocyte subpopulations is based on their migration or recirculating capabilities. In multiple animal species (24–26) and in man (27), there are two distinct populations of lymphocytes: One population, the recirculating lymphocytes, can freely migrate or recirculate into and out of the intravascular space in constant equilibrium with the much larger total body recirculating lymphocyte pool which travels through spleen, lymph node, thoracic duct, and bone marrow. A second population is the nonrecirculating pool of lymphocytes that are not readily capable of free migration and will live out their life span within the intravascular space. Glucocorticoid administration is capable of causing the recirculating lymphocyte to leave the intravascular space but does not affect the nonrecirculating lymphocyte (20, 22). Thus, the lymphocytopenia caused by glucocorticoid administration to normal man results from a redirection of normal lymphocyte traffic.

Another important feature of the corticosteroid-induced lymphopenia is its relative selectivity for T lymphocytes. Although quantitatively both T-

and bone marrow–derived (B) lymphocytes are depleted from the circulation (Figure 1*a*), there is a relatively greater effect on the T cell as compared to other lymphocyte subpopulations [Figure 1*b;* see refs. (2, 19–22)]. An interesting recent observation (28) is that within the T-cell populations, corticosteroid administration causes a greater depletion of those T cells with an Fc receptor for IgM ($T_M$) compared to those T cells with an Fc receptor for IgG ($T_G$). Since these T cells subsets may have different functions in regulation of the immune response (29), this may be one mechanism by which corticosteroids can exert a selective effect on immunologic regulation.

The precise mechanism whereby glucocorticoid administration alters lymphocyte recirculation and causes this profound lymphopenia has not been elucidated as yet. However, it has been shown that lymphocyte recirculation can be altered by incubating lymphocytes with trypsin (30), glycosidases (31), plant lectins (32), or allogeneic cells (33). Since it is known that corticosteroids are capable of causing changes in the surface

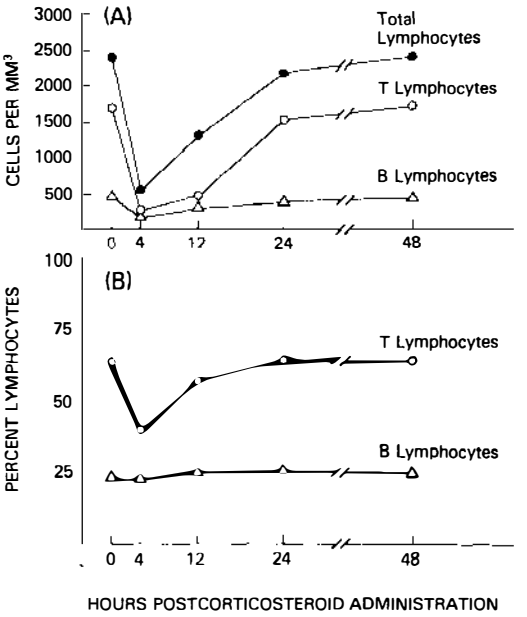


*Figure 1* Effect of corticosteroid administration to a normal human volunteer demonstrating the differential effects on lymphocyte subpopulations. Twelve milligrams of dexamethasone were administered orally at time 0 and serial determinations were performed. In *a* a marked decrease in the absolute number of lymphocytes as well as T and B subpopulations is evident. Part *b* emphasizes that a proportionally greater number of T lymphocytes than B lymphocytes are depleted from the circulation.

membranes of cells (3, 4), it would be reasonable to postulate, though it has not been proven, that glucocorticoids cause a change in the molecular configuration of certain lymphocytes allowing them to pass through the vessel endothelium. It will require further study to determine whether this glucocorticoid-induced change in lymphocyte recirculation results from effects of corticosteroid on the lymphocyte or on the blood vessel endothelial cell.

It is interesting to note that the ability of corticosteroid administration to cause lymphocyte depletion from the circulation is not confined to an isolated single bolus of drug. In animals, depot regimens designed to produce constant levels of corticosteroid result in a continuous lymphopenia (23). Alternate-day therapy with a short-acting steroid preparation will produce 48-hr cycles consisting of a lymphocytopenia 4–6 hr following drug administration with a return of lymphocyte counts to normal by 24 hr and remaining normal throughout the "off" day. This cycle of depletion and normalization of circulating lymphocyte counts will be repeated even after months and years of chronic alternate-day therapy (2). Thus, intermittent doses of corticosteroid as employed in alternate-day therapy do not produce a cumulative lymphopenia; the kinetics are related to each dose administration.



## *Monocytes-Macrophages*

Administration of corticosteroid produces a profound monocytopenia at 4–6 hr following drug administration with a return to normal (19, 20) or in some cases supranormal levels by 24 hr (34). By 48 hr circulating monocyte counts are always back to baseline. The circulating monocytopenia is quite profound (frequently to fewer than 50 cells per $mm^3$) and has been reported to be proportionately greater than the lymphocytopenia (34). The mechanism of the monoytopenia is not known and is quite difficult to study because of technical constraints of separating purified monocytes for labeling studies. In the mouse, hydrocortisone administration causes a moderate decrease in release of monocytes from the bone marrow, but this was not judged significant enough to account for the profound circulating monocytopenia (35). A redistribution phenomenon similar to that of the lymphocyte is the probable mechanism of corticosteroid-induced monocytopenia, but this remains unproven.

The ability of corticosteroids to decrease the accumulation of macrophages at an inflammatory site is discussed in the next section.

## *Neutrophils*

Administration of glucocorticoid produces a neutrophilic leukocytosis that reaches a peak at 4–6 hr following drug administration. This evaluation in

neutrophil count results from several processes: an accelerated release of mature neutrophils from the bone marrow (35), an increase in neutrophil circulating half-life (36), and a reduced neutorphil egress from the blood (37, 38). The ability of corticosteroid administration to profoundly decrease the number of neutrophils and monocyte-macrophages that accumulate at an inflammatory site is one of the most important effects of in vivo glucocorticoids. This effect is readily attainable at pharmacologic dosages of glucocorticoids and a significant effect is evident within 2 hr after a single dose of hormone (37). This decrease in accumulation of neutrophils and monocyte-macrophages at an inflammatory locus is probably the major mechanism of the anti-inflammatory effect of glucocorticoids and is the likely cause for the impairment of host defenses seen in patients on daily corticosteroid therapy (2).

It should be pointed out that this corticosteroid-induced decrease in accumulation of cells at inflammatory loci applies to the monocyte-macrophage as well as the neutrophil. In fact, both of these inflammatory cells seem to be approximately equally diminished at an inflammatory focus by a single dose or daily administration of corticosteroid (37). Interestingly, with alternate-day prednisone regimens, during the "on" day both monocyte and neutrophil accumulation were decreased (38), whereas on the "off" day monocyte but not neutrophil accumulation was decreased (38). This suggests that the monocyte-macrophage is more sensitive than the neutrophil to the anti-inflammatory properties of glucocorticoid administration.

The mechanism underlying this decrease in inflammatory cell accumulation may well be explained by alterations in adherence phenomena. Since in vitro chemotaxis of neutrophils is only inhibited at very high concentrations of corticosteroid that are probably not attainable in vivo (39), adherence of the neutrophil to the vessel endothelial cell has become the most likely site of glucocorticoid action. In 1952, Ebert & Barclay (40) reported that cortisone could decrease the accumulation of neutrophils at vascular endothelium after an inflammatory stimulus. Recent work by MacGregor (41–43) has demonstrated that administration of glucocorticoid to humans induces a plasma factor that dramatically decreases neutrophil adherence to nylon fiber columns. When this corticosteroid-induced plasma factor was mixed with an "adherence-increasing factor" found in inflammatory diseases, the increase in adherence was neutralized resulting in normal neutrophil adherence (42).

## *Eosinophils and Basophils*

Corticosteroid administration produces a profound decrease in circulating eosinophils, a fact that formed the basis of the Thorn test for adrenal

insufficiency (44, 45). This circulating eosinopenia was thought secondary to corticosteroid-induced eosinophil lysis. However, more recent evidence suggests redistribution of cells to other body compartments as a more likely mechanism (46). A recent study has demonstrated that corticosteroid administration will decrease migration of eosinophils into immediate-type skin test sites (47).

Because of the small numbers of circulating basophils, very little is known of the kinetics of circulating basophils.



## GLUCOCORTICOID EFFECTS ON LEUKOCYTE FUNCTION[2]

Some of the most difficult studies to interpret are investigations of glucocorticoid effects on leukocyte function. Many of the in vitro studies are done at concentrations of drug that are seldom if ever achieved in vivo. In vivo studies are performed on the cell populations remaining in the circulation after corticosteroid administration, and the cells studied have been washed free of drug. Thus, one must be cautious in interpreting these functional studies.

### *Lymphocytes*

A very large number of studies have been performed on the topic of corticosteroids and lymphocyte function, and there are a number of reviews of this subject (1, 2, 4, 48, 49). Most of the recognized lymphocyte functions—proliferation, mediator production, response to mediators, cytotoxic effector function—have been shown to be affected by corticosteroids [for details see ref. (2)]. However, several of these functions are relatively sensitive or resistant to glucocorticoids. Further, in several of these complex immune processes, the lymphocyte itself has been found relatively resistant, whereas accessory cells, e.g. macrophages, are comparatively sensitive to glucocorticoids.

It is well known that cutaneous delayed hypersensitivity, a local manifestation of cell-mediated immune reactions, is suppressed by daily glucocorticoid administration (48). However, cell transfer experiments have shown that this suppression results from decreased recruitment of macrophages (Figure 2) necessary for expression of hypersensitivity and is not due to a suppression of the sensitized lymphocyte (50–52). In an in vitro correlate of delayed hypersensitivity, the migration inhibition factor (MIF) assay, antigenic processing, and MIF production are unaffected by corticosteroid. However, steroid directly antagonizes the effect of MIF on the macrophage (53). Most studies of soluble mediators of the immune

[2]See Table 2.

Table 2 Glucocorticoid effects on leukocyte function in humans

| |
|---|
| *Lymphocytes* |
| Delayed hypersensitivity skin testing suppressed by inhibition of recruitment of monocyte-macrophages. |
| Lymphocyte proliferation to antigens suppressed more easily than proliferation to mitogens. |
| Mixed leukocyte reaction proliferation suppressed. |
| High in vitro concentrations suppress T lymphocyte–mediated cytotoxicity. |
| Antibody–dependent cell–mediated cytotoxicity not depressed. |
| Spontaneous (natural) cytotoxicity suppressed. |
| Regulatory effects on helper and suppressor cell populations. |
| *Monocyte-Macrophages* |
| Cutaneous delayed hypersensitivity suppressed by inhibition of lymphokine effect on the macrophage. |
| Probable blockade of Fc receptor binding and function. |
| Depressed bactericidal activity. |
| Possible decrease in monocyte chemotaxis. |
| *Neutrophil* |
| Probably no effect on phagocytic and bactericidal capability. |
| Antibody–dependent cellular cytotoxicity increased. |
| Probably decreased lysosomal release but little effect on lysosomal membrane stabilization at pharmacologic concentrations. |
| Chemotaxis inhibited only by suprapharmacologic concentrations. |

response, i.e. lymphokines, have found that corticosteroids do not affect the synthesis of the mediator by lymphocytes (53–55). A reasonable generalization is that glucocorticoids do not suppress lymphocyte production of lymphokines, but they do inhibit the ability of the mediator to recruit cells necessary for the expression of the response (2).

The effect of corticosteroids on lymphocyte proliferation has been the subject of many in vitro and in vivo studies. In general, the in vitro studies demonstrate that high enough concentrations of glucocorticoids will suppress the lymphocyte blastogenic response to various mitogens (56–58) although there is not complete agreement on this (59). The effect of in vivo administration of corticosteroid on mitogen-stimulated lymphocyte proliferation is controversial. Some studies have found suppression (60) while others have found suppression by some but not all mitogens (19). However, it is clear from multiple investigations that glucocorticoid administration will suppress responses to antigens more easily than responses to nonspecific mitogens (19, 61, 62). The reason for this is not clear but may relate to the ability of mitogens to activate a larger number of lymphocytes in any given population.

The proliferative response of the allogeneic mixed leukocyte reaction (MLR) can be blocked by pharmacologic concentrations of glucocorticoid (63, 64). Interestingly, a recent paper has provided data suggesting that

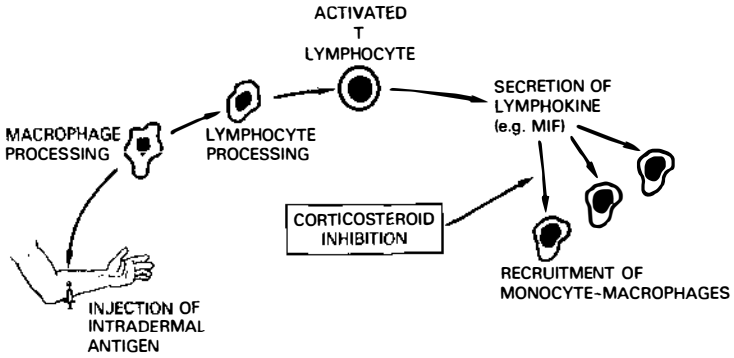


*Figure 2* Schematic representation of the probable site of inhibition of the delayed hypersensitivity skin test response. Corticosteroids do not affect the activated T lymphocyte but inhibit the recruitment of monocyte-macrophages.

physiologic concentrations of corticosteroid can suppress the autologous MLR between T cells and B cells without any suppression of the allogeneic MLR (65). This interesting finding suggests that corticosteroids may have a physiologic role in suppressing T-cell reactivity to self-antigens. An interesting hypothesis in this regard has been proposed that the elevation of corticosteroids during stress or trauma is an attempt by the body to prevent establishment of autoimmune disease against hidden antigens that are exposed during disease or trauma (66).

Glucocorticoid action on cell-mediated cytotoxicity is of considerable interest since cytolysis is considered to be one of the important effector functions in cell-mediated immunity. Many of the studies employ allogeneic systems in which the effector cell is presumed (though in many cases not proven) to be a T lymphocyte. Corticosteroids in vitro have been shown to depress direct cytotoxicity against fibroblasts in the mouse (67). In a rat model, in vitro glucocorticoids caused facilitation of the sensitization phase but a decrease in the effector phase of cytolysis (68); this suppression of cytolysis was felt to be secondary to hydrocortisone modification of lymphocyte surface membrane preventing its activation by target cell antigens (69). In vivo corticosteroids have been shown to decrease the ability of mouse splenic lymphocytes from lysing mastocytoma cell targets (70). As previously mentioned, these studies were performed in steroid-sensitive animal models and may not be applicable to man.

Data in humans reveal that glucocorticoids, in very large doses in vitro, can suppress the cytotoxicity of lymphocytes from skin graft recipients against donor fibroblasts (71). Cytotoxicity of lymphocytes from rubella-immune patients against rubella-infected hamster kidney targets is sup-

pressed by moderate concentrations (10 μg/ml) of hydrocortisone (72). Only high suprapharmacologic concentrations of hydrocortisone in vitro were capable of depressing MLR-induced cytotoxicity against allogeneic targets (64). Lymphotoxin release from PHA-stimulated lymphocytes could be inhibited by in vitro hydrocortisone (73). Thus, these data suggest that very high in vitro concentrations of corticosteroid are capable of suppressing lymphocyte (presumed T-cell) cytotoxicity. One in vivo study, designed to investigate the effect of corticosteroid administration on the ability of lymphocytes to become cytotoxic in an MLR, demonstrated decreased cytotoxicity that exactly paralleled the depletion of T lymphocytes from the circulation, suggesting the effect of steroid administration was to deplete effector cells and not to decrease their functional capabilities (63).

Antibody-dependent cell-mediated cytotoxicity (ADCC) has been recognized as a potent effector function of the lymphocyte, specifically the K-lymphocyte (74, 75). Most in vitro and in vivo studies in animals and man have found ADCC activity to be resistant to the effects of corticosteroids. One study in mice demonstrated that neither in vivo nor in vitro hydrocortisone had any effect on ADCC against chicken erythrocyte targets (76). In humans, K-cell function was shown to be slightly reduced after administration of prednisolone (77). However, other studies have demonstrated that glucocorticoids in vivo (34) or in vitro (78) produced no depression of ADCC. In fact, at 4 hr following drug administration, at the point of maximal lymphopenia produced by glucocorticoid administration, ADCC was actually significantly increased. This finding raises an important point about the in vivo effects of corticosteroids. The increase in ADCC was shown to be due to a relative enrichment in the circulation of lymphocytes bearing an Fc receptor for Ig (K cells), because corticosteroid administration had preferentially depleted non-Fc receptor-bearing cells from the circulation (Figure 3). Thus, the major in vivo effect of corticosteroid administration was to selectively deplete subpopulations of lymphocytes from the circulation. The resulting change in ADCC was all secondary to this redistribution effect.

A recently described form of cytotoxicity, spontaneous or natural cytotoxicity, has received attention because of its possible relationship to tumor immunity (79, 80). The effector cell in this form of cytotoxicity is also felt to be the K cell. Interestingly, in contrast to the findings with ADCC, glucocorticoids both in vivo and in vitro have been found to profoundly depress spontaneous cytotoxicity (78).

In recent years investigations have uncovered the crucial role that helper and suppressor cell-cell interactions play in regulation of lymphocyte function. B-cell activation toward antibody production has been shown to be

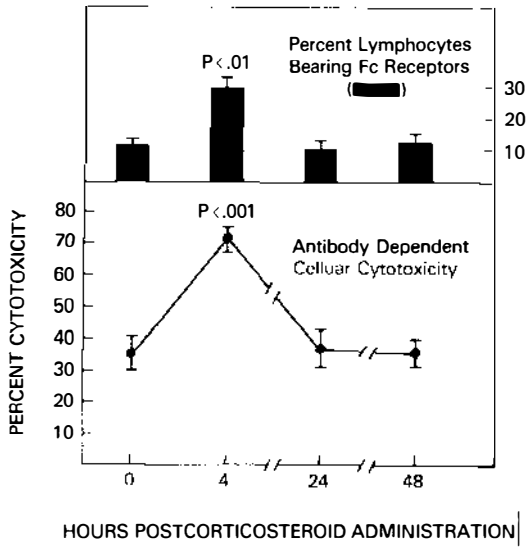


*Figure 3* The effect of corticosteroid (dexamethasone) administration in humans on antibody-dependent cellular-cytotoxicity (ADCC). The effector:target ratio was 10:1 and the target cells were Chang liver cells coated with antibody. Note that the level of ADCC strictly parallels the proportion of Fc receptor-bearing lymphocytes (K cells) in the circulation. This relative enrichment of K cells results from a selective corticosteroid-induced depletion of non-K cells from the circulation (see text).

under the control of at least two separate populations of T lymphocytes, $T_M$ and $T_G$ (29). Corticosteroids have important effects on both these populations of lymphocytes and could therefore potentially affect B-cell function through its action on these T cells. In vivo corticosteroids have been shown to selectively deplete $T_M$ cells more than $T_G$ (28), whereas in vitro glucocorticoid can directly suppress $T_G$ with little effect on $T_M$ cells (81). Similar studies have shown that corticosteroids can remove the suppressor effects of cell suspensions in some patients with common variable hypogammaglobulinemia (82), and glucocorticoids have been shown to inhibit a suppressor cell in human spleen (83).

When corticosteroids inhibit a suppressor influence, antibody production may actually increase. Enhancement of antibody production by corticosteroid administration has been reported in animals (84) and man (85). The addition of pharmacologic or physiologic concentrations of corticosteroid to an in vitro system of antibody production by human B lymphocytes inhibited the negative effect and produced an enhanced antibody response

(86). Similar enhancement was found in another in vitro system (87). The precise mechanisms of this glucocorticoid-induced enhancement of antibody production will require further study.

### *Monocytes-Macrophages*

As mentioned above, the ability of glucocorticoids to suppress cutaneous delayed hypersensitivity is related predominantly to the steroid's ability to block recruitment of macrophages (50–52); corticosteroid suppression of the MIF response is secondary to antagonism of MIF effect on the macrophage (53).

Results of animal studies of glucocorticoid effect on macrophage phagocytosis have been inconsistent. One group found that in vitro hydrocortisone decreased phagocytosis by mouse peritoneal macrophages but digestion was unimpaired (88). Another study reported that in vivo hydrocortisone produced no effect on phagocytosis by mouse peritoneal macrophages and little effect on intracellular killing (89). Studies in the guinea pig have revealed an enhanced susceptibility to toxic injury of peritoneal macrophages obtained from cortisone-treated animals (90).

Alveolar macrophage mediated cytotoxicity has been studied in a guinea pig model. In vitro or acute in vivo doses of corticosteroid had no effect on macrophage-mediated ADCC; however, chronic steroid therapy produced a significant decrease in macrophage-mediated killing (91). Interestingly, this chronic in vivo glucocorticoid regimen was shown to interfere with the macrophage's ability to bind to the antibody-coated target cell, suggesting that the Fc receptor on the macrophage cell surface had been altered (92). This blockade of Fc receptor function has also been reported with in vitro corticosteroids inhibiting human monocyte Fc receptors (93). If this ability to block Fc receptors is found to be a general property of corticosteroids, it may represent one of the important mechanisms of glucocorticoid action.

Studies on monocyte function in man have found a depression of bactericidal activity by both in vitro (94) and in vivo (95) corticosteroids. However, monocyte chemotaxis was markedly depressed by in vitro corticosteroid (94), whereas chemotaxis was unaffected by in vivo glucocorticoid (95). This dichotomy may represent the need for constant presence of corticosteroid to suppress monocyte migration, or it may represent a relative corticosteroid resistance of those monocytes that remain in the circulation after corticosteroid-induced monocytopenia. With regard to human monocyte-induced cellular cytotoxicity, one in vivo study found that corticosteroid administration decreased monocyte-mediated cytotoxicity, probably secondary to the profound steroid-induced monocytopenia (34).

In general, the monocyte circulatory kinetics and the monocyte-macrophage functional capabilities are relatively sensitive to the action of corticosteroids. Since the monocyte is felt to be the major cell involved in granuloma formation (96), this glucocorticoid sensitivity of monocytes may explain the clinical observation that corticosteroids are effective in many granulomatous diseases.

## *Neutrophil*

Several investigators have demonstrated that very high in vitro concentrations of corticosteroid are capable of suppressing neutrophil phagocytosis and bactericidal capability (2, 49, 97–99); however, these drug concentrations are rarely achieved in vivo in man. Multiple in vivo studies of neutrophil phagocytosis employing dosages as high as 1000 mg of methylprednisolone (60, 77, 100, 101) have found no impairment of phagocytosis or bacterial killing. In a study of neutrophil-mediated ADCC, cytotoxicity was actually found to be increased by corticosteroid administration (34).

The ability of glucocorticoids to stabilize lysosomal membranes and prevent release of inflammatory enzymes has been advocated as an important anti-inflammatory mechanism of corticosteroid action (102–104). This concept has been challenged by studies demonstrating that neutrophil lysosomes (the original studies were performed on liver lysosomes) are not stablized even by very high concentrations of corticosteroids (105). Other studies on lysosomes have demonstrated that high concentrations of in vitro corticosteroids can inhibit the release of lysosomal enzymes from neutrophils (99, 106, 107). Again, the relevance of this to the in vivo situation must be raised.

In vitro chemotaxis of neutrophils has been shown to be inhibited only by very high concentrations of corticosteroid (39, 94). As previously mentioned, an alteration in adherence may explain the corticosteroid-induced decrease in neutrophil accumulation at an inflammatory focus.

## *Eosinophils*

Although a number of functions of the eosinophil have been described (44, 108, 109), the effect of corticosteroids on these functions has not been studied. It is of some interest that corticosteroids have been found to be effective therapy in a subpopulation of patients with idiopathic eosinophilia or the Hypereosinophilic syndrome (110). Whether corticosteroids are efficacious because of their known eosinopenic effect or because of inhibition of an eosinophil functional capability is at present unknown.

# GLUCOCORTICOID EFFECTS ON HUMORAL FACTORS INVOLVED IN THE IMMUNE RESPONSE[3]

## *Antibody Production*

In corticosteroid-sensitive species, a corticosteroid-induced suppression of antibody production can be easily demonstrated (1). In humans, high dose daily administration of methyprednisolone (96 mg per day for 3 to 5 days) produced mild decreases in serum immunoglobulin levels secondary to increased catabolism and decreased synthesis (111). However, specific antibody synthesis in man is not suppressed by corticosteroids (1, 2, 85, 112). As previously mentioned, there are certain instances in which antibody production is actually enhanced by glucocorticoids (84–87).

## *Complement*

Corticosteroid-sensitive species are a very poor model in which to evaluate complement metabolism because chronic steroid administration produces a generalized catabolic state. However, in guinea pigs, which are relatively corticosteroid resistant, high doses of in vivo corticosteroids produced depressions of multiple complement components (113). It is unclear whether this magnitude of complement reduction (less than 60%) is of any physiological or clinical significance. In man, there is no evidence that corticosteroids affect complement metabolism (112).

## *Reticuloendothelial Clearance*

Glucocorticoid administration decreases the clearance of antibody-coated and antibody-complement–coated erythrocytes by the reticuloendothelial system (RES) in guinea pigs (114, 115). This decrease in clearance probably results from the effects of chronic steroid administration on the membrane Fc and complement receptor of the macrophage, as detailed above (91–93). This decreased clearance has potential importance in the treatment of immune hemolytic anemia (116).

## *Kinins*

These vasoactive peptides may play a significant role in the inflammatory responses of many disease states (117). Original reports suggested that glucocorticoids have important inhibitory effects on kinin activation in vitro (118) and in vivo (118, 119). However, these findings have been disputed, and the present status of glucocorticoid effect on kinins is in flux (112, 120).

[3]See Table 3.

**Table 3** *Glucocorticoid effects on humoral factors in humans*

| |
|---|
| Mild decrease in immunoglobulin levels but no decrease in specific antibody production. |
| Complement metabolism probably unaffected. |
| Decreased reticuloendothelial clearance of antibody–coated cells. |
| Effects on kinins and prostaglandins controversial. |
| Inhibit plasminogen activator release. |
| Potentiate the actions of catecholamines. |
| Possibly antagonize histamine–induced vasodilatation. |



## *Prostaglandins*

Corticosteroids have a variable effect on prostaglandin metabolism, with little effect reported in some systems (121) and inhibition reported in others (122, 123). The mechanisms and clinical significance of these observations will require further study.

## *Plasminogen Activator*

Glucocorticoids have been shown to block the production of plasminogen activator by mouse macrophages (124) and human neutrophils (125). It has been postulated that macrophages migrate into inflammatory sites by secreting plasminogen activator which activates plasmin, an enzyme that can digest some perinflammatory supporting tissues and facilitate migration (124). Glucocorticoids would have an anti-inflammatory effect by suppressing release of this enzyme.

## *Histamine*

Although corticosteroids have been reported to decrease histamine content of tissues in the guinea pig (126), steroids have little protective effect in animal anaphylaxis or histamine shock (112). Clinically, glucocorticoids are very effective therapy for allergic rhinitis and asthma; however, it is not clear whether this is secondary to the corticosteroid anti-inflammatory effect or some other mechanism (112, 126). Corticosteroids have been shown to produce vasoconstriction (see below) and this may physiologically antagonize histamine-induced vasodilation (127).

## *Catecholamines*

One theory of glucocorticoid action in asthma is corticosteroid potentiation of the actions of catecholamines (126). Although this potentiation has been demonstrated in leukocytes in vitro (128), it is not clear whether this mechanism is operative clinically.

## *Cyclic Nucleotides*

Corticosteroids have the ability to increase cyclic AMP in human lymphocytes (128) and can enhance the increase in cyclic AMP produced by

catecholamines and prostaglandin $E_1$ (128, 129). However, it is generally accepted that cyclic AMP is not the second message of glucocorticoid action (3), although their effects on tissues are very similar (3). As previously mentioned, their ability to potentiate the action of other agents on the cyclic nucleotides may explain the efficacy of glucocorticoid therapy in asthma (126).

## VASCULAR AND TISSUE EFFECTS OF CORTICOSTEROIDS THAT ARE GERMANE TO THEIR ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE ACTIONS

In inflammatory and immunological reactions there is extravasation of fluid and cells out of the vascular compartment into surrounding tissues. The ability of glucocorticoids to inhibit this extravasation is probably mediated through the effects of corticosteroids on leukocytes and humoral factors that have been explained above. However, there may be an action of glucocorticoids specifically on the vessel wall. It has been known for some time that glucocorticoids cause a decrease in leukocyte diapedesis and fluid accumulation and an increase in vascular endothelial integrity at an inflammatory focus (40). This is probably partially due to the well-described vasoconstrictive abilities of glucocorticoids in localized areas of the capillary bed (40, 130, 131). Interestingly, hemodynamic studies have demonstrated that corticosteroid administration produces an increase in cardiac output and a decrease in total peripheral vascular resistance in normal humans and in patients in shock (132). In fact, corticosteroids have been advocated as effective vasodilators in low output syndromes (133). This discrepancy may be explained by selective vasoconstriction of some capillary beds with vasodilation of others as has been described with catecholamines, or it may be due to a difference in the drug doses or experimental conditions employed. A possible explanation could be that corticosteroids cause vasoconstriction in inflammatory sites and vasodilation elsewhere.

## SUMMARY

Glucocorticoids have a multitude of effects on many of the stages in inflammatory and immune processes. In general, corticosteroids have greater effects on leukocyte traffic than on function, and they have more effect on cellular than humoral processes. Probably the most important physiological and clinical effect of corticosteroid administration in humans is their ability to inhibit the recruitment of neutrophils and monocyte-macrophages to an inflammatory site. It is this mechanism that probably accounts for the

increase in infections seen with daily corticosteroid therapy. Of note is the fact that alternate-day corticosteroids do not inhibit recruitment of neutrophils and are not associated with an increased infection rate. Glucocorticoids produce a marked lymphocytopenia secondary to a redistribution of lymphocytes out of the circulation to other lymphoid compartments; this redistribution selectively affects T lymphocytes more than other populations.

Glucocorticoids suppress delayed hypersensitivity skin testing by blocking the recruitment of monocyte-macrophages by sensitized T lymphocytes. Corticosteroids can inhibit a variety of functional capabilities of the lymphocyte and probably produce complex regulatory effects on suppressor and helper cell populations. Monocyte-macrophage function is relatively sensitive to the effects of glucocorticoids and this sensitivity probably accounts for many glucocorticoid suppressive effects. Neutrophil function is relatively resistant to these agents.

Glucocorticoid effects on immunoglobulin synthesis and complement metabolism are not felt to be clinically significant. However, corticosteroids have an important inhibitory effect on reticuloendothelial clearance of antibody-coated cells. Corticosteroid potentiation of the action of catecholamines and prostaglandins may have importance in certain disease states.

Corticosteroids are important and widely used therapies in the treatment of a large number of inflammatory and immunologically mediated diseases. Continued advances in understanding of the mechanisms of action of these agents should allow their more rational and effective use in clinical settings.

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