# THE ROLE OF ADRENOCORTICAL STEROIDS IN INFECTION, IMMUNITY AND HYPERSENSITIVITY[1]

FREDERICK G. GERMUTH, JR.

*Department of Pathology, School of Medicine, The Johns Hopkins University, Baltimore, Maryland*

Since the discovery of the therapeutic action of cortisone and the adrenocorticotropic hormone (ACTH) in rheumatoid arthritis (69), a vast literature has accumulated concerning the effects of treatment with these hormones on a wide variety of diseases. It has become evident that cortisone and ACTH have the remarkable ability of modifying the natural course of many inflammatory diseases of diverse nature. Although an understanding of the role of these hormones in inflammation must await detailed knowledge of their effects on cellular metabolism, studies on the effect of cortisone and ACTH on inflammation and infection of known etiology have yielded certain specific information. It is the purpose of this review to consider the current status of the role of adrenocortical hormones in infection, immunity and hypersensitivity.

## I. A BRIEF CONSIDERATION OF THE METABOLIC ACTIVITIES OF ADRENOCORTICAL SECRETIONS

*1. Mineralo-corticoids (11-desoxycorticosterone and related steroids).* These steroids are wholly concerned with the regulation of electrolyte and water balance (143). The administration of DOCA produces retention of sodium, chloride and water and an increased excretion of potassium in subjects with adrenal insufficiency and to a lesser extent in normal individuals (137, 141). As a result of electrolyte and water retention, an increase in plasma volume and a rise in blood pressure may result (137). Conversely, in the absence of this adrenocortical secretion, a loss of electrolytes and water results in a diminution of plasma volume leading to hypotension and at times vascular collapse (137). The regulation of electrolytes is accomplished primarily by direct action of DOCA on the renal tubules (122), although a slight effect on intracellular electrolytes and water, independent of the effect on the renal tubules, has been established in nephrectomized rats (149). Large doses of DOCA produce no discernible effect on inflammatory phenomena.

There is evidence suggesting that mineralo-corticoids are produced primarily in the glomerulosa zone of the adrenal cortex. The administration of large amounts of potassium, or restriction of sodium, produces hyperplasia of this zone in the rat (112). Large doses of DOCA cause atrophy of the glomerulosa zone (63). Since the varied physiologic actions of the different adrenocortical secretions are the consequence of minor differences in chemical structure, it is

[1] The survey of the literature bearing on this review was concluded in December, 1954. The references contained in the bibliography have been selected from a far larger number of articles reviewed by the writer. For previous reviews on this subject the reader is referred to references (43, 75, 80, 137, 138, 143).

likely that the secretion of hormones with a particular function is not entirely confined to one zone of the cortex. Further, the zonal concept of secretion could not easily be applied to the production of corticosterone, compound B, which exhibits both electrolyte-regulating and diabetogenic activities (143).

*2. Glycocorticoids (cortisone and hydrocortisone).* These hormones have only a slight and variable effect on electrolyte and water balance. Studies on sodium retention in patients with Addison's disease have shown that cortisone is approximately one-thirtieth as effective as DOCA (142). The administration of cortisone has a marked effect on protein, carbohydrate and lipid metabolism. Disturbance in protein metabolism is manifested by a decreased urinary nitrogen excretion in adrenal insufficiency and an increased excretion of nitrogen following cortisone therapy (144). The mechanism by which cortisone exerts an action on protein metabolism is still far from clear. It has been suggested that cortisone causes both an increase in protein catabolism and an inhibition of protein anabolism (71). It is generally believed that the diabetogenic effect of cortisone is the result of gluconeogenesis from protein (92). However, studies on the effect of cortisone on basal metabolic rates have indicated that cortisone may also inhibit carbohydrate utilization (143). That cortisone has some effect on lipid metabolism is indicated by the occurrence of lipemia and fatty livers in rabbits receiving large doses of this hormone (52, 118).

Cortisone and ACTH produce a variety of specific effects on tissues. These effects include alterations in the hemopoietic system, in the cardiovascular system and in growth. These alterations are related to the pharmacologic action of cortisone in inflammation and infection. They are discussed in the succeeding portions of this paper.

It is often stated that the zona fasciculata of the adrenal cortex is the site of greatest production of adrenal glycocorticoids. However, evidence for this belief is nothing more than suggestive. This zone may be greatly increased in size in Cushing's disease (83). Although stimulation of the adrenal cortex by ACTH produces hyperplasia of the zona fasciculata, the glomerular and reticular zones are also affected even though to a lesser degree (52, 112, 148).

*3. Sex hormones produced by the adrenal cortex.* These hormones do not appear to play a role in the response of the adrenal cortex to stress. That these substances may be secreted primarily in the reticular zone is indicated by the relationship between tumors and hyperplasia of this zone and the adreno-genital syndrome (17).

## II. ADRENAL INSUFFICIENCY AND RESPONSE TO STRESS INCLUDING INFECTION

Knowledge that adrenal secretions play an important role in infection is not new. In patients with Addison's disease and in adrenalectomized animals, increased susceptibility to stress, including infection, has frequently been observed (137). This susceptibility is characterized not by an increased tendency to local tissue damage by injurious agents or increased propagation of infectious agents, but rather by an inability of the vascular system to adjust to the additional demands made by stress. As a result, a prominent feature of adrenal in-

sufficiency is profound collapse of the circulation (137, 156). The inadequacy of circulatory adjustments in the adrenal-deficient animal is clearly shown by the sequence of events which follows the application of stress to the adrenalectomized animal. The work of Goldstein *et al.* (59) on the origin of muscular fatigability in the adrenalectomized animal is pertinent. Normal rats can swim without interruption for many hours. Adrenalectomized rats cannot sustain work such as swimming for more than a brief period of 20 to 30 minutes, even though they are kept in electrolyte balance by dietary salt. Study by the above workers of the relation of muscular fatigue to blood pressure in the adrenalectomized dog in normal electrolyte balance showed that work performance remained unaltered so long as the blood pressure was maintained above a critical level. Muscular fatigue occurred in the adrenalectomized animal secondarily to a failure of circulation.

It is probable that other stresses (injury, infection) constitute similar demands for proper circulatory adjustments which, in the absence of the adrenal hormones, cannot take place (59). In man, the relationship between acute adrenal insufficiency and circulatory collapse is well illustrated by the Waterhouse-Friderichsen syndrome. In this condition, produced by fulminating infection, vascular collapse is associated with widespread destruction of the adrenal cortex (116). Since similar alterations in the adrenal cortex can be induced in the rat by the administration of large doses of ACTH (148), it is possible that the destruction of the adrenal cortex in severe infection is related to a sudden release of excessive amounts of this hormone.

Failure of the circulation in adrenal insufficiency can be attributed to both a reduction in plasma volume and a loss of vascular tone, so that the integrity of the vascular system cannot be maintained (137, 156). Reduction in plasma volume is clearly the result of deficiency in mineralo-corticoids such as DOCA. However, even when electrolyte balance is maintained by dietary sodium, difficulties in vascular adjustments to stress (*e.g.*, the work of Goldstein quoted above) are encountered. There is considerable evidence in support of an impairment of vascular tone in adrenal insufficiency (156). Hypertension cannot be produced in the adrenalectomized rat or dog by experimental manipulation of the kidneys even though these animals are maintained in electrolyte balance by dietary sodium (156). A direct approach to the study of the effect of adrenal hormones on vascular response has been the observation of the functional behavior of the capillary bed in tissues. Studies on the vascular bed of the mesoappendix of the rat indicate a progressive loss of vascular activity following adrenalectomy as manifested by unresponsiveness of the arterioles to epinephrine and mechanical stimulation, dilatation of the capillary bed and, eventually, increased capillary permeability to colloidal dyes (156). The administration of cortical extract, DOCA, or cortisone restores the capillary bed of the adrenalectomized rat, maintained on dietary salt, to a normal state (156).

Although both DOCA and cortisone can maintain the integrity of the vascular system in adrenalectomized animals, the mechanism by which each performs this function appears to be quite different. The action of DOCA on the vascular

system appears to be secondary to its effect on salt and water balance. Marked hypertension cannot be produced by DOCA in the adrenalectomized or normal rat on a sodium restricted regimen. However, with the incorporation of liberal amounts of sodium and water in the diet of adrenalectomized rats, DOCA-injected animals become strikingly hypertensive (85). Injections of DOCA into normal rats have no demonstrable effect on the reactivity of the terminal vascular bed (156).

In contrast to the lack of direct action of DOCA on the vascular bed, numerous studies have indicated that cortisone has a direct effect on capillary tone. Marked hypertension can be induced in the adrenalectomized or normal rats on a sodium restricted intake by the administration of cortisone (85). Observations on the meso-appendix of normal rats indicate that the administration of ACTH or cortisone is accompanied by increased vascular reactivity to epinephrine, augmentation of vasomotion and narrowing of the terminal arterioles (156). Direct observations have been made on the circulation in the hamster cheek pouch following the administration of cortisone (154, 155). The resistance of the blood vessels to petechial formation as a result of negative pressure was increased by cortisone. The highly important mechanism by which cortisone increases vascular tone is not understood. Perhaps, this effect is secondary to its general action on protein metabolism. However, vasoconstriction can be produced locally by the topical administration of cortisone (3). The action of cortisone on vascular tone appears to be the singly most important physiologic effect of this hormone in modifying inflammatory reactions and infection.

### III. THE EFFECT OF CORTISONE AND ACTH ON THE SEQUENCES OF INFLAMMATION (NATIVE RESISTANCE)

*1. The effect of ACTH and cortisone on the vascular and cellular response to injury.* The increased vascular tone produced by cortisone and ACTH tends to suppress the vascular and cellular inflammatory response to injury resulting from widely different irritants including chemical and physical trauma (27, 49, 102, 103, 104, 109, 133, 152) and living agents (55, 57, 65, 95, 96, 100, 120, 121). The effect of cortisone and ACTH on the vascular reaction to injury has been directly observed by several investigators (39, 40, 155). Ebert and his colleagues studied the effect of cortisone on tuberculous inflammation and on anaphylactic reactions by the rabbit ear chamber—a method which permits direct observations of small blood vessels. In the normal rabbit infected locally with the tubercle bacillus, there was, as with all acute inflammatory reactions, progressive vascular damage characterized by dilatation of capillaries, sticking of white blood cells to endothelium and emigration of cells through the capillaries into tissue spaces. The administration of cortisone tended to restore the vascular pattern to normal and there was a distinct reduction in the amount of cells (exudate) leaving the vessels (39, 40). Similarly, with anaphylactic reactions produced by the injection of horse serum into previously sensitized rabbits, cortisone prevented the sludging of blood and decreased the diapedesis of leucocytes (40, 41). That the effect of cortisone in maintaining vascular tone and decreasing capillary permeability

occurs also in man has been directly demonstrated by observation of the vasoconstrictive action of cortisone upon superficial corneal vascularization (3).

The purpose of the vascular inflammatory response is to bring fluid and phagocytic cells to the injured area to rid the body of the noxious agent. Following cortisone and ACTH therapy, this stage of inflammation subsequent to the vascular changes is greatly modified. Because of the increased vascular tone leading to inhibition of vascular response, the exudation of fluid and cells is greatly reduced or delayed. The influx of both polymorphonuclear leucocytes (55, 57, 102, 121) and macrophages (25, 37, 39, 49, 95, 96, 114) is inhibited. As a result, necrosis due to chemical and physical agents may be more striking than in the untreated animal since the irritant can continue to act. Further, because of the paucity of phagocytic cells, living noxious agents can continue to multiply and disseminate through the tissues (55, 57, 95, 96, 100, 120, 121, 145). The increased susceptibility to infection following cortisone therapy appears to be almost entirely secondary to suppression of the protective inflammatory response.

The deleterious effect of cortisone on infection is well demonstrated in the case of experimental pneumococcal cutaneous infections in rabbits (55). The skin response (a measure of the exudation of fluid and cells) to pneumococcal infection was greatly diminished and delayed following cortisone therapy. Histopathologic examination of the infected skin sites showed striking differences in the cellular inflammatory response and in the persistence of bacteria. In the skin of control animals 48 hours after infection, there were numerous polymorphonuclear leucocytes, edema of the tissues, thrombosis of small blood vessels, hemorrhage and necrosis. Bacteria had been completely removed. In the cortisone-treated animals, the leucocyte response had been greatly suppressed and numerous bacteria were present. A persistent bacteremia occurred in the cortisone-treated rabbits and mortality was greatly increased as a consequence of cortisone therapy. Similar observations have been made with a wide variety of infections, both clinical and experimentally induced (57, 65, 79, 80, 81, 90, 95, 96, 120, 121, 139).

*2. The effect of cortisone and ACTH on the functions of the inflammatory cells.* Although there is now almost unanimity of opinion concerning the suppression of the vascular and cellular inflammatory responses to injury by treatment with ACTH or cortisone, there are divergent views concerning the effects of these hormones on the activities of the inflammatory cells.

*a. Neutrophilic leucocyte.* In acute inflammatory reactions in cortisone treated animals, polymorphonuclear leucocytes do not appear in the injured areas as rapidly, or in such profusion, as in untreated animals. This failure of accumulation of leucocytes is not due to a neutropenia, for the numbers of these cells in the blood is usually increased by cortisone therapy (52). While ignoring the probability that the inhibition of leucocytic migration results from the suppressant action of cortisone on vascular response, some investigators have accepted the failure of leucocyte migration as a factor in favor of a direct effect of cortisone on leucocytes. However, most studies have shown that motility, phagocytic and bactericidal functions of neutrophilic leucocytes are not affected by cortisone.

Mogabgab and Thomas (100) tested the phagocytic activity of leucocytes in the blood from cortisone-treated rabbits. They found the activity of these leucocytes to be the same as that of leucocytes of the blood obtained from normal animals. In addition, suspensions of heat-killed streptococci were injected into the pleural space of normal and cortisone-treated animals and the fluid was withdrawn and examined one and three hours later. The extent of phagocytosis appeared to be the same in both the cortisone-treated and normal groups. In experiments performed by the writer on the effect of cortisone on cutaneous pneumococcal infection (55) cortisone did not destroy the capacity of the leucocyte to phagocytize viable pneumococci. Bacterial stains clearly revealed the presence of numerous bacteria within the cells of the inflammatory exudate.

The studies of Crepea *et al.* (26) and the work of Rebuck and Mellinger (119) are often quoted in support of a suppressant effect of cortisone on the phagocytic activity of the leucocyte. In the former studies, whole defibrinated blood removed before and after treatment from patients suffering from a variety of ailments was used as the source of leucocytes. The blood was combined with pneumococci in the presence of specific antiserum. Phagocytic indices were said to be diminished during therapy. However, because of the paucity of observations, the results are nothing more than suggestive. In the latter study, phagocytic activity was tested by the application of india ink beneath human-skin windows. The topical administration of cortisone was found to suppress cellular exudation and the phagocytosis of india ink. Because the number of ink particles in the granulocytes of the cortisone-treated subjects was less than that in the controls, it was concluded that cortisone had interfered with the phagocytic ability of the leucocytes. However, the effect of the relative numbers of leucocytes present on the apparent phagocytosis by individual leucocytes was not taken into consideration. Wood (150) has pointed out in a series of well planned experiments the role of surface factors in phagocytosis. He has shown that the degree of phagocytosis by individual leucocytes is greatly dependent on the concentration of leucocytes present. The greater the number of cell surfaces present, the greater is the opportunity for foreign material to be trapped between leucocytic surfaces and subsequently engulfed. The apparent lack of phagocytic ability of leucocytes from cortisone-treated subjects could have resulted from a cortisone-induced decrease in numbers of leucocytes rather than a direct effect on leucocytic activity. With the evidence available at present, there is no reason to believe that cortisone inhibits phagocytosis in any other way than by suppression of the accumulation of leucocytes during inflammation.

*b. Eosinophilic leucocyte.* A reduction in the blood eosinophil count is one of the most constant effects of cortisone therapy. The degree of eosinopenia has been used as an indication of the adequacy of steroid therapy (143). The mechanism by which cortisone decreases the peripheral eosinophil count is not clear. The drop in eosinophil count is probably too rapid to be explained by a decreased production of eosinophils. Spain and Thalhimer (134) have postulated that eosinophils are sequestrated in the spleen during cortisone therapy. This view was based on the observation that cortisone produced a significant increase in

the number of eosinophilic leucocytes in the spleen of mice. However, splenectomy does not affect ACTH-induced eosinopenia in man (70). Several studies of a preliminary nature have indicated that cortisone may have a destructive effect on the eosinophil (105, 110). These observations require confirmation. Since the function of the eosinophil is unknown, the significance of the eosinopenia with regard to inflammatory reactions is not understood.

*c. Lymphocyte.* One of the most striking effects of cortisone and ACTH administration is a fall in the number of circulating lymphocytes and involution of lymphoid tissue, including the thymus, spleen and lymph nodes (1, 24, 52, 70, 111). The lymphocytopenia is usually transient. Numerous studies have emphasized the ability of cortisone and ACTH to increase the rate of lymphocyte destruction (21, 24, 36). However, lysis of lymphocytes following exposure to cortisone has never been demonstrated in a convincing manner. In fact, *in vitro* studies on the effect of cortisone on lymphocytes have yielded contradictory results (67, 73). The marked lymphoid atrophy and the lymphocytopenia following cortisone therapy appears to be at least in part the result of a hormonal inhibition of lymphocytic reproduction (24, 52). Cortisone treatment has suppressed lymphoid mitosis, which ordinarily occurs following antigenic stimulation (24). In areas of inflammation, both when cortisone is administered topically and systemically, lymphocytes are decreased in number (27, 119). The paucity of lymphocytes probably results from both the cortisone-induced lymphopenia and the suppression of the cellular inflammatory response. Like the lymphocyte, plasma cells are depleted from the lymph nodes and spleen if sufficient hormone is given.

*d. Macrophage and the reticulo-endothelial system.* Numerous observations have indicated that treatment with cortisone inhibits the accumulation of macrophages in inflammatory areas (25, 37, 39, 49, 95, 96, 114). This effect is clearly seen in experimental tuberculosis where the macrophage response is markedly inhibited by cortisone therapy (95, 96). Similarly, Ragan *et al.* (114) have noted a marked decrease in the number of macrophages surrounding foreign materials inserted in subcutaneous tissues of patients treated with cortisone. The suppression of macrophage accumulation is considered to be secondary to hormonal inhibition of the vascular inflammatory response rather than a direct effect, for the inability of macrophages to migrate while under the influence of cortisone has not been apparent in tissue cultures except at high concentration of this hormone (67). Further, the scarcity of macrophages in inflammatory areas is not the result of a decrease in numbers of circulatory monocytes, for the monocyte count is not consistently affected by cortisone administration.

The effect of cortisone on the functional activity of the macrophage is disputed. Phagocytosis of india ink introduced into the peritoneal cavity of mice was studied by Spain *et al.* (133). They concluded from gross visualization of the peritoneal cavity that the decreased disappearance of india ink in the cortisone-treated animals was a consequence of a reduced phagocytic ability of macrophages. However, they used conditions where the exudation of macrophages was required. When the suppressant effect of cortisone on macrophage

response was taken into account as in the experiments of Gell and Hinde (49), where phagocytosis by peritoneal macrophages of formolized suspensions of *Staphylococcus albus* was measured by counting the number of ingested bacteria under the microscope, no effect of cortisone on the degree of phagocytosis of bacteria by macrophages was observed.

Lurie (95, 96) has suggested that the macrophages of cortisone-treated animals have an enhanced phagocytic activity. This interpretation arose from observations made on the effect of cortisone on the lesions of experimental tuberculosis. Following treatment, tuberculous lesions consisted of small numbers of macrophages laden with swarms of tubercle bacilli. Impressed with the great numbers of bacilli within macrophages, Lurie concluded that the macrophages of the cortisone-treated animals had a greater ability to ingest bacteria. In tuberculosis, as well as in other infections, cortisone increases susceptibility to infection by inhibition of the inflammatory response. As a consequence of this action, bacteria are capable of better survival and multiplication within the tissues. In acute infections, rapid growth of bacteria leads to overwhelming septicemia and prompt death. However, in chronic infections, death does not occur acutely following cortisone therapy although survival is shortened. Eventually, in chronic infections, such as tuberculosis, large numbers of bacteria are available for phagocytosis by small and inadequate numbers of leucocytes. Further, since the tubercle bacillus, unlike many other organisms, such as the pneumococcus, can remain viable within leucocytes for long periods of time, there is opportunity for continued phagocytosis. Thus, the apparent increased phagocytic activity of macrophages in cortisone-treated tuberculous animals, as measured by the number of ingested tubercle bacilli, may result from the quantitative relationships which develop between the cells and the bacilli, rather than from a direct effect of cortisone on the cells *per se*.

Lurie has made the interesting observation that cortisone treatment inhibits the spread of experimental pulmonary tuberculosis to the regional bronchial lymph nodes, although lymph node involvement regularly occurs in untreated animals. Since cortisone enhances the apparent ability of the tubercle bacillus to grow within the lung, the suppression of lymphatic spread appears paradoxical. However, it is well known that tubercle bacilli are carried to lymph nodes by macrophages, and the possibility arises that the prevention of the lymphatic dissemination of tubercle bacilli by cortisone may result from the suppression of the accumulation of macrophages in the pulmonary lesions.

Because of the enhancing effect of cortisone on blood stream infection, much interest has centered on the effect of cortisone on the reticulo-endothelial system. This system is the principal mechanism for the clearance of foreign matter from the blood. Germuth *et al.* (55) and White and Marshall (147) showed that the blood clearance of virulent pneumococci immediately after intravenous injection into rabbits was unaffected by cortisone, although subsequently a progressive septicemia developed in the treated animals. The rate of clearance of unencapsulated pneumococci and of a strain of *Staphylococcus aureus* was unaffected by cortisone therapy and neither of these organisms produced a progressive

bacteremia (55). These results are in agreement with the experiments of Martin and Kerby (98), who showed that treatment with cortisone did not alter the percentage of bacteria arrested by the liver and spleen when standard doses of bacteria were injected into the rabbit.

In contrast to the consistent reports on the failure of cortisone to alter the immediate functional activities of the reticulo-endothelial system when tested by the injection of bacteria, those studies dealing with the uptake of colloidal particles by the reticulo-endothelial system have shown varied results. Gell and Hinde (49) demonstrated in rats that the blood clearance of colloidal radioactive gold was uninfluenced by cortical administration. Cornwell (23) found in rabbits that the uptake of colloidal radioactive gold was decreased slightly by cortisone therapy; the time of removal of one-half the injected material was 47 secs. in the normal animal and 2 minutes 20 secs. in the rabbit previously treated with 40 mgm. of cortisone per kgm. of body weight for 4 days. Heller (68) found that cortisone suppressed the rate of removal of radioactive chromium phosphate in rats.

In recent studies (10), Halpern and his associates have developed a quantitative method for measuring the rate of clearance from the blood of carbon particles of known size. The rate of clearance of carbon particles was found to vary inversely as the amount of carbon injected. The ingested carbon had a saturating effect upon the phagocytic activity, for when in a given animal successive doses of carbon were injected, the rate of clearance was decreased. Normal function returned after a three day interval. Pretreatment with large doses of cortisone did not alter the basic blood clearance of carbon particles. However, the recovery of blood clearance to normal following a "blocking" dose of carbon was retarded by treatment with cortisone. The authors believe that return to normal function after "blockade" depends on a formation of new phagocytic cells to take the place of those previously saturated with carbon. They suggest that cortisone may prevent the multiplication of reticulo-endothelial cells and thus retard recovery from "blockade".

Lurie (95, 96) observed a greater accumulation of carbon particles following the intravenous injection of india ink in the spleens of animals treated with cortisone. He has emphasized this observation in support of his contention that cortisone enhances the phagocytic activity of the macrophage system. However, as a result of lymphoid atrophy in the spleen of a cortisone-treated animal the size of the spleen is markedly reduced. Hence, an equal amount of carbon will be more concentrated, and it will appear in a histological preparation that there is more carbon than in the normal. The present writer has observed this repeatedly in animals treated with cortisone and injected with India ink. When this is taken into account, the accumulation of India ink in the cortisone-treated animals appears to be the same as in the controls.

Clawson (22) has investigated the effect of cortisone on the ability of reticulo-endothelial cells of the liver to destroy phagocytized bacteria. Rats pretreated with cortisone and receiving an intravenous injection of *Streptococcus viridans* were killed at varying intervals. Slices of liver were fixed in formaldehyde, stained

and the number of bacteria present within the Kupffer cells were counted. The number of bacteria per field was always greater in the treated animals, and the bacteria were also present for longer intervals after injection. From these observations it was concluded that cortisone depressed the ability of the reticulo-endothelial cells to destroy bacteria. However, the number of bacteria circulating in the blood was not followed. The apparent persistence of streptococci within the Kupffer cells could have been the result of continued phagocytosis as a consequence of the prolongation of the bacteremia by cortisone.

In summary, there is no convincing evidence suggesting that cortisone greatly influences the functional activity of the reticulo-endothelial system. The basic blood clearance of bacteria appears to be unaltered by cortisone. The significance of the few reports, indicating that cortisone may inhibit phagocytosis of colloidal material, is not clear. The rate of clearance of particulate matter from the blood is probably by no means a simple measure of phagocytic activity. Many other factors may be involved, perhaps the most important of which, aside from phagocytic function, is the rate and volume of blood flow and other vascular phenomena. In view of the fact that cortisone so profoundly influences vascular tone, the question naturally arises as to what effect this action might have on the removal of material from the bloodstream and the distribution of colloidal materials in various organs. Further experiments along this line are necessary.

The bacteremia induced by cortisone is not well understood. It is not simply a matter of increased dissemination of bacteria from a local site, for a progressive bacteremia can also be produced by the direct injection of bacteria into the bloodstream (55, 147). Progressive bacteremia usually follows a preliminary period of normal bacterial removal. Do bacteria exert a "blockading" effect on the reticulo-endothelial system, which in the presence of cortisone is more sustained, as appears to be the case with india ink? Or, do the bacteria in cortisone-treated animals set up metastatic infection as they migrate from the bloodstream into the tissue spaces devoid of an adequate protective inflammatory response? These questions remain unanswered.

*3. The effect of cortisone on repair.* There is considerable experimental evidence indicating that cortisone and ACTH when administered in large doses inhibit the formation of granulation tissue and healing (3, 15, 18, 113, 114, 126). Ragan *et al.* reported a delay in wound healing in experimental animals and in patients treated with ACTH or cortisone (18, 113, 114). Following incision into the skin, restoration of the epithelium took place normally but leucocytic infiltration, the ingrowth of blood vessels and fibroblasts, and collagen synthesis were markedly inhibited. Granulation tissue about chemically induced tissue necrosis is markedly inhibited by cortisone, both when applied locally or administered systemically (126).

Since healing involves numerous complicated processes including the preliminary inflammatory reaction, formation of new capillaries, proliferation of fibroblasts, and collagen synthesis, it is difficult to determine which of these many factors is responsible for the delay in healing following cortisone administration. It is generally held that cortisone exerts a direct effect on connective tissue. High

concentrations of cortisone have been reported to prevent fibroblastic multiplication in tissue cultures (8). The significance of this finding in regard to the *in vivo* action of cortisone on connective tissue is not clear. Layton (87) observed a decreased uptake of sulfate in embryonic and wound tissues *in vitro* in the presence of cortisone. He postulated an inhibition of the synthesis of chondroitin sulfate. Further observations are necessary.

Numerous articles have been written concerning the effect of cortisone on connective tissue permeability. The increased permeability of connective tissue to dyes following the injection of hyaluronidase is prevented by cortisone and adrenal cortical extracts (108). However, cortisone also inhibits the spreading of dyes following the application of non-specific irritants (104). The inhibition of hyaluronidase activity may be related to decreased capillary permeability rather than a specific effect of cortisone on connective tissue. Evidence for this assumption is found in the following observation. The intravenous administration of testicular hyaluronidase in rats induces an increased rate of disappearance of Evans blue dye, a decreased concentration of serum protein and an increased hematocrit. These manifestations of an increased capillary permeability due to the action of hyaluronidase are inhibited by pretreatment with ACTH or cortisone (11).

A paucity of new capillary formation has been noted as one of the most striking features of the inhibitory effect of cortisone on healing. Cortisone has depressed the formation of new vessels in cutaneous wounds of mice (133), in experimental skin wounds in man (25, 114), in healing bone fractures in rabbits (18), and in skin-autografts in rabbits (15). Jones and Meyer (78) found that cortisone inhibited vascularization of the cornea which ordinarily follows the injection of alkali. Ashton and Cook (3) have reported careful observations on the effect of cortisone upon the ingrowth of newly formed vessels into rabbit ear chambers. Following cortisone therapy, vasoconstriction of both arterioles and venules occurred, resulting in a reduced blood flow to the area of new growth, as evidenced by an almost complete lack of blood in the capillary network behind the advancing capillary sprouts. Pulsation of newly formed capillaries was not observed, and a zone of hemorrhage which ordinarily precedes the sprouting capillaries did not develop in the cortisone-treated animals. These investigators postulated that the inhibition of vascularization was probably due to the profound effect of cortisone on the circulation rather than to a direct inhibition of endothelial growth.

In view of the preceding observations, one wonders whether the inhibitory effect of cortisone on granulation tissue may not be secondary to its suppressant effect on the vascular and cellular inflammatory reactions. Evidence that injurious agents tend to persist longer in the tissues because of the suppression of inflammation by cortisone has already been cited. Further, the suppression of inflammatory reaction by cortisone may inhibit the flow of nutrient materials from the blood which are vital for rapid healing. Retardation of the formation of new blood vessels may block other vital processes of repair. Can it be that the maintenance of normal or increased vascular tone by cortisone in the face of

injury is the primary mechanism by which cortisone produces its profound effects on inflammation and healing?

Probably closely related to the effect of cortisone and ACTH on repair is the inhibitory effect of cortisone and ACTH on growth (7). Whether this inhibitory action is related to the general effect of cortisone on protein metabolism has not been defined. Since the processes of growth and repair are similar, many of the same questions raised in regard to the effect of cortisone on granulation tissue can also be raised here. Can the effect of cortisone on the circulation and perhaps the transfer of materials from the blood stream to the tissue cells adequately explain inhibition of growth? This question remains unanswered.

### IV. THE EFFECT OF ACTH AND CORTISONE ON ANTIBODY FORMATION AND ACQUIRED RESISTANCE

It was reported by Dougherty and his coworkers (21, 36) that the injection of adrenal cortical extract or ACTH resulted in a sudden rise of antibody titer in previously immunized animals. These workers attributed this non-specific anamnestic response to the release of antibody from lymphocytes, lysed as a result of treatment with these hormones. This work has been questioned from two points of view. In the first place, there are conflicting reports concerning the ability of adrenal extract, ACTH or cortisone to produce lysis of lymphocytes. Secondly, there is no substantial evidence that adrenal stimulation can cause a release of antibody. In studies in which more precise methods for the determination of antibody have been employed, Eisen *et al.* (42) using adrenal extract and Fischel *et al.* (45) and DeVries (32) using small doses of ACTH were unable to confirm the previous findings of Dougherty, Chase and White. Recent studies have shown that ACTH and cortisone when administered in large dosages can produce a decided inhibition of antibody levels in rabbits (16, 43, 44, 47, 53, 56), guinea-pigs (44, 54) and mice (135). Germuth *et al.* (53, 56) found that precipitating antibody to egg albumin was markedly reduced in rabbits and guinea-pigs treated with either ACTH or cortisone. Bjørneboe *et al.* (16) found that the administration of ACTH or cortisone to rabbits immunized with suspensions of formalin-killed pneumococci resulted in a marked inhibition of the concentration of circulating antipneumococcus antibody. Large doses of cortisone have no effect on antibody levels in passively immunized animals (46, 56). Since the inhibitory effect of ACTH and cortisone is only observed during conditions which require an active production of antibody, it is believed that cortisone interferes with some phase of antibody synthesis. Because of the inhibitory effect of cortisone on inflammation, the possibility has been entertained that cortisone may interfere with antigen assimilation (43). However, the inhibition of antibody synthesis by cortisone in animals, where the antigen is introduced directly into the blood-stream (16), is indicative of a more fundamental mechanism of action. The relationship between antibody depression and the marked lymphoid atrophy following cortisone treatment may be more than coincidental (53, 56). Other procedures, such as the administration of x-ray and nitrogen mustards, which result in the destruction of lymphoid tissue also inhibit antibody production (51, 56).

In view of the findings in animals showing that the production of circulating antibody can be suppressed by the administration of ACTH and cortisone, the effect of these hormones on acquired resistance to infection has been a matter of great concern. However, although an inhibition of antibody formation has been repeatedly implicated in the increased susceptibility of cortisone-treated animals to a variety of infections, there have been very few experiments bearing directly on this problem. In most studies with chronic infection, it has not been possible to assess the relative roles played by the anti-inflammatory effect of cortisone and the possible antibody-inhibitory effect of cortisone in the increased susceptibility to infection. It has been suggested that the decreased resistance to tuberculosis may be, in part, the result of antibody suppression (95, 96). However, the formation of hemagglutinating and complement-fixing antibody to tuberculin has not been inhibited by dosages of cortisone which have produced a marked increase in susceptibility to this infection (96, 109). Although there is little reason to believe that the antibody-inhibitory effect of cortisone is of sufficient magnitude to play a role in increased susceptibility to chronic infection, except perhaps with continued administration of tremendous doses of ACTH or cortisone, there is no evidence at all that it is of importance in acute infection. The increased susceptibility to acute infection occurs far too early to be accounted for by interference with antibody production and is clearly the result of anti-inflammatory action of cortisone (55, 138, 139). Probably one of the most valid reasons for questioning the importance of the antibody-inhibitory effect of ACTH and cortisone in increased susceptibility to infection is the observation that even large doses of cortisone and ACTH in animals are unable to effect the complete suppression of antibody response. It is well known that exceedingly small amounts of antibody, amounts often immeasurable by present techniques, are sufficient to induce acquired resistance.

Germuth *et al.* (55) have studied the effect of large doses of cortisone on the development of acquired resistance following pneumococcal infection in rabbits. A series of 10 rabbits were injected intravenously with 1 billion pneumococcus Type II organisms. Five were treated with large doses of cortisone for 9 days, while 5 received no treatment. Beginning 24 hours after infection, all 10 rabbits received penicillin intramuscularly in order to terminate the otherwise lethal infection ordinarily observed in the cortisone-treated group. Another group of 5 uninfected animals received cortisone alone. Three weeks after the first injection, all 3 groups of animals plus a fourth group of normal rabbits were challenged intravenously with 1 billion pneumococcus Type II organisms and the rate of clearance of these bacteria was determined. Both the previously infected controls and the previously infected cortisone-treated rabbits showed an accelerated rate of removal of bacteria from the bloodstream, indicative of an adequate immune response. Treatment with cortisone during infection had not interfered with the development of acquired resistance.

Although the significance of the antibody-inhibitory effect of cortisone in animals has been disputed, in man the situation is quite different, for suppression of antibody levels has not been observed by therapeutic doses of ACTH and cortisone. Mirick (99) vaccinated 59 patients with pneumococcus capsular poly-

saccharide. The production of mouse-protective antibody during treatment with ACTH and cortisone was found to be the same as that without treatment. Larson and Tomlinson (86) observed no inhibition of precipitin formation to pneumococcus polysaccharide in patients receiving cortisone treatment for rheumatoid arthritis. Havens *et al.* (66) found that ACTH and cortisone did not reduce the development of diphtheria antitoxin following toxoid injection. It has been stated that recovery from acquired hemolytic anemia treated with ACTH and cortisone has been associated with a reduction in titer of Coombs antibody (48). The significance of this observation requires further study. Although the failure of cortisone and ACTH to alter antibody levels in man may be in part due to species differences, it is noteworthy that the dosage of these hormones ordinarily employed in man are considerably smaller than those used to inhibit antibody formation in experimental animals.

### V. THE EFFECT OF CORTISONE AND ACTH ON HYPERSENSITIVITY REACTIONS

*1. Anaphylactic type hypersensitivity.* It is well established that treatment with cortisone and ACTH significantly alters the course of both experimental and clinical allergy (14, 20, 50, 51, 53, 56, 94, 101, 117, 125). Two separate mechanisms appear to be involved. In the first place, those forms of experimental allergy requiring the production of large amounts of antibody may be suppressed by partial inhibition of the antibody response by cortisone. Thus, in the rabbit, suppression of the active Arthus reaction is dependent on the inhibition of antibody response by ACTH or cortisone (56). Likewise, experimental serum sickness can be prevented by the administration of amounts of cortisone large enough to inhibit antibody formation (101). Since antibody formation in animals is not completely abolished even by large doses of cortisone and ACTH, it is to be expected that the antibody-inhibitory effect of these hormones would be insufficient to modify allergic reactions mediated by low levels of antibody. Thus, these hormones have no effect on anaphylactic shock in the guinea-pig (33, 54, 64).

The second mechanism by which cortisone appears to inhibit allergic reactions is by way of its tendency to increase vascular tone (anti-inflammatory effect). For instance, the vascular lesions of experimental serum sickness can be suppressed by doses of cortisone too small to influence antibody response (50). Further, the vascular manifestation of acute anaphylactic shock in the mouse can be prevented by prior treatment with cortisone (107, 132). That this inhibitory effect is dependent on the maintenance by cortisone of the integrity of the vascular system is suggested by the observation that this hormone has no marked effect on anaphylactic shock in the guinea-pig, which is manifested primarily by contraction of the bronchiolar smooth musculature. Certain allergic inflammatory reactions are not readily influenced by the anti-inflammatory action of cortisone. For example, the experimental Arthus reaction and the allergic skin tests in man are not suppressed by cortisone or ACTH. Possibly the artificial introduction of antigen into the skin in sufficient quantity to produce a macroscopic inflammatory reaction leads to circumstances both quantitatively and

qualitatively different from those existing naturally. It is well known that both clinical and experimentally-induced serum sickness type reactions can be inhibited by doses of ACTH or cortisone which produce no alteration in the response of the skin to a test dose of antigen (20, 50, 89, 94, 117, 136).

Although both the antibody-inhibitory effect and the anti-inflammatory action of cortisone may influence experimentally-induced allergy, there is no evidence to indicate that the antibody-inhibitory effect of cortisone operates in man. The failure of the usual therapeutic dose of cortisone to inhibit antibody levels in man following immunization with various types of antigen has already been discussed. That the beneficial effects of cortisone and ACTH on human allergy is not dependent on the suppression of antibody levels is further indicated by the persistence of the positive skin test for antibody in subjects in whom cortisone treatment has been effective in eliminating the naturally occurring allergic symptoms (94). Further, relief of allergic symptoms following cortisone treatment is too prompt to be attributed to any effect on antibody response, particularly since the half-life of the antibody already present in the body is approximately 13 days (34).

There is no evidence indicating that the effect of cortisone and ACTH on allergic reactions is specific. The same mechanisms involved in the suppression of non-specific inflammatory reactions appear to be operating here. Inhibition by cortisone of the vascular injury induced by allergy to intravenously injected foreign protein in the rabbit has been demonstrated by Ebert and Barclay by the use of the rabbit ear-chamber technique (40). The vasoconstrictive action of cortisone on allergic inflammation has also been demonstrated in studies of allergic ocular reactions (151). Cortisone and ACTH are capable of blocking the conjunctivitis and iritis which ordinarily occurs following the injection of foreign protein into the anterior chamber of the eye of a sensitized rabbit.

*2. Tuberculin type hypersensitivity.* Numerous studies have shown that cortisone will inhibit the local inflammatory reaction of the hypersensitive host to the intracutaneous injection of tuberculin (31, 54, 109). There is no reason to believe that the mechanism of action of cortisone on the tuberculin reaction is different from its effect on other inflammatory reactions. Since "antibody" in the tuberculin reaction appears to be fixed to the leucocytes and is not present in measurable quantity in the serum, this reaction cannot be defined in quantitative terms. Studies on tuberculin complement-fixing and hemagglutinating antibodies have shown that cortisone and ACTH in dosages sufficient to inhibit the tuberculin reaction are without effect on the titer of these antibodies (96, 109). The question as to whether cortisone can inhibit the cytotoxic action of tuberculin on tissue cultures of cells removed from a hypersensitive animal has been studied independently by two groups of investigators with contradictory results. Using the roller tube method of tissue culture, Leahy and Morgan (88) reported that the cytotoxic action of PPD (purified protein derivative) on the growing cells of splenic transplants from tuberculous guinea-pigs was inhibited by pretreatment of the cells with cortisone for 24 hours prior to the addition of PPD. More recently, Holden *et al.* (73), using Maximow's double coverslip lying drop method

of culture, were unable to demonstrate any protective action of cortisone on the cytotoxic action of PPD. This latter study was carried out on a large scale and is unusually well documented.

## VI. THE EFFECT OF ACTH AND CORTISONE ON THE PYROGENICITY AND LETHAL ACTION OF BACTERIAL TOXINS

In various febrile illnesses, cortisone and ACTH therapy has brought about a return in temperature to normal and a reduction in toxemia (79, 81). The symptoms of infection may be controlled by these hormones even though the underlying infectious agent has an increased capacity for dissemination. The action of ACTH and cortisone in alleviating the signs and symptoms of infection is not entirely explicable on the feeling of well-being which these hormones often incite. Attention has therefore been directed to the effect of cortisone and ACTH on the pyrogenicity and lethal action of bacterial toxins. Cortisone and ACTH have shown no protective effect against the action of exotoxins, such as diphtheria toxin in guinea-pigs (106, 123). However, there is no doubt that these hormones are capable of altering the febrile response and the tissue reactions produced by the endotoxins of gram-negative organisms. Lewis and Page observed that adrenalectomized rats were more resistant to the shocking action of typhoid vaccine (91). Cortisone has protected the mouse adrenals against the hemorrhagic effects of Shiga toxin and meningococci intoxication (106). Jackson and Smadel (76) were unable to demonstrate a protective action of ACTH and cortisone on the toxins of rickettsiae and *Salmonella typhosa* in mice. However, in experiments carried out by the present writer, pretreatment of rabbits with large doses of cortisone was found to have a marked protective effect on the pyrogenicity and lethal action of typhoid vaccine (55). The febrile response was noticeably reduced and only 2 of 26 treated rabbits (7.4 per cent) died, whereas 14 of 26 untreated animals (52 per cent) succumbed to the toxic action of typhoid vaccine. Although cortisone and ACTH exert an "antitoxic" effect when certain toxins are injected directly into animals, the role that this effect plays during the course of infection is difficult to ascertain because of the ability of the infectious agent to multiply more readily and produce overwhelming infection as a consequence of hormonal therapy. Under special circumstances, however, the beneficial antitoxic effect of cortisone during infection has been clearly shown. In experiments by the writer in which rabbits infected with hemolytic *Staphylococcus aureus* were treated with dosages of cortisone ineffective in producing a progressive bacteremia, cortisone appeared to protect the animals against the toxic action of the bacteria (55). Of a total of 12 infected animals treated with cortisone, all survived. However, 5 of 12 infected untreated animals (42 per cent) died within 24 to 48 hours. Kilbourne (84) found that the administration of cortisone may shorten or prolong survival of chick embryos infected with influenza B virus, depending on the timing of its injection. When cortisone was injected prior to infection, increased viral multiplication as a result of the anti-inflammatory effect of cortisone led to higher viral concentrations and more

rapid death. However, injection of cortisone 24 to 42 hours after infection resulted in prolongation of survival.

The antipyretic effect of cortisone and ACTH has been extensively studied by Duffy and Morgan (38) and by Bennett and Beeson (13). Both of these groups of investigators found that the febrile response of rabbits to bacterial endotoxins may be suppressed, accentuated, or unchanged after hormonal treatment, depending on the dose of hormone, time of administration and dose of endotoxin employed.

Many of the endotoxins derived from gram-negative bacteria which are capable of producing fever and transient leucopenia in man and animals are also potent in causing the Shwartzman reaction (12). Shwartzman found that the intravenous injection of a filtrate of typhoid bacillus resulted in hemorrhagic necrosis of the skin at sites prepared 24 hours earlier by intradermal inoculation of the filtrate. If two injections of endotoxin are given intravenously on successive days, bilateral cortical necrosis of the kidneys may result (generalized Shwartzman reaction). The effect of ACTH and cortisone on the Shwartzman phenomenon is as variable as their effects on the pyrogenicity of endotoxins. Inhibition of the Shwartzman reaction occurs if ACTH or cortisone is administered shortly before the intravenous "provocative" injection of bacterial toxin (97, 100, 130). However, the experiments of Thomas and his colleagues have shown that pretreatment with large doses of cortisone may result in a striking increase in susceptibility to this type of injury. Further, only a single injection of toxin is required to produce the Shwartzman reaction in rabbits heavily treated with cortisone (60, 138, 139, 140).

The mechanism by which cortisone and ACTH alter host response to bacterial endotoxins is not understood. It is possible that the mechanism of hormonal action on the pyrogenicity of endotoxins is different from that on the Shwartzman phenomenon. Recent work by Atkins *et al.* (4) has indicated that cortisone does not inhibit the leucopenia which characteristically accompanies the febrile response to endotoxins. The principal histologic change caused by the administration of large doses of pyrogens appears to be widespread vascular damage and thrombosis (12). The protective effect of ACTH and cortisone against the action of endotoxins could be related to the tendency of these hormones to maintain the integrity of the vascular system in the face of injury by a wide variety of irritants. The effect of excessive doses of cortisone on the vascular system is of interest in regard to the ability of high levels of this hormone to increase susceptibility to bacterial endotoxins. The vascular fragility exhibited by patients with Cushing's syndrome is familiar. Further, the administration of large doses of cortisone to rabbits has been reported by Rich and other investigators to lead to marked damage to the glomerular capillaries, consisting of aneurysmal dilatation, rupture and thrombosis (118). These findings suggest the possibility that large doses of cortisone might accentuate rather than protect against certain types of vascular injury. The increased susceptibility to glomerular thrombosis and cortical necrosis of the kidneys in the generalized Shwartzman phenomenon

following cortisone administration reported by Thomas and his co-workers may be related to the damaging effects of large doses of cortisone on the glomerular capillaries. It is of interest that both the glomerular lesions produced by cortisone and those produced by the Shwartzman phenomenon are inhibited by the administration of heparin (62).

A variety of colloidal materials such as thorotrast (thorium dioxide sol) and trypan blue have the same capacity to increase susceptibility to endotoxins as does cortisone (61). Since these colloidal substances are removed by the reticuloendothelial system, it has been postulated that the increased susceptibility to the Shwartzman phenomenon which follows their administration results from a "blockade" of a detoxifying function of this system (12). In line with this hypothesis, Thomas and his colleagues have suggested that the increased susceptibility to the Shwartzman phenomenon produced by cortisone may emerge from a similar mechanism (138, 139, 140). There is no convincing evidence to support either of these highly speculative concepts. In the first place, the effects of colloidal materials on other tissues, including the vascular system and plasma proteins, have not been adequately studied. Secondly, the administration of cortisone has not been shown to interfere markedly with the functions of the reticuloendothelial system.

## VI. SUMMARY AND CORRELATION

The vasoconstrictive action of cortisone with its resultant reduction in blood flow and inhibition of capillary permeability provide an attractive explanation for many of the findings associated with the treatment of inflammatory states by cortisone. The mechanism by which cortisone produces vasoconstriction is not clear. Whether cortisone potentiates naturally occurring vaso-constrictor substances, or antagonizes vasodilator agents, requires study. The possibility that the lymphoid atrophy, lymphocytopenia and eosinopenia may be secondary to the action of cortisone on the vascular system must be considered. It is of interest that the hemocytologic effects of cortisone have been reported to be inhibited by heparin (58).

The relationship between the vasoconstrictive action of cortisone and hormone-induced disturbances in protein metabolism requires clarification. Whether the amount of protein mobilized by the involution of lymphoid tissue is large enough to account for the increased protein catabolism and gluconeogenesis following cortisone administration remains unsettled (92). Further, the effect, if any, of these metabolic alterations on the sequences of inflammation is not at all understood.

The suppression of the inflammatory response by cortisone may be either harmful or beneficial depending upon the nature of the disease process. Suppression of the protective inflammatory response to injury by living agents produces increased susceptibility to infection. Subclinical infections may become clinically manifest and spontaneous infections are more likely to develop. This not only applies to artificially induced hypercorticalism which follows the administration of ACTH or cortisone, but, also, to the naturally occurring state,

Cushing's syndrome. Since cortisone tends to suppress inflammation and fever—objective signs of infection—, infection, even of an overwhelming nature, may remain unnoticed (80, 81). This is well recognized as one of the hazards of hormonal therapy. The effectiveness of borderline therapeutic doses of antibiotics is reduced by cortisone treatment (29, 74, 77). Therefore, large amounts of the specific antibiotic must be administered to control infection occurring during treatment with cortisone.

Since there is evidence suggesting that cortisone and ACTH protect against bodily injury produced by bacterial endotoxins, the possibility arises that combined treatment with cortisone and antibiotics may be advantageous in infection characterized by severe toxemia. This method of treatment has been carried out in typhoid fever with excellent immediate results. The value of the use of cortisone in replacement therapy in acute adrenal insufficiency associated with infection appears to be well established (9, 72).

Although the suppression of the inflammatory reaction by cortisone lowers resistance to infection, this same action may be beneficial in disease states where vascular changes and inflammation are undesirable, as in allergic reactions including periarteritis nodosa (6, 20). Further, in certain disorders of unknown etiology, such as systemic lupus erythematosus, rheumatoid arthritis and sarcoid, suppression of the inflammatory reaction by cortisone has yielded significant clinical improvement (5, 19, 127, 131).

It is apparent that there is much to be learned with regard to the basic mechanisms of cortisone action on the fundamental processes of inflammation, growth and healing. Such knowledge will undoubtedly contribute to the rational basis of cortisone therapy.

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