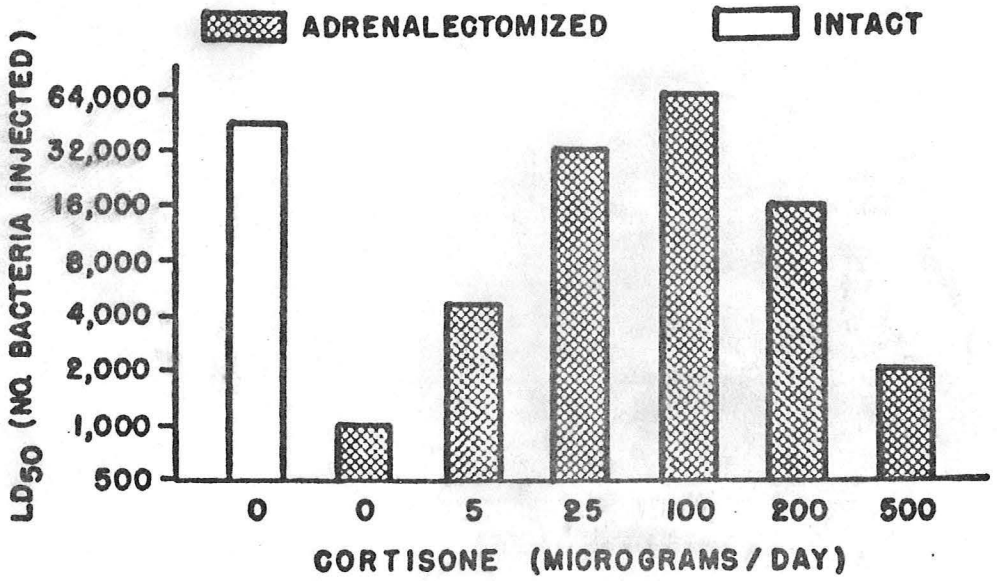
Infections Dis

FIGHT OR FLEE

(AND FIND THE RIGHT CORTISOL LEVEL?)



INTERNAL MEDICINE GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL

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Cover Figure: Effect of cortisone replacement on the susceptibility of adrenalectomized mice to pneumococcal challenge (98). Kass EH, Finland M. Advances in Internal Medicine.

GLUCOCORTICOID THERAPY FOR BACTERIAL DISEASES

Glucocorticoids have been advocated as adjunctive therapy for bacterial diseases for over 40 years, yet there is relatively little useful information to guide clinical use of these drugs in infected patients. This review will deal with four questions:

1. What is the function of glucocorticoids during stress or inflammation?

2. What is glucocorticoid deficiency? How often does it occur during bacterial diseases?

3. How do large doses of glucocorticoids improve the outcome of some bacterial diseases? Why have clinical trials given such different results?

4. When should glucocorticoids be given as adjunctive therapy for bacterial diseases?

A. GLUCOCORTICOIDS: GENERAL BACKGROUND (1,2,3)

Glucocorticoids are synthesized from cholesterol in the adrenal gland. Cortisol (hydrocortisone; 11β, 17α, 21-trihydroxy 4-pregnene 3,20-dione) is the major glucocorticoid in human plasma. The adrenal output of cortisol, which averages 15 - 20 mg/day, can increase up to 100 mg/day or more during stress. Plasma cortisol concentrations vary throughout the day, with a morning peak and afternoon-evening nadir, corresponding to fluctuations in pituitary ACTH secretion. Cortisol is bound in plasma to corticosteroid-binding protein (transcortin; $Kd = 2.4 \times 10^{-7}$ M) and, less tightly, to albumin ($Kd = 10^{-3}$ M). Less than 10% of plasma cortisol is normally unbound (free), but the protein binding capacity is saturated at approximately 28 ug/dl. The half-life of cortisol in plasma is approximately 80-120 minutes; the half-life increases with large doses and in hypothyroidism, liver disease, uremia, and pre-terminally, but not with acute stress or adrenal insufficiency. Cortisol diffuses freely throughout the body. CSF levels in monkeys were 2% of serum concentrations, yet the CSF cortisol was entirely free (4).

ACTH is the major hormonal stimulus for cortisol synthesis. Pituitary secretion of ACTH is modulated by hypothalamic peptides (corticotropin releasing factor [CRF] and arginine-vasopressin), as well as by a number of other circulating hormones, including interleukin-1. It is synthesized as part of a precursor protein (proopiomelanocortin) that also contains the sequences of MSH, beta-lipotropin, beta-endorphin, and met-enkephalin. The half-life of ACTH in plasma is 10 minutes or less. ACTH is released episodically from the pituitary; its short half-life and the rapid adrenal response time (2-3 minutes for secretion of cortisol) translate the ACTH signal into bursts of cortisol output, with rapidly fluctuating cortisol levels. There appear to be non-ACTH stimuli for cortisol release, although these are poorly characterized (1,2).

Cortisol and other glucocorticoids inhibit the release of both CRF and ACTH, completing a feedback loop.

B. GLUCOCORTICOIDS: MECHANISM OF ACTION

Glucocorticoids have an extraordinary impact on biological processes. It is thought that all physiologic actions of glucocorticoids are mediated by their binding to a specific cell surface protein, the glucocorticoid receptor [GR]. The glucocorticoid-GR complex then travels to the nucleus, where it binds to specific sites on chromosomal DNA, thereby modulating the transcription of specific genes. This general pattern is thought to apply to most cells, whereas the specific responses elicited by glucocorticoids may differ markedly in various types of cells. This heterogeneity in response probably reflects differences in the genes regulated by glucocorticoid-GR in different cells.

All cells are thought to have GR, and the cortisol-binding affinities of the GRs on different cells are thought to be quantitatively similar. Importantly, saturation of GR by glucocorticoids occurs. For example, GR on human blood monocytes have approximately 9,000 receptor sites for dexamethasone per cell, yet the specific binding of dexamethasone to these cells is saturable (5). The Kd for binding dexamethasone to the monocyte GR is approximately 7.7 nM (5). If one assumes a plasma cortisol level of 10 ug/dl and a free cortisol level of 1 ug/dl, the free plasma cortisol concentration is approximately 30 nM; as regards GR binding, this level would correspond to a dexamethasone concentration of approximately 5 nM. So physiologic cortisol levels roughly fall in the range over which changes in GR binding should occur. Effects of glucocorticoids on cells occur within the same concentration range (1,2,6,7) (Figure 6).

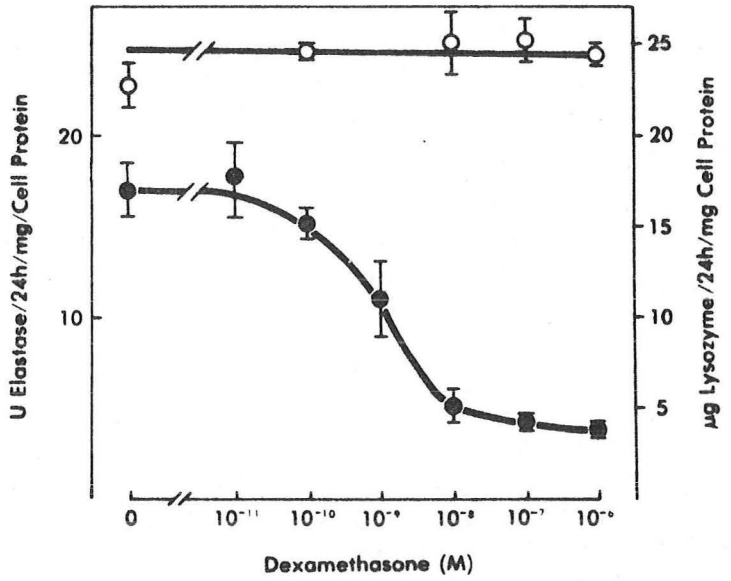


Figure 1. Effect of dexamethasone on secretion of elastase and lysozyme by human mononuclear cells (6). Copywright 1978, Rockfeller University Press. Werb Z, Foley R, Munck A. The Journal of Experimental Medicine.

Glucocorticoids also down-regulate GR synthesis in various cells (8); in vitro, this occurs at concentrations of glucocorticoid that are also in the physiological range. Both saturation and down-regulation of GR would seem to limit the ability of glucocorticoids to act via GR above a certain concentration limit--such actions may occur through pathways that are not receptor-mediated (or that involve low-affinity, non-saturable binding sites on cells), although such pathways have not been characterized.

C. THE PITUITARY-ADRENAL AXIS IN INFLAMMATION

It has been known for many years that bacterial infection stimulates increases in plasma cortisol and ACTH levels. In fact, bacterial endotoxin (Pyromen; Lipexal) was once used as a provocative stimulus to test the hypothalamic-pituitary-adrenal axis in man (9). ACTH (and growth hormone) levels rise and fall quickly after endotoxin challenge, while plasma cortisol increases more slowly and remains elevated longer (10) (Figure 2).

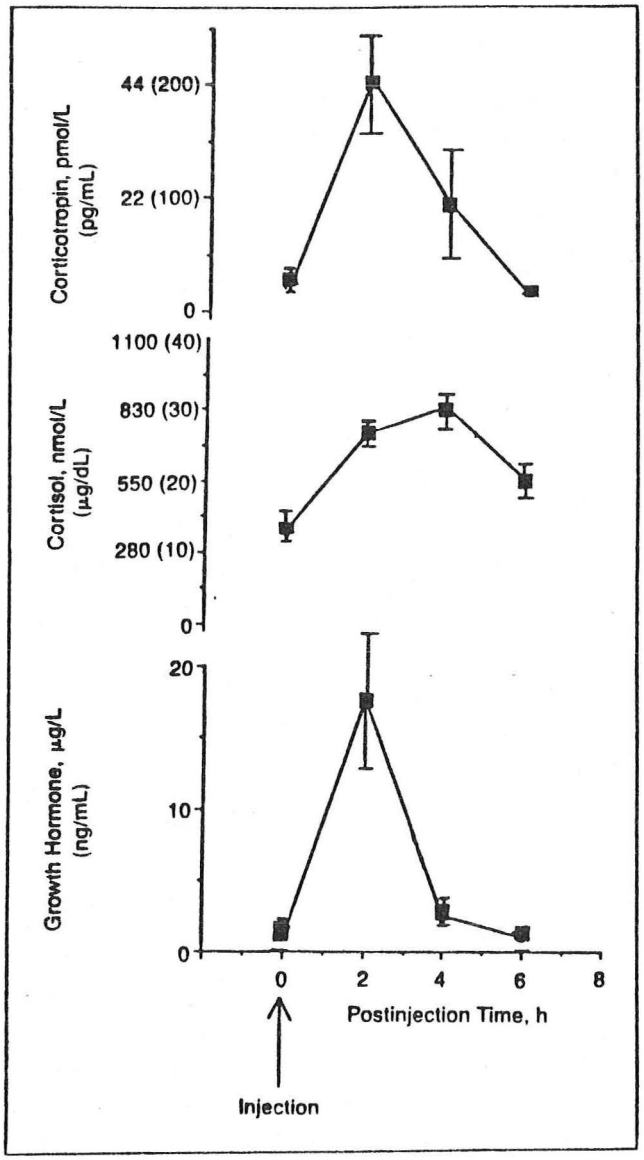


Figure 2. Effect of endotoxin injection on corticotropin, cortisol, and growth hormone levels in human volunteers (10). Copyright 1988. American Medical Association Revhaug A, et. al. Archives of Surgery.

On the other hand, the ability of pituitary hormones to modulate leukocyte function, and of leukocyte products to influence CNS activities, has only recently been recognized. It has become increasingly apparent during the 1980's that the interrelationships between the immune and nervous systems are much more extensive and complex than was previously imagined (11,12,13).

Recent evidence indicates, for example, that interleukin-1, one of several protein hormones released by macrophages that have been stimulated by bacterial products, increases ACTH release from the pituitary (14,15), though its site of action in the hypothalamus and/or pituitary is debated (16). This finding probably explains the ability of bacterial endotoxin to stimulate ACTH and cortisol release into plasma. Interestingly, cachectin/TNF, which shares many other activities with IL-1, apparently does not induce ACTH release (14). Glucocorticoids, which are released into blood following ACTH stimulation of the adrenal, inhibit the production and action of IL-1 and cachectin/TNF (as well as other cytokines) in vitro and in vivo. It would thus appear that there is a finely tuned stimulation-feedback system that involves interleukin-1, ACTH, cortisol, and probably other hormones, interacting with various cellular targets. In addition, circulating blood lymphocytes appear to have receptors for ACTH, which theoretically could allow direct (down-) modulation of their function by ACTH (17), and macrophage tumoricidal activity is actually down-regulated by ACTH in vitro (18). Under certain circumstances (such as stimulation with bacterial endotoxin) blood mononuclear cells appear to express ACTH-like molecules (19,20), and one patient with ectopic ACTH production was apparently cured by resecting an inflammatory mass (21). Blalock and colleagues have argued that leukocytes are similar to anterior pituitary cells with respect to control of the proopiomelanocortin gene by a positive signal (CRF) and feedback inhibition by dexamethasone.

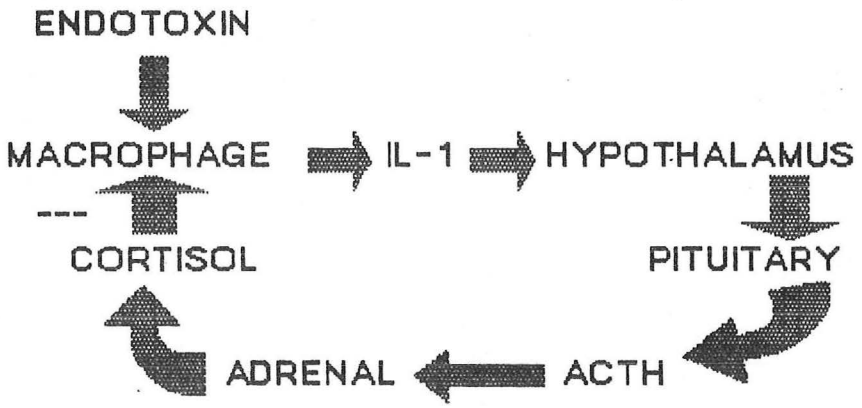


Figure 3. Simplified signal-response diagram.

In summary, (1) leukocyte-derived cytokines can modulate the pituitary-adrenal axis to increase circulating ACTH and cortisol concentrations; (2) cytokine synthesis in monocytes is down-regulated by cortisol; (3) leukocytes may have ACTH receptors which may mediate direct effects of ACTH on these cells, suggesting that ACTH may also down-regulate leukocyte function.

Although this discussion focuses on glucocorticoids, several other hormonal interactions between neural and immune cells have also been described (see references 11-13,22).

D. EFFECTS OF GLUCOCORTICOIDS ON THE INFLAMMATORY RESPONSE

a. Inhibition of arachidonate metabolism. Perhaps the best known effect of glucocorticoids is their ability to inhibit phospholipase A_2, thus down-regulating the synthesis of both prostaglandins and leukotrienes from phospholipid-derived arachidonic acid (23). In isolated cell systems (such as human endothelial cells [24]), down-regulation of prostanoid synthesis occurs at physiologic concentrations of glucocorticoid.

For several years it has been proposed that glucocorticoids inactivate phospholipase A_2 by stimulating the synthesis of a "second messenger" protein (25,26). In some laboratories this protein was found to mimic many of the anti-inflammatory actions of glucocorticoids. Unfortunately, some of the results have not been reproducible and there is now controversy and confusion in the field.

Other proposed glucocorticoid second messengers include glucocortin (27) and vasocortin (28).

It is thought that this effect on arachidonic acid metabolism is the basis for the well-known ability of glucocorticoids to reduce vascular permeability, thus decreasing tissue edema. In fact, cyclooxygenase inhibitors have quite similar effects on protein and fluid movement across vessel walls (29).

b. Down-regulation of cytokine synthesis/release. Dexamethasone modestly increases transcription of the gene for cachectin/tumor necrosis factor (cachectin/TNF) in murine macrophages, but when the cells are stimulated with bacterial endotoxin, dexamethasone greatly suppresses the normal increase in cachectin/TNF synthesis (30).

For both cachectin/TNF and interleukin-1 beta synthesis in monocytes, dexamethasone has post-transcriptional effects that seem quantitatively more important than its down-regulation of transcription. One site of action is mRNA stability: both cachectin/TNF and interleukin-1 mRNA stability is increased by dexamethasone (30,31). In addition, dexamethasone dramatically inhibits translation of IL-1 mRNA (31). These findings suggest, not surprisingly, that multiple second messengers may mediate glucocorticoid effects on inflammatory cytokine synthesis. The net result, however, is a decrease in the synthesis of both cytokines, provided that the glucocorticoid is present at the time that the inflammatory stimulus (here, endotoxin) is introduced.

In addition to IL-1 and TNF/cachectin, glucocorticoids also inhibit synthesis of IL-2, interferon-gamma, and other cytokines.

This action of glucocorticoids would also theoretically block the transmission of the inflammatory signal from the initial (signalling) cell to secondary (target) cells, thus interrupting many of the local and systemic features. Unfortunately, little is known about the abiity of glucocorticoids to interfere with the effects of inflammatory cytokines on their target

cells, although blocking arachidonic acid metabolism should inhibit at least some actions of TNF-cachectin (32) and interleukin-1. Indeed, a recent report indicates that adrenalectomized mice are very sensitive to lethality from intravenous TNF/cachectin and I1-1, whereas treatment with dexamethasone restores the mice to the normal, resistant state (33). Endogenous glucocorticoid may thus block some responses to these cytokines.

c. Inhibition of leukocyte mobilization to inflammatory sites. The mechanism(s) by which glucocorticoids down-regulate leukocyte (particularly, neutrophil) mobilization to infected sites are unknown. Possiblities include (1) down-regulation of neutrophil sensitivity to chemotactic signals from complement fragment C5a (34) and (2) inhibition of the expression of the leukocyte adhesion complex (integrin family) that promotes the adherence of neutrophils to vascular endothelial cells, a putative first step in the localization of neutrophils to sites of inflammation.

In vitro, inhibition of neutrophil aggregation in response to activated complement requires quite high doses (1 mg methylprednisolone/ml) (34), suggesting that this mechanism does not account for responses observed with much lower doses *in vivo*. Although an inhibitory effect of glucocorticoids on the expression of the leukocyte adhesion complex (Mol, or CDw18 [35]) might account for many of the findings, this has not been studied. In any case, a major effect of glucocorticoids may be to decrease neutrophil adherence to vascular endothelium (36). Interference with neutrophil margination may also explain the ability of exogenous glucocorticoid to produce leukocytosis in man. Interestingly, very low doses of hydrocortisone (50 mg) are just as effective as high doses (80 mg prednisolone) in producing leukocytosis (37).

d. Effects on lymphocyte function, lymphocytes. Low doses of glucocorticoid reduce circulating lymphocyte and monocyte counts within a few hours of injection. This is thought to reflect redistribution of these cells into other sites--in man, these cells are not killed by low doses of glucocorticoids. Suppressor T cell function is diminished (38) and B cell immunoglobulin synthesis is decreased *in vitro*, yet effects on antibody formation *in vivo* have been less impressive and glucocorticoid effects on immunoglobulin synthesis are not thought to be clinically significant (39). Although physiologic responses of monocytes to various stimuli are preserved, the bactericidal and fungicical ability of monocytes from steroid-treated humans is strikingly decreased (40) and monocyte secretion of several enzymes is diminished by glucocorticoids *in vitro* (6).

E. WHAT IS THE FUNCTION OF GLUCOCORTICOIDS DURING STRESS OR INFLAMMATION?

Stress of virtually any sort generates an increase in circulating levels of glucocorticoid. Indeed, it is commonly accepted that patients undergoing treatment with glucocorticoids require increased dosage when stressed by surgery, infection, or the like. The importance of glucocorticoids for the survival of patients with Addison's disease has been obvious since cortisone appeared in 1948 (1,2).

How exactly do glucocorticoids benefit the stressed animal? For many years it has been assumed that an outpouring of glucocorticoid from the adrenal gland is somehow necessary to support the circulation or to defend the body against the threat posed by the stress itself. The role of

glucocorticoids in carbohydrate metabolism, for example--stimulating gluconeogeneis, in synergy with catecholamines and glucagon--has been said to contribute to survival during stress by preventing insulin from causing dangerous hypoglycemia and by providing more glucose to the stressed organism for energy expenditure (1,2,41,42). The importance of circulating glucocorticoid for maintenance of circulatory support--independent of mineralocorticoid effects--also is documented (1). On the other hand, the anti-inflammatory and immunosuppressive actions of glucocorticoids have been difficult to incorporate into such explanations, since suppression of host defenses during microbial invasion would seem to be detrimental and lack survival value.

In an influential review, Munck, Guyre, and Holbrook proposed (1984) that "(1) the physiological function of stress-induced increases in glucocorticoid levels is to protect not against the source of stress itself, but against the normal defense reactions that are activated by stress, and (2) the glucocorticoids accomplish this function by turning off those defense reactions, thus preventing them from overshooting and themselves threatening homeostasis" (7).

In support of their hypothesis, Munck and his colleagues noted that glucocorticoid receptors have been found in virtually all nucleated cell types, including leukocytes, and these receptors have similar properties. Specifically, the concentrations of glucocorticoid required to modulate cytokine production and arachidonic acid metabolism in vitro are within the physiological glucocorticoid concentration range. These observations support the notion that the antiinflammatory actions of glucocorticoids can result from physiologic, as well as pharmacologic, concentrations of steroid. On the other hand, Munck et. al. were careful to qualify their hypothesis: "It is not designed to account for the body's requirement for basal, permissive or normalizing levels of glucocorticoids in the absence of stress" (7). They surmise that occupation of basal levels of glucocorticoid receptors is involved in normal gene regulation, and that fully occupying the receptors during times of stress would maximally damp potentially harmful defense mechanisms.

The Munck hypothesis is quite provocative. First, it encourages consideration of other ways in which neural influences may interact with the inflammatory/immune apparatus. The various, multiple hormonal signals between neural and inflammatory cells would cooperate to mount an effective defense against invading microbes while avoiding hazardous excess that might damage the host. Inflammation would thereby be confined to the local site of antimicrobial action. Second, it forces clinicians to consider the role of glucocorticoids during infection in a new way: to ask not "do infected patients ever need replacement steroid?" but rather "is there an optimal glucocorticoid concentration that is needed to protect the stressed patient from his own inflammatory response?"

F. WHAT IS THE NORMAL CORTISOL RESPONSE TO STRESS?

A number of different criteria have been formulated for interpreting the results of the rapid ACTH stimulation test (43,44). In general, basal plasma cortisol levels should be greater than 5 ug/dl. Thirty to 60 minutes following the intravenous administration of 0.25 mg (1,24) ACTH ("Cortrosyn"), cortisol level should rise at least 7 ug/dl or exceed 22 ug/dl. These criteria were developed from observations in unstressed

individuals. During stress, including infection, much is known about the frequency of profound adrenal insufficiency, yet there is virtually no information to indicate whether a given cortisol concentration is adequate to control the patient's inflammatory response.

Consider, for example, some recent findings in burned patients (45). Mean AM plasma cortisol levels, averaged over several days, correlated directly with the size of the burned surface area. The relationship held regardless of the clinical outcome or concomitant therapy with thyroxine. Interestingly, there was no correlation between ACTH levels and cortisol in the same samples, suggesting again that non-ACTH stimuli may promote cortisol release.

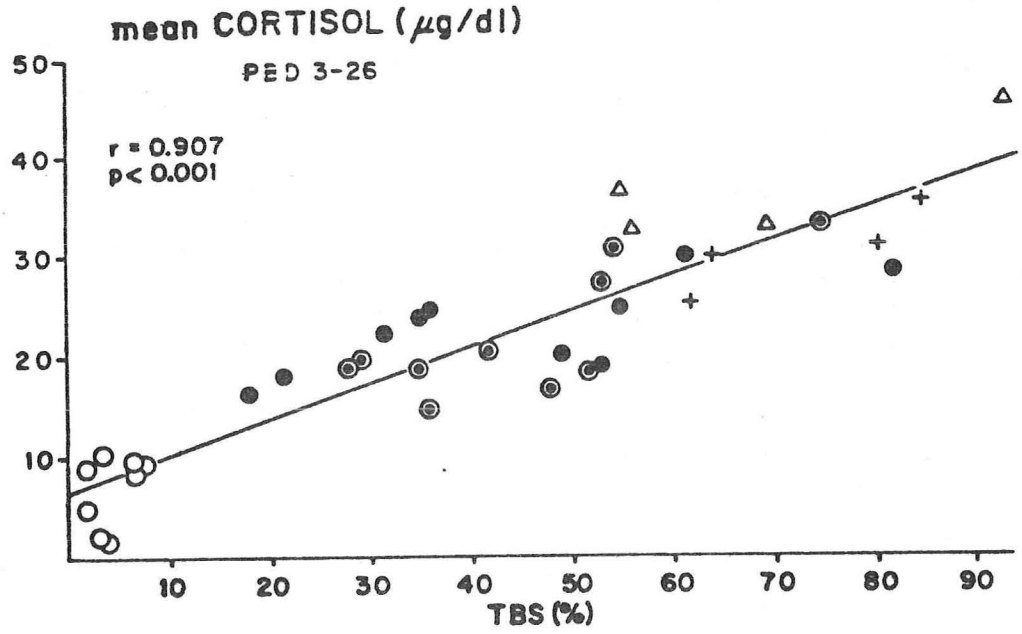


Figure 4. Relationship between AM cortisol (mean of several days' determinations) and total body surface area burned (TBS) (45). Copyright 1982, William and Wilkins Co. Vaughan GM, et. al., Journal of Trauma.

So the stress of a thermal burn can be quantitated in such a way that the normal AM cortisol level for a given burned patient can be determined. It would theoretically be possible to construct a nomogram:

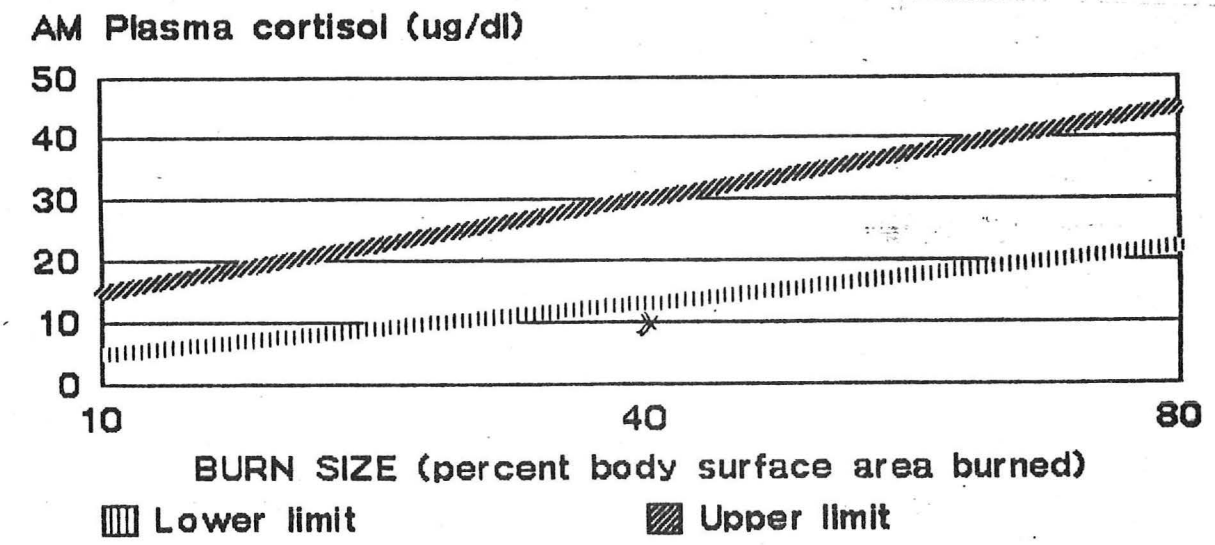


Figure 5. Theoretical monogram, constructed from data in Figure 4.

A point that fell within the upper and lower limits would indicate a normal response; the response to ACTH stimulation would be irrelevant. A point that fell below the lower limit might reflect sub-normal adrenal reserve, failure of CRF or ACTH release, or other mechanisms. Replacement doses of cortisol could be estimated with some accuracy: bring the patient back into the normal range.

Such precise quantitation is obviously not possible in infected patients, since the inflammatory stress itself cannot be quantitated. More to the point, even if we were able to describe the normal response to infection, this would beg the critical question: what is the optimal cortisol level necessary to prevent or reverse dangerous overshooting of the inflammatory process? Perhaps the normal response is not enough--severely stressed individuals might do better if the normal response relationship shown above had a steeper slope. To carry the argument even further, perhaps the reason that some patients' inflammatory process initially gets out of control is a failure to up-regulate cortisol secretion in response to the inflammatory stimulus--either too little or too late.

G. GLUCOCORTICOID THERAPY FOR BACTERIAL DISEASES

A comparison of commonly used drugs (data from Baxter [1] and Bondy [2]):

Steroid	Relative potency		$t_{\frac{1}{2}}$ (min) mean	Affinity for	
	Glucocort.	Mineralocort.		glucocort. receptor	CBG
Hydrocortisone (Solu-Cortef)	1.0	1.0	110	1.0	1.0
Dexamethasone (Decadron)	30	-	160	7.1	0.01
Me-prednisolone (Solu-Medrol)	5	0.02	220	2.2	0.58

The clearance of most pharmaceutical steroids is slower than that of cortisol and is not linearly related to dose. The increased potency of dexamethasone is probably related to its greater affinity for the glucocorticoid receptor and its lower protein binding. Little is known about the pharmacokinetics of high dose glucocorticoids.

ADRENAL INSUFFICIENCY

(1) Adrenal hemorrhage, necrosis.

When considered in the above terms, the published studies of adrenal function in infected patients seem quite limited. The goal of all such studies, since the landmark paper of Waterhouse (46), has been to define the frequency of profound, clinically significant adrenal insufficiency. For a while it was believed that adrenal insufficiency (due to hemorrhage or necrosis) was the basis for shock in septic patients. Indeed, it does appear that occasional patients with bacterial sepsis will have clinically significant adrenal insufficiency, with either extremely low basal cortisol levels or lack of ACTH stimulation (47,48,49). On the other hand, most septic patients--even those in shock--have elevated basal cortisol levels and/or respond appropriately to ACTH stimulation (50,51). One clue to the recognition of significant adrenal insufficiency may be the presence of cutaneous petechiae (52), since it is thought that adrenal hemorrhage is only one manifestation of a generalized hemorrhagic process. In a study of Brazilian patients (4 - 60 years old) with meningococcal disease, all 21 patients with cutaneous petechiae failed to raise plasma cortisol levels following ACTH stimulation (Figure 6). On the other hand, the basal cortisol levels in these patients, including those with petechiae, were all above 10 ug/dl. Their adrenals may have been maximally stimulated, as one child (with a basal cortisol of 13 ug/dl) had massive adrenal hemorrhage at autopsy (52). There was no relationship between basal cortisol level and the increment seen with ACTH stimulation.

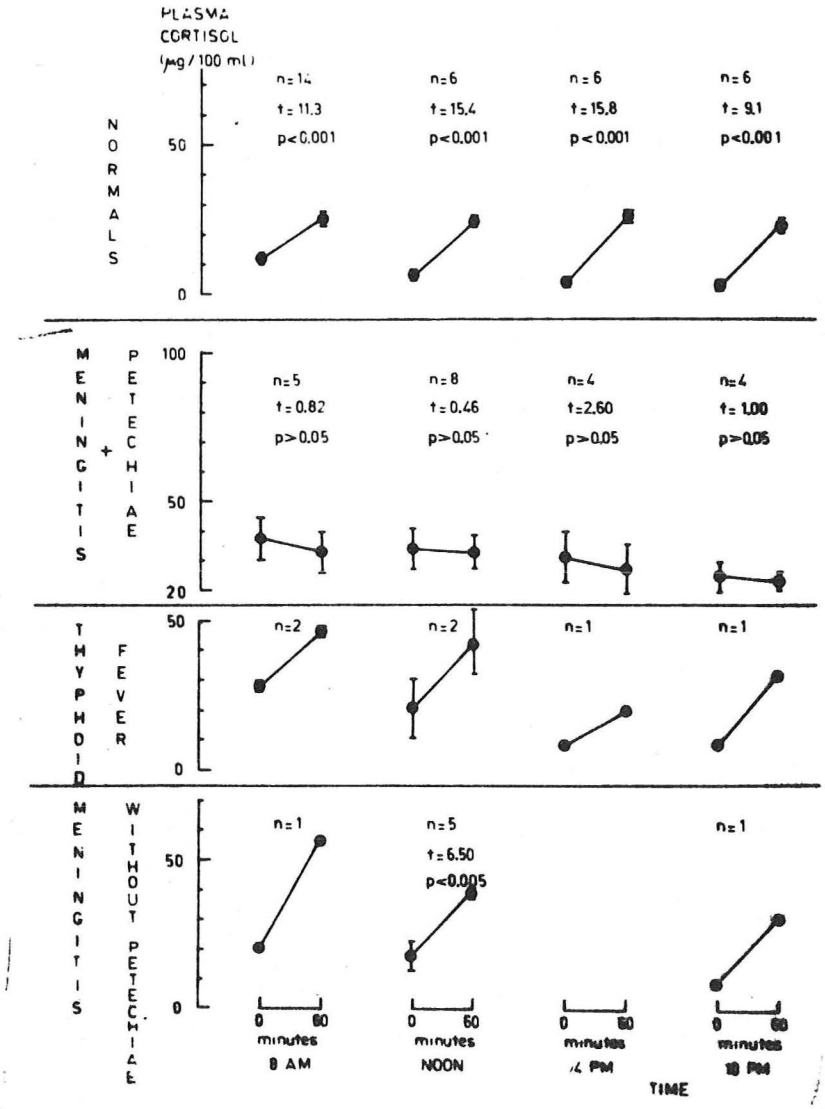


Figure 6. Results of ACTH stimulation tests in patients with various forms of meningococcal disease, performed at different times of day. Patients with typhoid fever are included as controls (52). Copywright 1978, The University of Chicago Wajchenberg B, Leme CE, Tambascia M, et. al. The Journal of Infectious Diseases.

Comments:

(1) Adrenal insufficiency, per se, is not the primary reason for shock in septic patients. It is much more likely that cachectin/TNF or other hormonal mediators (bradykinin, platelet activating factor, etc) are responsible for septic shock as well as for the DIC that leads to adrenal hemorrhage.

(2) Adrenal insufficiency may contribute to shock in a small subset of patients. It has been impossible to identify these patients prospectively, although the presence of widespread petechiae may be the best clue (it is certainly one of the hallmarks of a poor prognosis in meningococcemia).

(3) On the other hand, if the Munck hypothesis is correct, maintaining optimal concentrations of glucocorticoid might benefit the septic patient by down-modulating hormonal signals that perpetuate the septic state. What is this "optimal" cortisol level? The cortisol concentration needed to prevent overshoot of inflammatory mechanisms will presumably differ from patient to patient; severely ill patients who have measurably high plasma cortisol concentrations might in fact have sub-optimal cortisol levels. Their failure to generate even higher cortisol output may result from sub-optimal CRF or ACTH release from hypothalamo-pituitary or leukocytic sources. Neither the spot cortisol level nor the ACTH stimulation test will detect this deficiency.

In essence, the clinical focus on the detection of adrenal insufficiency, as defined by basal and stimulated cortisol levels, addresses one extreme situation (profound adrenal hemorrhage, necrosis) but not a more difficult and perhaps more important question: in the severely stressed patient, is normal cortisol output enough? Harder still: does the inflammatory response overshoot because endogenous cortisol secretion is insufficient to damp the stimulus, or occurs too late?

(2) Infiltration of the adrenal glands by infectious agents.

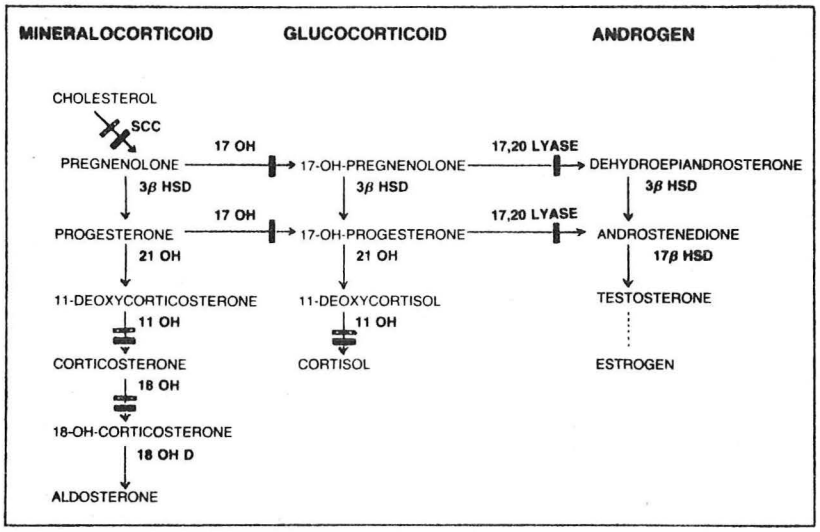
Adrenal infiltration commonly produces profound, clinically significant adrenal insufficiency. Microorganisms that invade the adrenal gland include mycobacteria (M. tuberculosis, M. avium-intracellulare), fungi (Histoplasma capsulatum, Blastomyces dermatitidis), and viruses (cytomegalovirus). A common theme is the ability of these agents to infect monocytes and macrophages; infiltration of the adrenal glands, which have a rich supply of macrophages, occurs as part of disseminated infections in which monocyte-macrophages in many other organs (e.g., spleen, liver, lung) are usually also involved.

The differential diagnosis of adrenal infiltration includes amyloidosis, hemorrhage, and metastatic tumor. CT and MRI scanning has greatly improved the recognition of adrenal infiltration (53,54).

(3) Pharmacologic adrenal insufficiency

Ketoconazole, an oral imidazole now widely used for treating fungal diseases, inhibits the synthesis of ergosterol in fungi and of cholesterol in mammalian cells. It also interferes with cytochrome P-450 enzyme systems in various organs.

Ketoconazole blocks the synthesis of both testosterone and cortisol (55). Its interference with the C_{17-20} lyase probably explains the greater suppressibility of testosterone secretion in human patients. Ketoconazole inhibits a number of other steps in steroid synthesis, however, including cholesterol side-chain cleavage (SCC), 17 alpha-hydroxylase, 11 beta hydroxylase, and 18-hydroxylase (Figure 7).



Main Pathways of Adrenal Steroidogenesis.
SCC denotes cholesterol side-chain cleavage, HSD hydroxysteroid dehydrogenase, OH hydroxylase, and OH D hydroxy dehydrogenase. Black bars indicate ketoconazole inhibition, and black-and-white bars metyrapone inhibition.

Figure 7. Inhibition of adrenal steroidogenesis by ketoconazole (55). Copyright 1987, Massachusetts Medical Society, Sonino N. The New England Journal of Medicine.

Ketoconazole thus inhibits cortisol and aldosterone synthesis as well.

These anti-androgen effects have been exploited in the therapy of precocious puberty, prostatic cancer, and hirsutism associated with polycystic ovary syndrome (55). The effects on cortisol synthesis have led workers to use ketoconazole for the therapy of Cushing's disease and adrenal tumors.

A major side effect in male patients receiving high doses is gynecomastia. Patients may also develop adrenal insufficiency. When ketoconazole (400 or 600 mg) is given to normal subjects, the plasma cortisol response to ACTH is blunted for 6 - 8 hours. Basal cortisol levels are usually normal, however, and symptomatic adrenal insufficiency is rare. ACTH levels have usually been elevated (56).

Although overt adrenal insufficiency has rarely been attributed to ketoconazole, a special situation may exist in the patient with AIDS who is taking ketoconazole in the presence of disseminated CMV, histoplasmosis, or M. avium- intracellulare disease involving the adrenal glands (57,58). This combination would seem a natural set-up for Addison's disease and clinicians should have a low threshold for performing ACTH stimulation tests in these patients.

CLINICAL TRIALS OF GLUCOCORTICOID THERAPY FOR BACTERIAL DISEASES

SEPSIS SYNDROME

The term "sepsis" refers to a set of clinical signs and symptoms, including fever, chills, hyperventilation, and hypotension, that suggest systemic infection. Two recent studies have given the sepsis syndrome more precise definition:

(1) R. C. Bone et. al. (Methylprednisolone Severe Sepsis Study Group) Clinical evidence of infection; temperature greater than 38.3°C or less than 35.6°C; heart rate greater than 90 beats/min; respiratory rate greater than 20/min; and one or more of the following: altered mentation, arterial pO_2 less than 75 mm Hg while breathing room air (without another explanation), elevated lactate; urine output less than 30 ml/hr (59).

(2) VA Cooperative Study. Four of the following, within an 8 hour period: temperature greater than 38.9°C or less than 35.5°C; heart rate greater than 100/min; respiratory rate greater than 28/min or arterial pO_2 less than 32; systolic blood pressure less than 90 mm Hg; total white cell count less than 3,500 or greater than 15,000 per mm^3, or less than 35% or greater than 85% neutrophils, or greater than 20% bands; platelet count less than 100,000 per mm^3; surgery during the previous 48 hours, or an obvious septic site (60).

These criteria were used to enroll patients into two large multi-center trials of methylprednisolone therapy in septic patients. The Bone et. al. study, which required that patients have evidence for organ hypoperfusion, enrolled 382 patients and positive blood cultures were obtained from 47%. The VA Cooperative Study attempted to enroll patients before organ hypoperfusion had developed; 42% of the 223 patients in this study had positive blood cultures. Approximately 60% of the positive blood cultures in both studies contained gram-negative bacteria, so that overall only 25% of the patients with clinical sepsis had documented gram-negative bacteremia. These results reinforce the conclusions that the sepsis syndrome is not always accompanied by detectable bacteremia, and that gram-positive as well as gram-negative infections can produce clinical "sepsis".

These studies also indicate that sepsis remains a life-threatening process, despite modern antibiotic therapy: 30% of Bone's patients and 21% of the VA Cooperative Study patients died as a direct or indirect consequence of the septic episode--and most patients with complicated or potentially fatal underlying diseases (burns, uncontrolled diabetes, etc) were excluded from entering the studies.

The sepsis syndrome presents a major challenge: how to control/reverse a complex physiologic derangement that is, in essence, the host's inflammatory reaction gone out of control, and that is not amenable to (and may possibly be worsened by) antimicrobial therapy. The most efficacious therapeutic interventions would theoretically be effective in both gram-positive and gram-negative bacterial sepsis. Accordingly, glucocorticoid therapy has received much attention in this disorder.

Strategic considerations. 1. Timing. As noted above, glucocorticoids block the synthesis/release of IL-1 and TNF/cachectin by cells that have been stimulated with LPS or other potent activators. There is much evidence, however, that effective inhibition requires that the glucocorticoid be added prior to, or simultaneous with, the introduction of the stimulus. A delay of as little as two hours is sufficient to abolish the glucocorticoid effect *in vitro* (30). In animal models of sepsis or endotoxemia, steroids have also been beneficial only when given before, with, or shortly after the bacterial stimulus. Finally, the clinical study by Sprung (61) found that patients treated with high-dose methylprednisolone had a higher frequency of shock reversal when treated within 4 hours of the onset of shock.

2. Antibiotic-induced bacterial lysis. It also appears that antibiotics, given to infected animals, break apart bacteria and thus release inflammation-inducing bacterial components such as endotoxins (62,63). Long suspected to occur in man, definitive proof of such antibiotic-induced lysis has been elusive. It has nevertheless been argued that a major benefit of steroid therapy may be to blunt the inflammatory response to this stimulus. For example, Johnston and Greisman (63) gave rats peritonitis with Proteus or Klebsiella. Methylprednisolone, 30 mg/kg, was given 2 hours later, and kanamycin was given 4 hours after the bacterial inoculum. Plasma endotoxin levels were estimated with the Limulus lysate test.

Treatment group	% survivors	Plasma endotoxin level	
		survivors	deaths
No therapy	29	1	4.7
Kanamycin	56	5.8	16.0
Kanamycin plus methylprednisolone	84	4.8	15.0

(Data from Johnston and Greisman [63])

Kanamycin therapy thus increased the levels of endotoxin in plasma, whether or not glucocorticoid was given. The glucocorticoid significantly reduced mortality, however. Johnston and Greisman concluded that, for optimal benefit, steroid should be given along with antibacterial agent(s). If the antibiotic-induced lysis syndrome occurs in man, it seems quite possible that, if given simultaneously with antibiotics, glucocorticoids might blunt the inflammatory "spike" that occurs when bacterial products are released.

Recent clinical trials. Clinical studies of steroid therapy in sepsis have been flawed by inadequacies such as small numbers of patients (61), uneven use of antimicrobial agents in control and steroid groups (64), use of very low doses of steroids (65), delay in the administration of steroids (61), and uncertainties about randomization of patients (64). Two recent multi-center studies were designed to enroll patients quickly and give them short-term, high-dose steroid therapy. It was strongly anticipated that steroids, given in this fashion, would be beneficial.

Key features of the studies:

	BONE et. al.(59)	VA COOPERATIVE STUDY(60)	SPRUNG(61)
Total enrolled	382	223	59
Organ hypoperfusion required at entry	yes	no	yes
Methylprednisolone dose	30 mg/kg q6h X 4 doses	30 mg/kg then 5 mg/kg/hr x 9 h	30 mg/kg
Time to initiation of steroid	less than 2h	2.8 h (mean)	17.5h
Mortality: placebo	29%	22%	69%
steroid	59%	21%	76%

In the earlier study by Sprung, benefit was seen in patients who received methylprednisolone within 4 hours of the onset of shock. Accordingly, in the Bone and VA studies, patients were enrolled prospectively and adjunctive therapy was begun promptly. It is harder to imagine more optimal response time in a clinical setting. Nevertheless, neither of the recent studies found significant benefit from methylprednisolone therapy. In the Bone study, the excess mortality in the steroid group was related largely to secondary infections. In the VA study, the only possible benefit of methylprednisolone was seen in the small subgroup (51 patients) that had gram-negative bacteremia. In this subgroup, steroid-treated patients had fewer pulmonary complications and a lower incidence of coma; they also had a lower mortality rate (7% vs 27%), but this difference was not statistically significant. Both recent study groups concluded that empiric, high-dose methylprednisolone therapy was not indicated in patients with presumed sepsis.

Neither of the recent clinical reports indicated the temporal relationship between the onsets of antimicrobial and steroid therapies. It seems likely, however, given the very short delay before the administration of steroids, that there would have been only a short interval between antimicrobial and steroid dosing.

A more optimistic interpretation of the data from the two clinical studies might focus on the patients with gram-negative bacteremia in the VA study. This study enrolled patients at a somewhat earlier stage of sepsis (often before organ hypoperfusion), used lower doses of methylprednisolone, and did see some apparent benefit in the gram-negative bacteremia subgroup. Given that 75% of the patients in these clinical studies did not have gram-negative bacteremia, however, and the negative results in the Bone study, high-dose methylprednisolone cannot be recommended for septic patients.

ADULT RESPIRATORY DISTRESS SYNDROME

High-dose steroid trials have also been performed in patients with established or anticipated ARDS (67,68). These studies will not be reviewed here in detail: they conclude, in keeping with the above results, that industrial-dose steroid therapy is not currently indicated.

TYPHOID FEVER

In striking contrast to the above results in septic patients, a recent randomized, double-blind trial showed that dexamethasone therapy significantly reduced mortality in patients with severe typhoid fever (69). The Indonesian patients enrolled in the study had an abnormal state of consciousness (delirium, obtundation, coma) or shock (less than 90 mm Hg systolic blood pressure, plus evidence for decreased organ perfusion), associated with fever and a blood culture that grew Salmonella typhi or S. paratyphi A. The dexamethasone dose was 3 mg/kg, followed by 8 doses of 1 mg/kg every 6 hours. All patients also received chloramphenicol. The following results were obtained:

STUDY DRUG	DIED	LIVED	TOTAL CASES
Dexamethasone	2 (10%)	18	20
Placebo	10 (56%)	8	18

(The difference in mortality was significantly different, $p = 0.003$, Fisher's exact test.)

The authors of the report speculated that, since Salmonella typhi is principally an intracellular pathogen that lives in monocytes and macrophages, glucocorticoids may reduce the production of arachidonic acid metabolites, act as antioxidants, decrease release of mediator hormones, etc., in bacteria-infected cells.

The patients in this study also had a mean age of 20 years, while the VA and Bone's patients averaged 60 and 53 years of age, respectively, and Sprung's patients averaged 50 years of age.

BRAIN ABSCESS

Bacterial infection of the cerebrum goes through three recognizable phases. During cerebritis, bacteria and inflammatory cells (largely neutrophils) are present. There is local edema, and the vascular supply may be compromised. A necrotic center develops. Collagen is slowly deposited in the periphery of the lesion, so that eventually an abscess develops, surrounded by a capsule. This process typically takes 2 to 3 weeks in animal models; the intermediate stage is called the transition period by some workers.

Computerized tomography has allowed evaluation of the impact of steroid therapy on these different stages. Methylglucamine iothalamate, the contrast dye used for the studies, diffuses across the disrupted blood brain barrier and produces contrast enhancement surrounding the focus of inflammation--the

typical "ring enhancement" seen on CT. Enzmann and his colleagues have studied the time course of enhancement decay by performing serial CT scans in animals and patients with brain abscesses (70,71,72). During the cerebritis stage, contrast enhancement maintains a steady plateau over one hour after injection of contrast, and contrast diffuses from the ring into the center of the lesion. When the lesion is encapsulated, in contrast, contrast enhancement peaks shortly after injection (10 min) and then decays, so that at 60 minutes there is about one-half the initial contrast. Contrast does not diffuse into the center of the abscess. In both dogs and man, steroid therapy greatly reduces contrast enhancement. The impact of glucocorticoid treatment is particularly striking during the cerebritis stage (70).

Glucocorticoid therapy would thus seem particularly useful in patients with bacterial cerebritis who have clinically important mass effect. Certain important caveats should be noted. First, the experimental data suggest that glucocorticoid therapy, when given early in the course of infection (i.e. during the cerebritis stage) may interfere with (a) host antibacterial defense (73,75) and (b) diffusion of some antimicrobial agents (e.g., penicillin G) into abscess cavities (74). Two animal studies also found that early steroid therapy inhibited capsule formation (73,75). Second, the clinical data are conflicting, with collected series of patients that suggest either benefit or hazard from steroid therapy (76,77,78). Finally, although CT and MRI have grealy improved the detection and anatomical definition of cerebral mass lesions, they do not provide an etiologic diagnosis--and glucocorticoid therapy is almost certainly contraindicated in Herpes simplex encephalitis, an anatomically focal disease that may be confused with bacterial cerebritis.

Optimally, glucocorticoid therapy would be reserved for those patients who (1) have proven bacterial brain abscess, (2) are receiving high-dose antimicrobial therapy that is appropriate for brain abscess pathogens, and (3) have clinically significant mass effect. The appropriate dosing regimen and the proper timing remain unknown. Since the goal is to reduce brain swelling, it may be possible to begin with high-dose dexamethasone and then use CT scans to guide the rapidity of the taper.

Glucocorticoids are widely used to reduce cerebral edema associated with tumors. The mechanism is probably a reduction in vascular permeability (79). It is interesting that nonsteroidal agents (ibuprofen and indomethacin) have been found to decrease tumor-induced protein extravasation in rats with gliomas; their effect was equal to that of dexamethasone and methylprednisolone (80). As with meningitis, the beneficial effects of nonsteroidal agents may actually be quite useful without the side effects of steroids. Clinical studies are needed.

CEREBRAL MALARIA

This non-bacterial disease is included because it illustrates an important concept. Plasmodium falciparum malaria may produce life-threatening cerebral involvement. Warrell et. al. studied the effects of dexamethasone (0.5 mg/kg then 10 mg q6h for 7 doses) in patients with cerebral malaria in Thailand (81). A double-blind, randomized trial showed that dexamethasone treatment prolonged unconsciousness and increased the frequency of complications.

In both the Warrell paper and an accompanying editorial by R. A. Fishman, the important distinction between vasogenic and cellular (cytotoxic) cerebral edema was underscored. Vasogenic edema is characterized by increased capillary endothelial permeability (hence, increased contrast enhancement on CT) and by high CSF protein levels. In contrast, cytotoxic edema produces an increase in brain cellular volume with a reduction in extracellular space; there is no contrast enhancement. As discussed above, glucocorticoids reduce vasogenic edema, probably by decreasing vascular permeability. In cerebral malaria, the brain capillaries are packed with parasitized erythrocytes. The brain is studded with petechial hemorrhages. The CSF protein is only mildly elevated. Evidence for cerebral edema is controversial. So it is not surprising that steroids did not benefit these patients. On the other hand, the explanation for the prolonged coma observed in steroid-treated patients is uncertain.

Other studies (cited in reference 81) suggest that corticosteroids may increase and prolong parasitemia and increase the frequency of secondary infections in patients with falciparum malaria.

BACTERIAL MENINGITIS

In two carefully performed studies, Drs. George McCracken, Mark Lebel, Bishara Freij, George Syrogiannopolos and their colleagues in the UT-Southwestern Department of Pediatrics have found that dexamethasone treatment confers significant benefit to infants and children with bacterial meningitis (82). In the two studies (data combined), two hundred patients were enrolled in a prospective, double-blind, placebo-controlled trial. One hundred and two patients were treated with cefuroxime and dexamethasone (0.15 mg/kg q6h for 4 days) whereas the remaining 98 were given cefuroxime and placebo. The following is a brief summary of their results:

No difference in treatment groups: demographic characteristics, clinical severity of illness, types of etiologic agents, duration of illness before admission. Rate of CSF sterilization, median bactericidal titers of CSF after 24 hours of therapy. Mortality (very low in both groups). Frequencies of residual neurologic abnormalities at 6-week and 1-year follow-up examinations.

Dexamethasone group greater than placebo group: mean increase in CSF glucose concentration, mean decrease in CSF lactate concentration, mean decrease in CSF protein--all significantly different at 24 hours.

Dexamethasone group less than placebo group: days with fever (1.5 vs 4 days), development of sensorineural hearing loss (4% vs 18%), particularly profound hearing loss requiring hearing aid placement (1% vs. 12%).

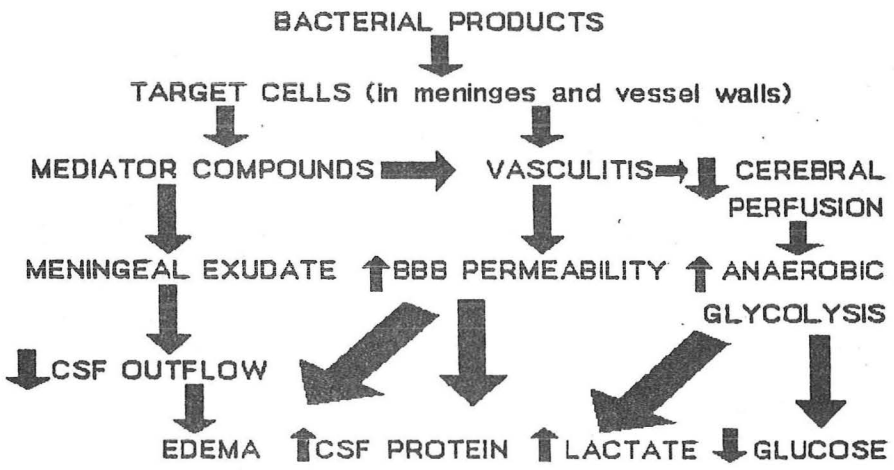
Infants and children who received dexamethasone in addition to an effective antibiotic thus became afebrile more rapidly, had more rapid resolution of CSF abnormalities, and were less likely to develop sensorineural hearing loss. These differences were all statistically significant.

This is a landmark clinical study that sets high standards for future work. Previous glucocorticoid trials in children with meningitis had reached conflicting conclusions, possibly because detailed analysis of auditory function was not performed. DeLemos and Haggarty (83) gave 40 mg methylprednisolone every 6 hours for 12 doses to children with meningitis. In this large (117 patients) double-blind trial, methylprednisolone shortened the course of fever but was actually associated with more neurologic abnormalities (18.7% vs. 3.5% in placebo group) and a greater frequency of residual damage. Hearing loss was not studied. In a separate trial, Belsey et. al. (84) found that dexamethasone (4.8 $mg/m^2/day$) seemed to decrease the frequency of complications in children with meningitis, yet the authors discounted this result because the dexamethasone-treated patients were in better condition at the onset of treatment. Again, hearing loss was not studied. In the only trial in adults, Bennett and others gave hydrocortisone (100 mg TID, then slowly tapered) to 85 patients with bacterial meningitis (65). There was no impact on mortality in these patients, most of whom had pneumococcal meningitis (the overall case fatality rate was 44%). Other end-points were not evaluated.

How do glucocorticoids modify the course of meningitis?

The ability of bacterial cell wall products to provoke meningeal inflammation in experimental animals, noted in the 1930's by Branham and her coworkers, has recently been rediscovered and carefully documented. Bacterial lipopolysaccharide (from gram-negatives such as H. influenzae) and peptidoglycan (from pneumococci and other gram-positives) are able to elicit striking meningeal inflammation in the absence of intact bacteria, whereas other bacterial surface molecules (e.g., capsular polysaccharides) are essentially non-stimulatory. Both peptidoglycan (including peptidoglycan fragments) and LPS elicit CSF leukocytosis, raise intracranial pressure, and increase brain water (edema). It is suspected that these changes are mediated by cytokines, prostanoids, or other mediators, but the precise mediator compound(s) are unknown.

A tentative scheme for the pathogenesis of meningitis:



Using this simplified scheme, it appears that glucocorticoids may interrupt meningeal inflammation at several key points.

a) Glucocorticoids decrease meningeal exudation of neutrophils. Methylprednisolone reduced meningeal inflammation (as measured by size of exudate present in brain sections) in rabbits with experimental pneumococcal meningitis (85). Interestingly, in this as in other studies, the severity of meningeal inflammation was not reflected in the CSF leukocyte counts; glucocorticoids actually increased CSF leukocyte numbers, both in this rabbit experiment and in the clinical study discussed above. The basis for the steroid-induced decrease in meningeal exudate is not clear, though perhaps glucorticoids inhibit the expression of the leukocyte adhesion complex that facilitates sticking of PMN to other cells (35).

One product of meningeal exudation may be a decrease in the outflow of CSF from the subarachnoid space, contributing to increased intracranial pressure. In elegant studies, Sheld and coworkers measured CSF outflow resistance in rabbits with experimental meningitis (86). They infused artificial CSF via a small catheter directly into the supracortical subarachnoid space and measured CSF pressure at different infusion flow rates. With pneumococcal infection, the CSF outflow resistance rose strikingly. Treatment with penicillin did not reduce the outflow resistance, whereas treatment of infected rabbits with methylprednisolone dramatically reduced outflow resistance. The basis for increased CSF outflow resistance is presumably a decrease in fluid transport across the arachnoid villi, which become altered during inflammation. The mechanism of the methylprednisolone effect was uncertain, but may have been linked to the reduction in neutrophil infiltration in or adjacent to the arachnoid villi.

The most dramatic clinical effect of dexamethasone treatment in the Southwestern study was a striking reduction in sensorineural hearing loss. There is considerable evidence that deafness occurs when there is spread of bacteria and inflammation from the subarachnoid space to the cochlea via the cochlear aqueduct, a channel that is patent in children (87). The ability of dexamethasone to decrease neutrophil infiltration may be particularly important in this regard, although its effects on local edema and vascular integrity may also be critical.

(b) Glucocorticoids decrease blood brain barrier permeability. Other studies have shown that leukocytes are not required for experimental animals to develop increased blood brain barrier permeability and brain edema. These changes are more likely the consequence of direct stimulation of vascular lining (e.g., endothelial) cells by bacterial products, or the secondary stimulation mediated by cytokines or prostanoids. Here glucocorticoids can have dramatic inhibitory effects.

In rabbits with experimental pneumococcal meningitis, dexamethasone and methylprednisolone reduced brain edema below levels attained in control infected animals (88). While dexamethasone lowered CSF pressure in these animals, which were not treated with antibiotics, methylprednisolone did not. (This is the best clue to the apparent superiority of dexamethasone observed in the clinical trials cited above.) In a subsequent study, Syrogiannopoulos et. al. tested the ability of dexamethasone to alter the inflammatory response to H. influenzae meningitis in rabbits (89). Although there were no

statistically significant differences between groups treated with ceftriaxone alone and ceftriaxone plus dexamethasone, beneficial trends were noted in certain parameters (brain water content, CSF pressure). The latter findings are of particular interest with regard to the reported ability of another cell-wall active antibiotic, cefotaxime, to release endotoxin from bacteria in CSF and actually enhance CSF inflammation (90). If dexamethasone were blocking the inflammatory response to bacterial endotoxin, dexamethasone plus antibiotic should be superior to antibiotic alone.

The effects of cyclooxygenase inhibitors on the course of experimental meningitis may be relevant here. Diclofenac, oxindinac, and indomethacin all blunted CSF leukocytosis in rabbits challenged with pneumococcal cell walls (91). Methylprednisolone had a similar effect. Interestingly, oxindinac also prevented the burst in CSF leukocytosis that occurred when the animals were infected intracisternally with live pneumococci and then treated with ampicillin, which presumably lysed the bacteria and released inflammatory cell wall components. Other authors have found that oxindinac or dexamethasone prevents the leakage of high molecular weight serum proteins into CSF that occurs in rabbits with pneumococcal meningitis (92). Indeed, the ability of glucocorticoids to decrease diffusion into CSF or brain abscess contents has also been noted for antibiotics such as ampicillin and gentamicin (74,93). It would appear from these studies using cyclooxygenase inhibitors that, by analogy, the ability of glucocorticoids to inhibit prostanoid synthesis may play a key role in their anti-inflammatory action in experimental meningitis.

(c) Glucocorticoids improve cerebral perfusion. Cerebral blood flow decreases during meningitis, although the mechanism is not known. Focal vasculitis can also occur, involving arteries (focal infarcts) as well as veins (cortical venous thrombophlebitis). There is also loss of autoregulation of cerebral blood flow, so that cerebral perfusion pressure is dependent upon systemic arterial pressure. One result of cerebral underperfusion is an increase in anaerobic glycolysis, with increased glucose utilization (thus, hypoglycorrachia) and lactate production. Glucocorticoids apparently improve cerebral perfusion, though again the mechanism is not understood--a direct vascular effect, or a secondary consequence of reducing brain edema and intracranial pressure? In the Southwestern meningitis study, dexamethasone increased CSF glucose and decreased CSF lactate relative to the placebo controls.

In summary, these experimental animal models suggest a number of possible explanations for the mechanism of action of glucocorticoids in meningitis. On the other hand, while the drug presumably reduces brain edema, lowers intracranial pressure (possibly by decreasing blood brain barrier permeability and increasing CSF outflow), and improves brain perfusion, the precise connection between these events and improved outcome is not yet apparent from the animal studies. The most promising clue is the apparent similarity between the effect of cyclooxygenase inhibition and that of dexamethasone administration--future studies will doubtless test the hypothesis that oxindinac or other nonsteroidal agents could be used instead of dexamethasone with similar clinical benefit and less toxicity. Further study of the antibiotic-induced bacterial lysis phenomenon in CSF is also needed, as it seems likely that at least part of the steroid effect may be related to prevention of inflammation that is initiated after antimicrobial

therapy is begun. The role of inflammatory mediators such as IL-1, cachectin/TNF, and eicosanoids in the pathogenesis of meningitis is under active investigation.

Other important questions remain. Is dexamethasone superior to alternative drugs (e.g., non-steroidal anti-inflammatory drugs)? What is the optimum dose and duration? Can these findings be applied to adults with bacterial meningitis, in whom pneumococcal meningitis (which has a high case fatality rate) is most common and the frequency of hearing loss is said to be lower than in children?

TUBERCULOUS MENINGITIS

The evidence that favors glucocorticoid therapy in tuberculous meningitis is much less convincing. There are, however, three studies that describe a beneficial effect of steroids, particularly in patients with severe disease (confusion, stupor, or focal neurological signs) (94,95,96). The most convincing report is that of O'Toole et. al. (95), in which 23 Indian patients were enrolled in a randomized, stratified fashion. Dexamethasone was given (2.25 mg every 6 hours during the first week, with a subsequent slow taper). Survival was not significantly greater in the steroid-treated group, although there was a favorable trend (45% survived, vs. 25% in the control group). The steroid group did show more rapid declines in CSF protein and cell counts, however, as well as a more rapid fall in CSF pressure.

Most authorities recommend that dexamethasone be used only in patients with severe tuberculous meningitis, when reducing cerebral edema may possibly prolong survival.

CONCLUSIONS

How can one reconcile the striking clinical benefit seen in the typhoid fever trial and the Southwestern meningitis study with the lack of benefit in the two recent multi-center sepsis trials? Several observations seem pertinent:

(1) Pediatric meningitis is a relatively uniform disease. It occurs in previously normal infants and children. In most cases, Hemophilus influenzae is the etiologic agent. Antimicrobials are generally quite effective; despite frequent bacteremia, septic shock is unusual and the case-fatality rate is less than 10%. The major benefit of glucocorticoid therapy was the prevention of hearing loss; since few patients died, there was no detectable impact on survival. Presumably glucocorticoid therapy benefited patients by diminishing cerebral edema and decreasing the accumulation of neutrophils in the subarachnoid space and/or the perilymph--in other words, its primary action was at a local site of inflammation, rather than systemic.

(2) In contrast, adult patients with sepsis comprise a heterogeneous population of individuals, most of whom have some serious underlying disease. Sepsis is produced by a wide range of pathogens. Most patients are in shock or nearly so--here the goal of steroid therapy is to reverse or prevent a systemic inflammatory reaction, not a localized one. The desired end-point

is an improvement in survival; less attention has been paid to possible effects of glucocorticoid therapy on other parameters, although in some studies there were statistically significant differences in outcomes (such as coma or ARDS) that favored the steroid-treated group (56). Identifying key subpopulations of patients may be essential for the recognition of apparent benefit or harm.

The ability of glucocorticoid to improve the outcome of typhoid fever patients may relate to the site of bacterial infection (predominantly in macrophages)--or possibly to the generally healthy status and younger age of the patients prior to this community-acquired, relatively uniform disease.

(3) The doses of glucocorticoid used in the various sepsis studies were strikingly different. The following Table compares the glucocorticoid doses for the controlled, randomized trials of glucocorticoid therapy in sepsis. All four of the recent unsuccessful trials in patients with sepsis or ARDS used higher doses than were previously used in trials that reported some benefit from glucocorticoids. The meningitis studies used doses that were lower than those used in any of the sepsis studies; the typhoid study used apparoximately 36 mg/kg/day of methylprednisolone (dexamethasone equivalent).

GLUCOCORTICOID DOSES USED IN SEPSIS TRIALS

(methylprednisolone, mg/kg/day)

	Year	Indication	Dose	Outcome	Suprainfections
Schumer	1976	sepsis	30-60	beneficial	no
Sprung	1984	sepsis	30-60	(beneficial)	yes
VA Coop	1987	sepsis	75	(beneficial)	no
Bone	1987	sepsis	120	harmful	yes
Bernard	1987	ARDS	120	not beneficial	no
Weigelt	1985	ARDS	120	harmful	yes

Two animal experiments also suggest strongly that there is an optimal dose of glucocorticoid for the infected animal. First, Kass and Finland (98) determined the dose of specific antiserum that would protect 50% of intact mice against 50,000 pneumococci. They then adrenalectomized mice and treated various groups of animals with different doses of cortisone prior to challenging all of the mice with pneumococci. Adrenalectomy markedly enhanced susceptibility to pneumococcal disease, as shown by the much lower LD_{50} (Figure 8). The effect of cortisone was striking: a dose-related improvement in survival, then a reduction in resistance with higher doses. Kass and Finland concluded that "the optimal dose of corticosteroid is critical and an excess is likely to be harmful. Objective means for determining the optimal dose clinically are not yet available." Their paper was published in 1958.

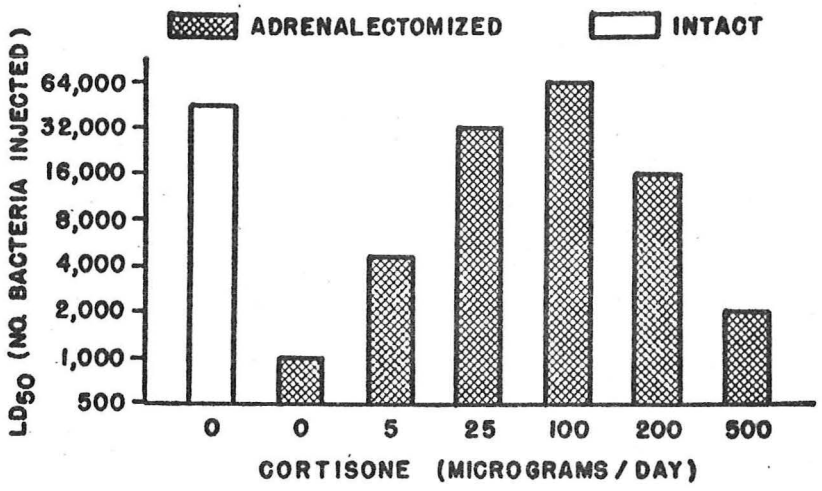


Figure 8. Effect of cortisone replacement dose on susceptibility of adrenalectomized mice to pneumococcal challenge (97).

Kass EH, Finland M. Advances in Internal Medicine

Greisman has reported similar results using his model of peritonitis in mice. After inoculation of bacteria intraperitoneally, kanamycin was given at a dose/time titered to allow 50-75% mortality. Methylprednisolone was then given, 2 hours before the kanamycin was administered. Again there was a clear relationship between methylprednisolone dose and survival, with higher doses actually having a detrimental effect (98).

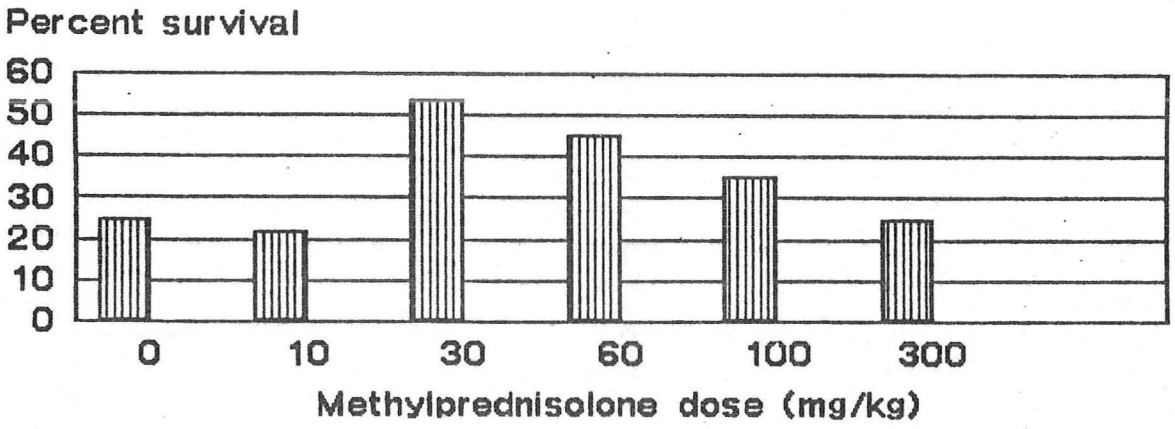


Figure 9. Effect of methylprednisolone dose on survival of mice challenged with Proteus mirabilis and treated with a standard dose of kanamycin.

Why were such high doses of glucocorticoid chosen for the recent studies? Schumer (59) had used 30 mg/kg methylprednisolone (repeated once if necessary) for sepsis with reported benefit. Although his study was strongly criticized for its nonuniform use of antibiotics, he did not report significant side effects from this dose. Sprung (57) used a similar dose. The groups led by Bone, Weigelt, and Bernard apparently felt that increasing the dose had greater potential benefit than risk. Studies in baboons also suggested that 30 mg/kg methylprednisolone, followed by an infusion of the drug at lower dose, was optimal; this approach was taken by the VA Cooperative Study (60). Although little is known about the biological effects of massive doses of glucocorticoids, it is unlikely that all of their effects are mediated via glucocorticoid receptors. These receptors are saturated and their number is down-regulated by much lower concentrations of glucocorticoid.

In summary, my review of this literature has impressed me with the lack of basic knowledge concerning the role of glucocorticoids in down-regulating the inflammatory response. There is little scientific information to guide glucocorticoid therapy in individual patients. It does seem that the development of profound inflammatory overshoot in some patients, but not in others with similar apparent stimuli (e.g., gram-negative bacteremia), may relate in part to the size or rapidity of increases in circulating cortisol concentrations--in other words, some individuals may be able to damp their inflammatory responses more effectively than others. The optimal response may prevent unregulated spread of the inflammatory cascade to distant (systemic) sites while allowing local inflammation to wall off and destroy the invading microbes. Non-glucocorticoid down-regulators may obviously also be involved.

There are many possible explanations for the diverse results of clinical studies of adjunctive glucocorticoid therapy in bacterial diseases. Principal among these are differences in patient populations, underlying diseases, the doses of glucocorticoid used (and perhaps the preparation used), the timing of steroid administration, and the clinical outcomes studied. In general, glucocorticoids have been beneficial when given promptly in low or moderate dose to patients with localized disease, and particularly when response has been judged by a clinical outcome other than survival.

Finding the best dose for different clinical situations will obviously be difficult, yet most other study variables have now been optimized. Identification of subpopulations of patients that could be benefited by steroid therapy would also seem possible in future studies. Better understanding of the antibiotic-induced lysis syndrome may help account for different responses to glucocorticoid therapy and also improve dosing schedules.

It should also be noted that many of the effects of glucocorticoids on inflammation can be produced using non-steroidal antiinflammatory agents. Although the evident side-effects of steroid therapy have been limited principally to suprainfections and possibly gastrointestinal bleeding--both of which might be minimized if high dose regimens are avoided--the nonsteroidal agents would potentially avoid these adverse effects while achieving the same clinical benefit derived from glucocorticoids. Further study of these drugs in the diseases discussed here is clearly indicated.

GLUCOCORTICOID THERAPY FOR BACTERIAL DISEASES: SUGGESTIONS

Secure recommendations are impossible, given the limited data available. The following suggestions are simply a summary of the literature reviewed. The doses are expressed as dexamethasone equivalents for the first day of therapy. Subsequent dosing usually involves a taper; see original papers for further information. The choice of dexamethasone is arbitrary, although most of the demonstrations of benefit from glucocorticoid therapy have used this drug. Note that none of the suggestions is for "high dose" steroids.

Condition	Daily Dose (dexamethasone)	Comment
Brain abscess	2-4 mg q6h	Only for brain edema with clinically significant mass effect
Bacterial meningitis	0.15 mg/kg q6h	Demonstrated efficacy only in pediatric patients; not officially recommended
TB meningitis	2-3 mg q6h	Only for severe disease
Typhoid fever	3 mg/kg then 1 mg/kg q6h	Only for severe disease
"sepsis"	3 mg q6h	For septic patients with petechiae, (?) DIC (use 50-100 mg hydrocortisone q6h)
	"	If associated with adrenal enlargement or hemorrhage on CT, if patient is receiving glucocorticoid therapy, if clinical findings suggest adrenal insufficiency, or (?) if pt. is receiving ketoconazole (use hydrocortisone)
Pituitary apoplexy	"	Complication of sphenoid sinusitis, pituitary tumor; fever and (often) hypotension. May not be microbial.
	higher dose	Not indicated
ARDS		Not indicated

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