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# REVIEW: Hypothalamic Pituitary Adrenal Function during Critical Illness: Limitations of Current Assessment Methods

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**Context:** Activation of the hypothalamic-pituitary-adrenal (HPA) axis represents one of several important responses to stressful events and critical illnesses. Despite a large volume of published data, several controversies continue to be debated, such as the definition of normal adrenal response, the concept of relative adrenal insufficiency, and the use of glucocorticoids in the setting of critical illness.

**Objectives:** The primary objective was to review some of the modulating factors and limitations of currently used methods of assessing HPA function during critical illness and provide alternative approaches in that setting.

**Design:** This was a critical review of relevant data from the literature with inclusion of previously published as well as unpublished observations by the author. Data on HPA function during three different forms of critical illnesses were reviewed: experimental endotoxemia in healthy volunteers, the response to major surgical procedures in patients with normal HPA, and the spontaneous acute to subacute critical illnesses observed in patients treated in intensive care units.

**Setting:** The study was conducted at an academic medical center.

**Patients/Participants:** Participants were critically ill subjects.

**Intervention:** There was no intervention.

**Main Outcome Measure:** The main measure was to provide data on the superiority of measuring serum free cortisol during critical illness as contrasted to those of total cortisol measurements.

**Results:** Serum free cortisol measurement is the most reliable method to assess adrenal function in critically ill, hypoproteinemic patients. A random serum free cortisol is expected to be 1.8 $\mu$g/dl or more in most critically ill patients, irrespective of their serum binding proteins. Because the free cortisol assay is not currently available for routine clinical use, alternative approaches to estimate serum free cortisol can be used. These include calculated free cortisol (Coolens' method) and determining the free cortisol index (ratio of serum cortisol to transcortin concentrations). Preliminary data suggest that salivary cortisol measurements might be another alternative approach to estimating the free cortisol in the circulation. When serum binding proteins (albumin, transcortin) are near normal, measurements of total serum cortisol continue to provide reliable assessment of adrenal function in critically ill patients, in whom a random serum total cortisol would be expected to be 15 $\mu$g/dl or more in most patients. In hypoproteinemic critically ill subjects, a random serum total cortisol level is expected to be 9.5 $\mu$g/dl or more in most patients. Data on Cosyntropin-stimulated serum total and free cortisol levels should be interpreted with the understanding that the responses in critically ill subjects are higher than those of healthy ambulatory volunteers. The Cosyntropin-induced increment in serum total cortisol should not be used as a criterion for defining adrenal function, especially in critically ill patients.

**Conclusions:** The routine use of glucocorticoids during critical illness is not justified except in patients in whom adrenal insufficiency was properly diagnosed or others who are hypotensive, septic, and unresponsive to standard therapy. When glucocorticoids are used, hydrocortisone should be the drug of choice and should be given at the lowest dose and for the shortest duration possible. The hydrocortisone dose (50 mg every 6 h) that is mistakenly labeled as low-dose hydrocortisone leads to excessive elevation in serum cortisol to values severalfold greater than those achieved in patients with documented normal adrenal function. The latter data should call into question the current practice of using such doses of hydrocortisone even in the adrenally insufficient subjects. **(*J Clin Endocrinol Metab* 91: 3725–3745, 2006)**

ACUTE AND CHRONIC stressful events in life initiate a well-coordinated physiological response to maintain homeostasis (1–5). The activated stress response system results in alterations in cardiovascular function, intermediary metabolism, and immune-mediated inflammation. Whereas the central components of the stress response are in the hypothalamus and brain stem, the peripheral components include the hypothalamic-pituitary-adrenal (HPA) axis as well as the systemic and adrenomedullary sympathetic system (1–5). The importance of the HPA function and glucocorticoid secretion in the stress response was noted many decades ago by Selye (6), who found that adrenal hypertrophy, gastric ulceration, and thymolymphatic dystrophy were the classical triad of the stress response.

Regulations of the components of the stress response system are interdependent and interwined (1–5). For example, CRH stimulates secretion of norepinephrine through specific receptors in the hypothalamus, whereas norepinephrine stimulates CRH secretion through $\alpha$1 noradrenergic receptors (1–5). Both components of the central stress response system are stimulated by cholinergic and serotonergic neurotransmitters and are inhibited by $\gamma$-aminobutyric acid-

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Abbreviations: ANF, Atrial natriuretic factor; CABG, coronary artery bypass graft; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit; LPS, lipopolysaccharide; MIF, migration inhibitory factor; TL, TOLL-like.

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benzodiazepine and proopiomelanocortin peptides (1–5). Other areas of the brain differentially activate a subset of vagal and sacral parasympathetic efferents that mediates the gut response to stress (1–4). Detailed reviews of the components of the autonomic nervous system and their regulation have been discussed extensively in the literature (1–5).

The essential role of the adrenal for survival was first noted by Addison in 1855. Although epinephrine was the first adrenal hormone to be isolated, its failure to prevent death in adrenalectomized animals suggested that the adrenal cortex was essential for survival (7). Subsequent studies over the years revealed the adrenal cortex to include three zones or regions whereby each region is not only regulated differently but also has a specific set of enzymes and produces a specific class of steroids. Whereas the secretion of mineralocorticoids by the zona glomerulosa is regulated by the renin-angiotensin system, the synthesis and secretion of glucocorticoids by the zona fasciculate and adrenal androgens by zona reticularis are controlled by the HPA system. Destructive or infiltrative disease entities affecting the adrenal gland tend to cause partial or complete loss of the three classes of steroids (mineralocorticoids, androgens, and glucocorticoids) secreted by the three zones of the adrenal and result in what is described as primary adrenal insufficiency. In contrast, partial or complete loss of ACTH secretion causes decreased glucocorticoid and adrenal androgen secretion and is referred to as central adrenal insufficiency.

This review will focus on HPA function in critically ill patients. The review will not address the causes, diagnosis, or treatment of primary or central adrenal insufficiency because detailed studies and reviews on these topics have been published (8–12). This review will not examine adjustments in glucocorticoid therapy during critical illness in patients previously known to have primary or secondary adrenal insufficiency because these issues have been extensively reviewed (9, 13). Instead, the main focus of this review is to address important limitations in studies examining HPA function during critical illnesses in patients who were not previously known to have adrenal dysfunction.

## Overview

Activation of the HPA axis is one of several important responses to stressful events and critical illnesses (1–5). Cortisol, the primary glucocorticoid hormone secreted by zona fasciculate of the adrenal cortex in response to activation of the HPA axis, has an important role in many of the physiological functions necessary during trauma, critical illnesses, and other stresses. The cellular actions of cortisol include, but are not limited to, its effects on gluconeogenesis; the antiinflammatory effects on the immune system; as well as its influence in the maintenance of vascular tone, endothelial integrity, increased sensitivity to pressors, reduction of nitric oxide-mediated vasodilatation, and modulation of angiotensinogen synthesis. The important role of cortisol for survival from major stressful events was recognized many years ago in experimental animals (14, 15) The essential role of cortisol for survival in humans is best appreciated in patients with partial or complete deficiency of glucocorticoids during stressful events (9–11, 13, 16, 17).

Numerous studies have documented activation of the HPA axis during acute and chronic stressful events such as in patients undergoing surgery (16, 18–22), those with sepsis (23–37), trauma (31), burns (38), and others with different critical illnesses (39–49). In general, the degree of activation of the axis is proportionate to the stress. Activation of the axis as frequently determined by measurements of random serum total cortisol concentrations indicates that the latter are uniformly elevated in the critically ill. Although the degree of elevation in serum cortisol concentration may not correlate linearly with the illness severity, some studies demonstrated that patients with the highest cortisol levels have the highest mortality as well (35). In some studies, activation of the HPA axis in the critically ill has been demonstrated by measuring Cosyntropin-stimulated serum cortisol levels. As will be discussed later, many of the methods and measures used to determine glucocorticoid secretion have significant limitations that can often lead to data misinterpretation.

Over the past few years, newer data on glucocorticoid secretion and/or therapy during critical illness were published. Most of the published data focused on a subgroup of patients with severe sepsis and/or septic shock. Despite, and perhaps because of, the recent data, many controversies in this field became evident. This article will review the physiology of the normal response to critical illnesses and examine potential limitations of published data on assessment of adrenal function and others using glucocorticoids in treating patients with critical illnesses. The article will also discuss some of the confounding factors limiting these studies, including the methods used to define normal secretion. Examples of these limitations are cited, and approaches to address these confounding factors are discussed. The newly introduced yet poorly defined and characterized concept of relative or functional adrenal insufficiency is a very controversial topic that will also be discussed in this review.

## I. Normal Physiology of HPA Function

In healthy subjects, cortisol secretion is regulated by ACTH secretion by the pituitary, which, in turn, is primarily regulated by hypothalamic secretion of CRH. Secretion of CRH is pulsatile and is followed by the pulsatile release of ACTH from the pituitary. As discussed earlier, the autonomic nervous system modulates CRH secretion by the hypothalamus (1–5). ACTH, in turn, stimulates the synthesis and secretion of cortisol by the fasciculata layer and also dehydroepiandrosterone (DHEA) by the reticularis zone of the adrenal cortex. Even though the primary regulator of aldosterone secretion is the renin-angiotensin system, this steroid is also secreted in response to ACTH. Cortisol secretion is regulated by the hypothalamic secretion of CRH and subsequently by the pituitary release of ACTH. The negative feedback exerted by secreted cortisol (or any exogenously administered glucocorticoid) on CRH and ACTH synthesis and secretion maintains a tightly regulated system. Whereas ACTH regulates DHEA and its sulfated compound, DHEA-S, secretion by zona reticularis, the latter steroids do not directly contribute to the negative feedback loop influencing ACTH secretion. Whereas DHEA and DHEA-S have important physiological effects, their function during critical

illnesses is not well characterized. It was postulated that the latter adrenal steroids might have immune modulating influence, and, therefore, their secretion and function should be further investigated during critical illnesses.

Vasopressin is also a known modulator of ACTH secretion. Because vasopressin stimulates the release of ACTH in healthy subjects, it is used as a diagnostic test for conditions associated with ACTH excess or deficiency. However, the stimulatory effects of vasopressin on ACTH secretion require the presence of CRH.

## II. Alterations in HPA Function during Critical Illness

The classical regulators of the axis continue to be operable in critically ill patients but with significant alterations. In addition to hypothalamic hormones, CRH, and vasopressin, the autonomic nervous system as well as inflammatory cytokines such as IL-1, IL-6, and TNF$\alpha$ have long been recognized as important modulators of the HPA function during critical illness (5, 20). During an inflammatory process, these cytokines are capable of stimulating and maintaining glucocorticoid production to high levels (5, 50–54). IL-6 receptors are present on pituitary corticotrophs as well as adrenal cortical cells (51, 52). It is believed that cytokines released from the site of injury or after exposure to endotoxin activate the HPA by stimulating the classical pathway of CRH and ACTH secretion (5, 50–53). These cytokines act synergistically to augment ACTH secretion beyond that achieved by CRH alone (5, 50).

The HPA axis is highly activated during stressful events as evidenced by elevated plasma ACTH levels, increased cortisol secretion, and elevated serum total and free cortisol levels (37, 45). In addition to increased adrenal production or secretion of glucocorticoids during critical illness, impaired glucocorticoid clearance can contribute to the greatly increased serum cortisol concentrations (55). This would be especially likely in patients with impaired hepatocellular function, hepatic blood flow, or renal or thyroidal function (55). The increased cortisol secretion is best appreciated by the marked elevation in the free fraction of the hormone (37, 45). Cortisol secretion during critical illnesses is not only excessive, reaching levels greater than those achieved in patients with Cushing's syndrome, but also less suppressible by exogenous glucocorticoid administration such as dexamethasone (56, 57). An example of the poor suppressibility of the HPA axis during stress is illustrated in Fig. 1. In that example (Fig. 1), plasma ACTH and serum cortisol levels were serially determined in patients with normal HPA function after surgical removal of brain tumors. The levels of both hormones (ACTH, cortisol) were not suppressed for more than 2 d despite the administration of large (24 mg/d) doses of dexamethasone. Furthermore, ACTH and cortisol responsiveness to exogenous CRH is enhanced during critical illnesses (57). Even though ACTH continues to be the dominant factor stimulating cortisol secretion by the adrenal cortex throughout the critical illness, other factors play a significant modulating influence on the axis. Such factors include arginine vasopressin (especially in volume-contracted subjects), endothelin, atrial natriuretic factor (ANF) (58), and a variety of cytokines such as IL-6 (50–54). Macrophage-migration inhibitory factor (MIF) is another modulator of the HPA function, especially during a severe inflammatory process such as septic shock (59, 60). Although the exact role of MIF during critical illness is not well defined, this factor appears to have both proinflammatory and antiinflammatory effects (59–61) and is considered to have a role in the homeostatic and physiological actions of glucocorticoids *in vivo* (61).

Recent evidence suggests that the early defense against bacterial or viral infection is initiated by TOLL-like (TL) receptors. These are family pattern recognition receptors for the detection and response to microbial ligands (62–64). These receptors are expressed on human adrenal cortical cells (62–64). The role of TL receptors during critical illness is still not well defined. Recent data in humans demonstrate the existence of TL receptor mutations with a high degree of polymorphism (65, 66). It is possible that the latter polymorphism in the population could be a contributing factor for

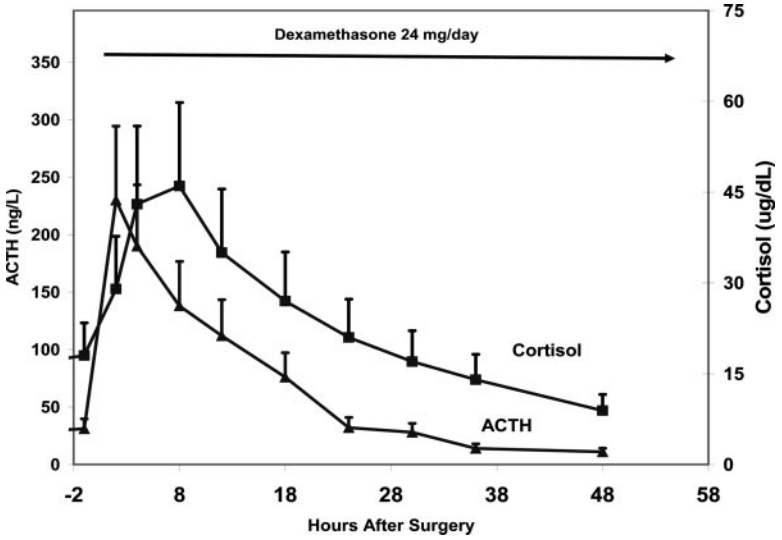


FIG. 1. Mean (± SD) plasma ACTH and serum total cortisol concentrations measured in five patients with brain tumors who had previously had normal adrenal function and who had surgery (time 0) and who were given dexamethasone (4 mg iv every 6 h) starting at 3 h after surgery and continued every 6 h. The data indicate that despite continued dexamethasone administration, ACTH and cortisol levels were similar to those in patients who did not receive glucocorticoids and were not suppressed for at least 48 h. To convert serum cortisol levels from micrograms per deciliter to nanomoles per liter, multiply the value by 27.59. To convert plasma ACTH values from nanograms per liter to picomoles per liter, multiply by 0.2202.

some of the individual variations noted in the response to stress.

Recent studies on the actions of glucocorticoids suggest that the effects of these steroid molecules are a continuum from permissive to suppressive effects that are observed over the range of concentrations achieved *in vivo*. Whereas physiological concentrations are associated with permissive effects, the high concentrations observed during serious illnesses are associated with suppressive or antiinflammatory effects (67, 68). The latter antiinflammatory effects of glucocorticoids are what is most known and appreciated about these steroid molecules. Much less is appreciated about the permissive and, at times, proinflammatory effects of glucocorticoids (67, 68). Glucocorticoids can alter their effects on target tissues through modulation of the density and binding affinity (69) and by altering cytokine receptors in glucocorticoid-dependent cells (70). Glucocorticoids also modulate the production of MIF by macrophages (59–61) and also by altering the hepatic acute phase response and their known effects of cell apoptosis (71, 72).

Resistance to glucocorticoid action, whether it is caused by defects in the glucocorticoid receptor or postreceptor alterations, has been proposed to occur during some critical illnesses, particularly in severe sepsis and septic shock. Inflammatory cytokines, when produced at lower concentrations, appear to stimulate cortisol secretion and enhance its binding to its own receptor (73). However, when cytokine production is excessive, as is the case during an overwhelming inflammatory response, it leads to decreased numbers as well as binding affinity in glucocorticoid receptors (74) and also other postreceptor alterations. Both of these events can lead to glucocorticoid resistance, particularly at the tissue site of excessive cytokine production (74). It is not clear at this point whether MIF secretion contributes to the state of relative glucocorticoid resistance.

## III. Short-Term Stresses *vs.* Protracted Critical Illness

It has become evident over the past few years that different neuroendocrine paradigms exist for the acute, short-lived (hours to a few days) critical illness and that of the protracted and prolonged critical illness (75) (lasting many days or weeks). Patients with protracted chronic illnesses have already survived their respective acute phase injury. Having survived the short-term illness provides reasonable assurance that their HPA function was adequate. There are metabolic, nutritional, and hormonal differences between these two settings of critical illness. Studies have shown that alterations in somatotroph function and the pituitary thyroidal axes are distinctly different between the two instances of critical illness (75). Similarly, regulation and maintenance of the HPA function represent another, albeit more subtle, but important, difference in the two settings of critical illness. Another major difference between acute and protracted critical illnesses is that many of the modulating factors known to influence synthesis and secretion as well as measurements of secreted glucocorticoids are more applicable to patients with protracted critical illness than those with acute, self-limiting stresses. These modulating factors will be addressed below. The differences between the latter two settings of critical illnesses are not limited to glucocorticoid secretion but are also observed in adrenal androgen secretion, as will be discussed below. It is therefore evident that it would be difficult to extrapolate data obtained in an acute critical illness setting to that of the protracted chronic phase. Nevertheless, the comparison would be helpful as long as the limitations are acknowledged.

In general, the HPA displays a biphasic pattern during the course of a critical illness (58, 75, 76). During the initial phase of an illness, such as surgery, uncomplicated trauma, burn, infection, or sepsis, the HPA axis is primarily activated through increased CRH secretion and cytokine production. Biochemically, the initial phase is characterized by elevated plasma ACTH and cortisol concentrations (58, 76). The hypercortisolism in this setting provides energy and protects the body and is reflected by increased gluconeogenesis, maintenance of intravascular volume, and inhibition of the acute inflammatory reaction. In contrast, studies in protracted critical illness showed a decrease in plasma ACTH concentrations despite persistence of the state of hypercortisolism. These features suggest that cortisol secretion is being regulated and stimulated by alternative pathways other than the classical hypothalamic CRH. As discussed earlier, such factors include ANF, endothelin, substance P, and a variety of cytokines. The persistent hypercortisolism observed in protracted critical illness serves to provide similar benefits related to providing energy, maintaining volume, and minimizing inflammation. However, the persistence of hypercortisolism is also likely to contribute to some of the longer-term complications observed with protracted critical illness such as hyperglycemia, myopathy, poor wound healing, and psychiatric alterations.

As stated earlier, this review will discuss some of the often overlooked, confounding factors and limitations in the biochemical assessment of adrenal function. The review will also address newer approaches to avoid and minimize these limitations. Relevant published data on three different forms or examples of critical illnesses will be reviewed. The first form of stress to be reviewed will be that of normal subjects during experimental endotoxemia. The latter is considered an experimental model for an acute inflammatory process. The second example of a short-term, stressful event to be reviewed is that of patients undergoing different surgical procedures. These two examples represent instances of short-term critical illness where the duration of stress is hours to days. In one of these stresses (experimental endotoxemia), the stress induces a dominant inflammatory response. The last and most extensively studied form of stress is that of patients with a variety of medical and surgical illnesses who are studied in intensive care units (ICUs). Although patients with a variety of diagnoses are included in such publications, many of them have focused on patients with a specific illness such as septic shock. These patients have been studied at different times after the onset of their critical illnesses, and, therefore, glucocorticoid secretion could be regulated differently. Despite these and many other limitations, reviewing such data would help improve our understanding of these events.

## IV. Three Examples of Stressful Events

### *A. HPA function during experimental endotoxemia*

Experimental endotoxemia in humans is a well-characterized model of acute inflammation (77–81). The iv administration of Gram-negative bacterial lipopolysaccharide (LPS) endotoxin results in an acute inflammatory process that manifests as fever, tachycardia, leukocytosis, and immune cell activation. This is followed by cytokine secretion (TNF$\alpha$, IL-6), the release of catecholamines, and activation of the HPA axis (77–81). LPS causes an increase in stress and counterregulatory hormones within 1 h of its administration (77–81). A rise in plasma ACTH, catecholamines, cortisol, and GH have been demonstrated after LPS injection (77–81). Serum cortisol levels increase within 2 h of LPS injection from an average of 320 nmol/liter (11. 5 $\mu$g/dl) to nearly 800 nmol/liter or 29 $\mu$g/dl (77–81). LPS administration increases the release of the antiinflammatory cytokine (IL-10), which may serve a protective role during sepsis (79). When hydrocortisone was infused directly before the LPS injection, the antiinflammatory cytokine, IL-10 levels were greatly increased (79). Based on these studies, it was concluded that stimulation of IL-10 release may contribute to the antiinflammatory properties of glucocorticoids (79). Experimental endotoxemia has been quite a helpful approach in understanding the body's response to acute inflammation. It is important to point out that despite the established inflammatory response to LPS, experimental endotoxemia is not considered a good model for sepsis or septic shock. Therefore, it is imperative that data obtained in patients during experimental endotoxemia cannot be extrapolated or applied to others with sepsis or septic shock.

### *B. HPA function during controlled, short-term, stressful events (e.g. surgery)*

The need for glucocorticoids during any stressful event such as a surgical procedure is due, in part, to the known effects of these steroids on several components of the host response to the stress of surgery. In this respect, glucocorticoids help support and stimulate cardiovascular response to stress. Additionally, glucocorticoids support many of the components of the inflammatory response to tissue injury occurring during surgery. Glucocorticoids stimulate the release of IL-10, the major antiinflammatory cytokine (82). Such effects of glucocorticoids can be achieved with minimal to moderate increase in secretion. However, higher quantities of cortisol would be necessary when the inflammatory response to tissue injury is more extensive and/or prolonged, as is the case in patients with septic shock.

Several studies investigated the HPA axis during and after minor as well as major surgical procedures. Published data on adrenal function and activity were reported in patients with normal HPA function who had various surgical procedures (18) including abdominal surgery (20), cholecystectomy (19), open heart surgery, coronary artery bypass graft (CABG) surgery (22), and pituitary adenomectomy (21). The studies generally show that the HPA is activated especially after extubation whereby plasma ACTH levels are increased and are associated with elevated serum cortisol concentrations. Thereafter, plasma levels of ACTH decline rapidly to normal levels, whereas serum cortisol concentrations decrease slowly, reaching high normal values approximately 48–72 h after the procedure. A typical example is illustrated in Fig. 2, demonstrating the changes in ACTH and cortisol levels in the perioperative period in patients with normal pituitary-adrenal function who had surgical adenomectomy of non-ACTH-secreting adenomas. This example is quite similar to others published in literature on patients after major surgical procedures (18). In such instances, mean serum cortisol levels obtained 2–4 h after extubation are approximately 40 $\mu$g/dl, whereas plasma ACTH concentrations are also elevated at 100–150 ng/liter.

A recent study conducted in patients who underwent CABG surgery demonstrated that the degree of rise in serum cortisol concentration measured in the immediate postoperative period is sufficient to control the intense inflammatory reaction caused by the procedure itself (83). The latter study noted that serum levels of the glucocorticoid-stimulated cytokine, IL-10, were elevated after such surgery and did not increase any further with various amounts of exogenous glucocorticoids (83).

It is important to emphasize that such critically ill patients not only have elevated baseline serum cortisol levels but also enhanced responsiveness to Cosyntropin stimulation (22). The latter study demonstrated that patients undergoing CABG surgery have higher baseline and Cosyntropin-stimulated serum cortisol levels in the immediate postoperative period, compared with their own values preoperatively (22). The latter finding reported in patients who had CABG (22) was quite similar to that previously reported in other critically ill patients with various illnesses (45). An important finding in that study was that the Cosyntropin-induced incremental rise in serum cortisol levels cannot be used to define normality of adrenal function (22). The study investigators noted, just as was previously observed in normal subjects (84), that nearly 40% of these stressed patients who also had normal adrenal function had a blunted ($<$9 $\mu$g/dl) Cosyntropin-induced increment in serum total cortisol concentrations. As will be discussed below, the latter response pattern had been advocated by some investigators (32, 36) to define critically ill patients with relative adrenal insufficiency. As will be emphasized subsequently, such a definition should be questioned and not be used to characterize adrenal dysfunction without considering the actual baseline or stimulated serum cortisol levels.

It became apparent many decades ago that patients with adrenal insufficiency may not survive a surgical procedure without being given glucocorticoid supplementation (13). It was conventional wisdom to use stress doses of hydrocortisone in patients with adrenal insufficiency during surgical procedures (13). A study by Udelsman *et al.* (15) conducted in monkeys that had adrenalectomies challenged the practice of giving large doses of glucocorticoids for minor or moderate surgical procedures. In that study, Udelsman *et al.* (15) examined the effects of different doses of glucocorticoid replacement on hemodynamic adaptation during surgical procedures (cholecystectomy) in adrenalectomized monkeys. Their study showed that physiological glucocorticoid replacement was necessary and sufficient to tolerate the surgical procedure (15). Furthermore, the study demonstrated

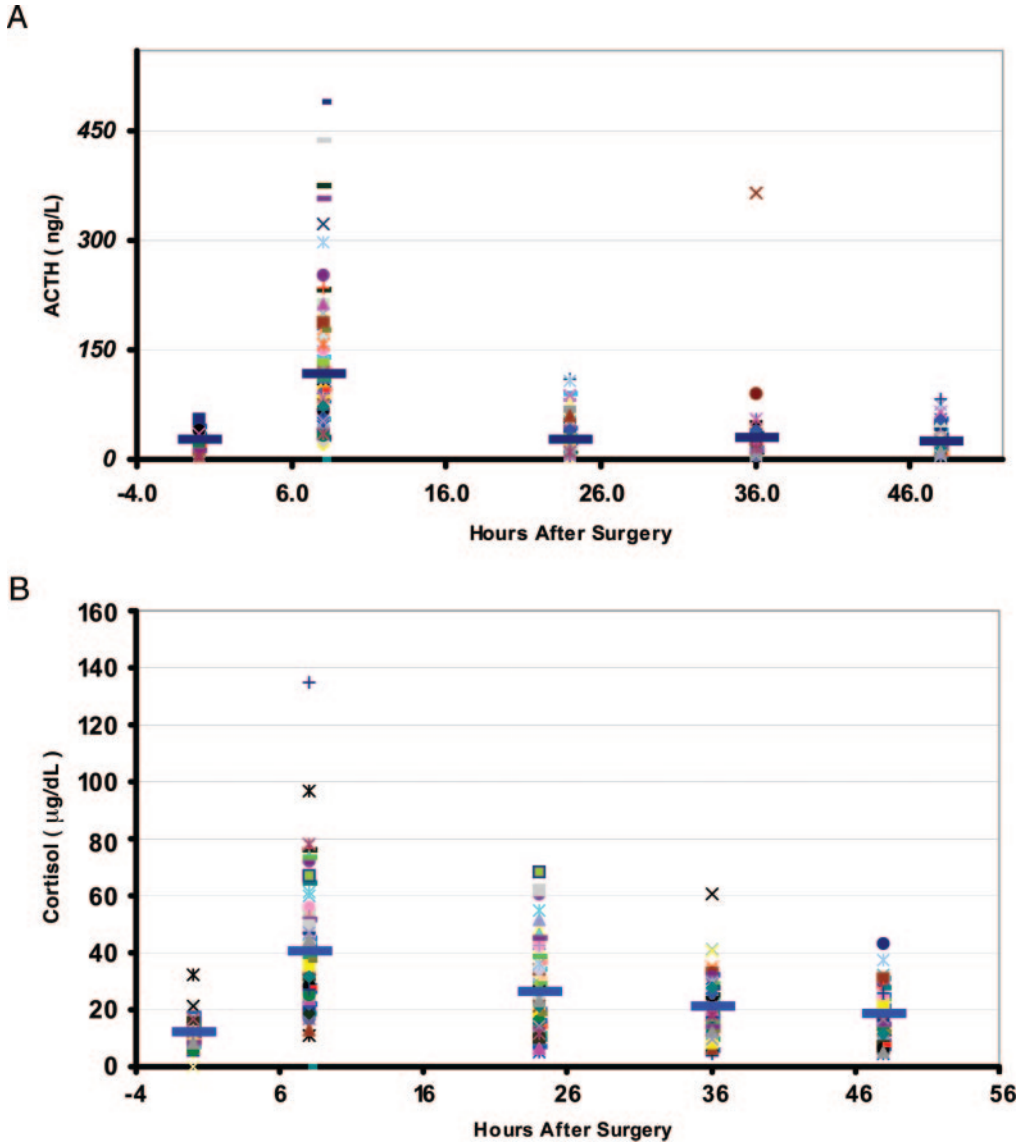


FIG. 2. Plasma ACTH levels in nanograms per liter (*top*) and serum total cortisol concentrations in micrograms per deciliter (*bottom*) measured before and during the first 48 h after pituitary surgery in patients who had normal pituitary adrenal function before and after adenomectomy. Patients with ACTH-secreting adenomas were excluded from this analysis. Each data point represents a measurement on a patient, whereas the *horizontal markers* represent the mean at each time point. The SD values for plasma ACTH levels at 0, 8, 24, 36, and 48 h were: 9, 70, 12, 28, and 9.9 ng/liter, respectively. The SD values for the serum total cortisol concentrations at the same time periods were: 3.8, 13, 10, 7.5, and 5.9 μg/dl, respectively. To convert serum cortisol levels from micrograms per deciliter to nanomoles per liter, multiply the value by 27.59. To convert plasma ACTH values from nanograms per liter to picomoles per liter, multiply by 0.2202.

that the hemodynamic and metabolic parameters as well as the postoperative survival in the animals given physiological replacement were similar to those noted in animals treated with supraphysiological doses of glucocorticoid (15). Since then there has been a shift in clinical practice in favor of giving lower doses of glucocorticoids according to the complexity and duration of the procedures (13). There is, however, no uniformly acceptable dose for each particular surgical procedure.

### *C. HPA function during spontaneous, uncontrolled critical illnesses*

Published data on the HPA function during critical illnesses include studies in patients with a variety of medical and surgical illnesses. Whereas some studies included heterogeneous groups of patients with several diagnoses (39–49), many others reported on more homogenous groups of patients such as those with septic shock (23–37), trauma (31), and others with major burns (38). One of the most important limitations and difficulties in reviewing such data are that they represent patients with different illnesses of variable duration and who have different nutritional support. Most of the published data detailing the HPA function during critical illness were obtained in patients with severe sepsis and septic shock (23–37). It is primarily in the latter groups of patients that studies have investigated the value of glucocorticoid administration in various forms and dosages on mortality. In reviewing published data on adrenal function during critical

illness, one will encounter an amazingly wide range of values for serum cortisol levels. Importantly, patients with severe sepsis and shock appear to be distinctly different from other critically ill subjects in that they have significant inflammation and predictably have a high morbidity and mortality. There are, however, obvious examples of patients with other illnesses (*e.g.* after CABG, pancreatitis, *etc.*) who are as critically ill as those in septic shock.

As will be discussed below, the definition of what constitutes normal adrenal response to critical illness continues to be debated. Consequently, published data have used a variety of biochemical criteria to define abnormalities in adrenal function during critical illness. These issues and limitations will be addressed in some detail in the following sections. As detailed in Tables 1 and 2, the incidence/prevalence of adrenal dysfunction (regardless of how it is defined) is much higher in patients with septic shock (40–65%) than in other ICU patients with other diagnoses (0–25%). The latter group includes data on patients who had CABG, those with ruptured abdominal aortic aneurysm, and others with a variety of other illnesses. The differences in prevalence/incidence of adrenal dysfunction, regardless of how it was defined, among different underlying conditions vary significantly and point to different pathophysiology. A very recent study by Ho *et al.* (37) showed that cortisol levels in patients with septic shock were distinctly different from those seen in others with sepsis only. Serum total and free cortisol concentrations in the former group of patients were higher than those in the latter group (37).

Some studies examined the prognostic value of measured serum baseline or Cosyntropin-stimulated increments in serum cortisol during critical illnesses (24, 25, 35, 36). Several investigators have noted that nonsurvivors of critical illnesses have higher baseline serum cortisol concentrations than those who survived their illness (35). The recent study by Ho *et al.* (37) showed the same findings when serum free cortisol concentrations were examined instead of total cortisol levels. Other studies examined the prognostic value of the incremental rise in serum cortisol after Cosyntropin stimulation during critical illnesses (24, 36). In introducing the concept of relative adrenal insufficiency, Rothwell *et al.* (24) stressed the prognostic value of the Cosyntropin-stimulated increment in serum cortisol concentrations. The authors reported that patients who had an inadequate increment in serum cortisol (<250 nmol/liter) after Cosyntropin stimulation were much more likely to die (13 of 13) than a similar group of septic patients (six of 19) who had an adequate response (>250 nmol/liter) to the same stimulus and despite the fact that the respective baseline serum cortisol levels in the two groups were similar (24).

Similarly, a study by Annane *et al.* (36) showed that a blunted response to Cosyntropin of less than 9 $\mu$g/dl (250 nmol/liter) was associated with a higher chance of not surviving the critical illness (septic shock). A very recent study by Arlt *et al.* (85) examined the prognostic value of measuring baseline and Cosyntropin-stimulated serum cortisol as well as adrenal androgen concentration in patients with septic shock (85). The latter study showed that among the patients in severe sepsis, those who did not survive had higher baseline total cortisol concentrations than those who did (85). The authors found that baseline DHEA and DHEA-S levels in survivors and nonsurvivors of septic shock were similar (85). Interestingly, however, the same study reported that nonsurvivors of septic shock had a higher cortisol to DHEA molar ratio than those who did survive (85). Thus, the latter ratio could be yet another prognostic marker in this setting (85).

## V. Modulating Factors and Limitations of Current Methods Assessing HPA Function during Critical Illness

A thorough and critical review of the HPA function in the three different forms of stresses would lead one to appreciate several important modulators that influence the quality of the data and their interpretation (Table 3). These variables introduce significant limitations to many of the published studies, particularly those with data on patients with protracted critical illnesses, in which data interpretation can be compromised. Whereas some of these factors have been addressed, others are overlooked. The following is a detailed discussion on eight of these confounding factors.

### *A. Serum total vs. free cortisol concentrations*

Transcortin has a low capacity and high affinity, whereas albumin has a high capacity and low affinity for binding cortisol (86–89). In humans and at physiological concentrations, transcortin can bind up to 25 $\mu$g/dl of the circulating cortisol. As transcortin becomes saturated, a larger proportion of circulating plasma-bound cortisol will be albumin bound. A steady decrease in the percent bound cortisol was noted when albumin concentrations in isolated albumin solutions or plasma were decreased to less than 2.0 gm/dl (87).

The current consensus is that the free rather than the pro-

**TABLE 1.** Serum total cortisol levels in patients with septic shock

| Ref. | No. of patients | Criteria used to define relative adrenal insufficiency | Patients with relative adrenal insufficiency (%) |
|---|---|---|---|
| Rothwell *et al.* (24) | 32 | Increment of < 250 nmol/liter | 19 |
| Bouachour *et al.* (25) | 22 | Increment of < 200 nmol/liter | 75 |
| Soni *et al.* (27) | 21 | Peak level of < 500 nmol/liter | 24 |
| Briegel *et al.* (28) | 20 | Increment of < 200 nmol/liter | 45 |
| Oppert *et al.* (30) | 22 | Baseline of < 1000 and increment of < 200 nmol/liter | 55 |
| Marik and Zaloga (34) | 59 | Baseline of < 690 nmol/liter | 61 |
| Annane *et al.* (36) | 189 | Increment of < 248 nmol/liter | 54 |
| Ho *et al.* (37) | 45 | Increment of < 248 nmol/liter | 33 |
| Moran *et al.* (46) | 68 | Baseline of < 500 nmol/liter | 32 |

One microgram per deciliter of cortisol equals 27.59 nmol/liter.

**TABLE 2.** Serum total cortisol levels in critically ill patients without septic shock

| Ref. | No. of patients | Primary diagnosis | Criteria used to define relative adrenal insufficiency total cortisol levels | Patients with relative adrenal insufficiency (%) |
|---|---|---|---|---|
| Sibbald *et al.* (23) | 26 | Sepsis | Blunted response | 19 |
| Aygen *et al.* (26) | 49 | Sepsis | Peak Cosyntropin-induced level of < 500 nmol/liter | 16 |
| Riordan *et al.* (29) | 96 | Meningococcal disease | Baseline level of < 500 nmol/liter | 3 |
| Ho *et al.* (37) | 19 | Sepsis | Post Cosyntropin increment of < 248 μg/dl | 0 |
| Jurney *et al.* (41) | 70 | Mixed ICU diagnoses | Peak Cosyntropin-induced level of < 500 nmol/liter | 1.4 |
| Span *et al.* (42) | 159 | Mixed ICU diagnoses | Increment value of < 200 and a peak Cosyntropin-induced level of < 500 nmol/liter | 1.2 |
| Beishuizen *et al.* (43) | 570 | Mixed ICU diagnoses | Cosyntropin-induced level of < 550 nmol/liter | 25 |
| Rivers *et al.* (44) | 104 | Vasopressor-dependent ICU patients | Baseline level of < 550 and Cosyntropin-induced level of increment of < 248 nmol/liter or a peak level of < 828 nmol/liter | 24 |
| Barquist and Kirton (48) | 1054 | Mixed ICU population | Baseline level of 413 and/or peak Cosyntropin-induced level of < 690 nmol/liter | 0.66 |
| Braam *et al.* (49) | 54 | Ruptured AAA | Peak Cosyntropin-induced level of < 550 nmol/liter | 2 |

One microgram per deciliter of cortisol equals 27.59 nmol/liter. AAA, Abdominal aortic aneurysm.

tein-bound fraction of cortisol is responsible for its physiological function (86–89). Because more than 90% of circulating cortisol in human serum is bound to proteins (transcortin and albumin), we postulated that alterations in binding proteins would affect measured serum cortisol levels (45) and thus the interpretation of tests assessing adrenal function. The importance of the fall in serum transcortin on measured serum cortisol concentrations was recently recognized in patients with sepsis (31), trauma (31), and others undergoing major surgery (90). In these reports, the authors (31, 90, 91) recommended the use of a calculated correction factor, termed the free cortisol index (defined as serum cortisol divided by transcortin serum concentrations), as a surrogate marker that better defines glucocorticoid secretion. The latter studies did not provide measurements of the actual serum free cortisol concentrations and did not take into account the impact of hypoalbuminemia that often accompanies low serum transcortin levels.

One of the mechanisms introduced to explain the decrease in serum transcortin concentration during critical illness is its cleavage by the elastase secreted by activated neutrophils at the site of inflammation (92). The latter process would result in delivery of free cortisol in target cells and, in this instance, at the site of inflammation (92). It is not known whether this process is modulated by the prevailing systemic concentration of free cortisol in the serum.

**TABLE 3.** Factors modulating measured serum total cortisol concentrations in critically ill patients

| Factor | Mechanism | Impact | Clinical examples |
|---|---|---|---|
| Drugs/medications | | | |
| Estrogens | Increased transcortin | Higher total cortisol; normal free cortisol | Estrogen, oral contraceptives, pregnancy, hepatitis |
| Ketoconazole | Decreased synthesis of cortisol | Lower serum cortisol; low free cortisol | Patients receiving the drug |
| Spironolactone | Interference in the assay depending on antibody specificity | Generally higher levels; variable influence, depending on assay specificity | Patients on the drug |
| Aminoglutathemide | Inhibit cortisol synthesis | Lower serum total and free cortisol | Patients on the drug, *e.g.* medical adrenalectomy for metastatic breast cancer |
| Etomidate | Decreased synthesis due to 11 β hydroxylase-inhibition | Lower serum cortisol levels; decreased responsiveness to Cosyntropin | Use of the drug |
| Assay(s) method | Different assay antibody specificity; heterophile antibody | Variable influence | Values measured in different laboratories; subjects with positive heteropile antibody |
| Illness type/severity | | | |
| Hepatitis/liver disease | Increased transcortin | Generally higher levels | Patients with hepatitis |
| Septic shock | Possible glucocorticoid resistance; significant inflammatory response | Increased levels despite symptoms suggestive of adrenal insufficiency | Patients with septic shock |
| Malnutrition | Lower transcortin, albumin | Relatively lower total but appropriate free cortisol | Patients with malnutrition |
| Nephrotic syndrome | Lower transcortin and/or albumin | Relatively lower total but normal free cortisol | Patients with nephrotic syndrome |
| Dilutional | Lower transcortin and albumin | Relatively lower total cortisol but normal free cortisol levels | Cardiopulmonary bypass, excessive iv fluids |
| Illness severity | Increased production | Generally proportionate to stress | Patients with septic shock |

In a study involving 66 critically ill patients, we noted that the patients have markedly increased glucocorticoid secretion that is indiscernible when only serum cortisol level is measured. Such patients had a 7- to 10-fold increase in serum free cortisol concentrations (45). Despite normal adrenal function, as determined by appropriately elevated baseline and Cosyntropin-stimulated serum free cortisol levels, approximately 40% of hypoproteinemic patients had subnormal Cosyntropin-stimulated serum total cortisol levels. The study suggested that caution should be exercised in interpreting baseline and Cosyntropin-stimulated serum total cortisol data in critically ill patients with hypoproteinemia. A very recent study conducted in patients with sepsis and others with septic shock showed similar findings, supporting the superiority of serum free cortisol over that of total cortisol in defining the HPA function (37). The authors of the latter study reported (37) that reasonable estimates of the prevailing serum free cortisol concentrations can be calculated using the method of Coolens *et al.* (89). Additional data, involving a larger number of patients, particularly those with hypoproteinemia, are needed before this method of calculating free cortisol can be confidently applied in critically ill patients.

### *B. Serum cortisol assays*

Commercially available assays for serum cortisol determine the total (free plus protein-bound fractions) hormone concentration. The specificity, sensitivity, coefficient of variation, and performance of these commercially available assays are not uniform because they show wide variations in immunoassay characteristics (93). It is possible that the variations in assay characteristics might be even more significant in critically ill subjects, especially those with septic shock. Some patients have heterophile antibodies in their sera that interfere in several immunoassay systems, including that of cortisol (94, 95). The prevalence of these heterophile antibodies is not known (94, 95). The most specific assay uses mass spectrometry but is not commonly available. It is evident from the degree of variation in assay results that different cortisol immunoassays may over- or underestimate the actual cortisol value.

### *C. Standard tests used in the assessment of HPA function during critical illnesses*

Several approaches to evaluate adrenal function in critically ill patients have been adopted by various investigators. Whereas some relied entirely on random serum total cortisol concentrations, a few used the low dose (1 $\mu$g), although most have used the standard dose (250 $\mu$g) Cosyntropin in defining normal adrenal function (Tables 1 and 2). There is, however, no consensus as to which, if any, of these approaches should be used as the criteria for normal function. Most have used baseline and/or Cosyntropin-stimulated serum cortisol data obtained in healthy subjects as the criteria to define normal adrenal function in the critically ill. Recent data, however, demonstrated one of the limitations of the latter approach (22, 45). In that respect, it was shown that critically ill subjects have a higher baseline as well as Cosyntropin-stimulated serum cortisol levels (22, 45). The reliance of total serum cortisol concentrations in such patients with a high likelihood for being hypoproteinemic introduces another significant limitation of these data (45).

Even with the above limitations, the available data are so variable that it would be difficult to achieve a consensus. Random serum total cortisol levels of anywhere from 15 and up to 34 $\mu$g/dl have been advocated as a criterion for normality by some investigators (Tables 1 and 2). Others who use Cosyntropin-stimulated levels have used either an increment above baseline (most use $>9$ $\mu$g/dl) and/or a peak response of 20–25 $\mu$g/dl (Tables 1 and 2). Thus, depending on which criterion was used, the incidence of adrenal dysfunction in critically ill subjects ranged from 0 to more than 60%, as shown in Tables 1 and 2. Recent and earlier data indicate the use of the Cosyntropin-stimulated increment in serum total cortisol (commonly taken as $>7$–9 $\mu$g/dl) as a diagnostic criterion in critically ill patients can be misleading because nearly 40% of critically ill patients who have no known adrenal disease and who recovered from their illness without glucocorticoid therapy would have been misdiagnosed (22) with relative adrenal insufficiency. It is evident that the Cosyntropin test is not necessarily the best approach in defining normal adrenal function unless primary adrenal insufficiency is the major consideration. The Cosyntropin test is an imperfect test in patients suspected of having central (hypothalamic or pituitary deficiency) glucocorticoid deficiency. Most patients with central adrenal insufficiency have partial rather than complete ACTH deficiency and might therefore have normal response to Cosyntropin (10, 96). It is important to note that measurements of Cosyntropin-stimulated serum cortisol levels in patients receiving dexamethasone are unreliable because even a short course of the latter glucocorticoid can alter the response.

The incremental rise in serum total cortisol levels has been used by some investigators to define adrenal dysfunction in critically ill subjects, particularly those with septic shock. The report by Rothwell *et al.* (24) depicted the Cosyntropin-induced increment as an important prognostic feature in patients with sepsis. The authors introduced the term relative adrenal insufficiency to describe the blunted response to Cosyntropin in these patients (24). Since then, many investigators adopted the latter definition and used that approach to explore potential benefit from glucocorticoid administration. Whereas the concept of relative adrenal insufficiency will be discussed in a subsequent section, it is reasonable to consider possible explanations for the blunted ($<250$ nmol/liter or 9 $\mu$g/dl) Cosyntropin-induced increment in serum cortisol levels.

It is important to emphasize that, in patients with normal levels of transcortin, cortisol binding to the latter binding protein is saturated at cortisol concentrations of 22–25 $\mu$g/dl (86–89). An increase in serum cortisol above that level (*e.g.* with Cosyntropin stimulation) would be mostly reflected by an increase in the albumin bound and free fractions of cortisol in the circulation. Current assays for serum cortisol determine the total serum level (transcortin bound, albumin bound, and free). It is therefore reasonable to suggest that a decrease in serum transcortin level, which is a characteristic feature of many critically ill subjects, especially those with septic shock, would result in an increase in the percent free cortisol as was recently demonstrated (37, 45). Thus, the low

or blunted Cosyntropin-induced increment in serum total cortisol in critically ill subjects could very well be a physiological reflection of reduced transcortin levels in critically ill subjects. Our own data on the Cosyntropin-induced increment in serum total cortisol concentrations are consistent with this explanation (Table 4). The percent of patients who had a Cosyntropin-induced increment in serum cortisol levels of less than 9 μg/dl was significantly lower ($P = 0.002$) among critically ill patients with near-normal serum albumin and transcortin concentrations than those with hypoproteinemia (one third *vs.* one half), despite the fact that both groups had similar free cortisol levels. Similarly, 17% of healthy volunteers had such a Cosyntropin-induced increment. In the setting of septic shock, available data suggest that a blunted (<250 nmol/liter) Cosyntropin-induced increment in serum cortisol is a poor prognostic feature associated with increased mortality (24, 36). It is not known whether this would be true for other forms of critical illnesses.

Alternative explanations for the blunted Cosyntropin-induced increment in serum cortisol should also be considered, particularly in patients whose baseline serum cortisol levels are not elevated. Could it represent possible adrenal insufficiency, at least in some patients? This would be likely in patients with normal or near normal binding proteins (transcortin and albumin). Our study (45) showed that 40% of hypoproteinemic critically ill subjects would have a Cosyntropin-stimulated (peak) serum cortisol of less than 18.5 μg/dl (~500 nmol/liter). In contrast, all of the critically ill with near-normal serum proteins had a peak Cosyntropin-stimulated serum cortisol level of more than 20 μg/dl (45). Importantly, the serum free cortisol levels in the latter two groups were similar. Thus, it would be safe to state that in critically ill subjects with an albumin of more than 2.5 gm/dl, the peak Cosyntropin-stimulated serum cortisol would be expected to be more than 20 μg/dl with a median value of 32 μg/dl. A Cosyntropin-stimulated serum cortisol of less than 20 μg/dl in this setting of critical illness (albumin > 2.5 gm/liter) would be highly indicative of adrenal insufficiency.

Only limited data are available on the use of low-dose (1 μg) Cosyntropin testing in critically ill patients (97–101). Whereas some studies noted similar findings between the two testing doses of Cosyntropin, others found that the standard dose provides better assessment and higher increments in serum total cortisol concentrations. At this point, most of the data in the literature have used the standard-dose Cosyntropin stimulation, and the available data on the low-dose test are limited and are not sufficient to make sound recommendations.

Other tests assessing the integrity of the entire HPA axis have been used in many instances in which evaluation of adrenal function was attempted. Such tests include the use of insulin-induced hypoglycemia, metyrapone testing, and determining the pituitary (ACTH) and adrenal (cortisol) responses to the administration of the hypothalamic hormone, CRH. The limited data available on the latter test (CRH) demonstrated enhanced responses but without any additional diagnostic accuracy (57). Although the insulin-induced hypoglycemia is considered the gold standard in the assessment of adrenal function, it is impractical and unsafe in the setting of critical illness. Similarly, metyrapone is not only hard to obtain, but the test is also very unsafe, and the data are difficult to interpret in the setting of critical illness. Hypotension is a potent stimulus for activation of the HPA axis as well as vasopressin release. In that respect, some investigators have looked at the serum total cortisol levels during hypotension as an assessment tool for these patients (34, 102).

In summary, there are limitations to all of the tests used to define adrenal function in critically ill patients. Despite these limitations, baseline and Cosyntropin-stimulated serum total (and preferably free) cortisol levels remain the most practical approaches. As will be discussed below, additional value is likely to be obtained by measuring the other ACTH-dependent steroids, namely DHEA and its sulfated ester, DHEA-S. Insufficient data are currently available to suggest the alternative use of the low dose (1 μg) test. Acknowledging and appreciating the limitations of the Cosyntropin testing are important in interpreting data in these patients.

**TABLE 4.** Baseline and Cosyntropin-stimulated serum free and total cortisol levels in healthy subjects and critically ill patients with hypoproteinemia (albumin ≤ 2.5 g/dl) and others with near-normal serum albumin levels (>2.5 g/dl)

| | Critically ill patients albumin ≤ 2.5 g/dl (n = 58) | Critically ill patients albumin > 2.5 g/dl (n = 59) | Healthy volunteers (n = 53) | *P* values | |
|---|---|---|---|---|---|
| | | | | Between patient groups | Compared with healthy volunteers |
| Baseline serum total cortisol, μg/dl | 14.8 ± 7.2 | 21.8 ± 10.2 | 8.1 ± 4.2 | <0.001 | <0.001; <0.001 |
| Range | 5.3–35.6 | 13.2–65 | 3.8–23.7 | | |
| Cosyntropin-stimulated serum total cortisol, μg/dl | 25.0 ± 9.9 | 36.5 ± 9.7 | 27.9 ± 5.9 | <0.001 | 0.11; <0.001 |
| Range | 10–50.5 | 22–65 | 18.1–43.7 | | |
| Baseline serum free cortisol, μg/dl | 4.76 ± 3.82 | 4.01 ± 3.04 | 0.69 ± 0.37 | 0.34 | <0.001; <0.001 |
| Range | 1.3–13.9 | 1.4–12.5 | 0.3–1.3 | | |
| Cosyntropin-stimulated serum free cortisol, μg/dl | 9.11 ± 5.91 | 9.21 ± 4.95 | 3.12 ± 1.23 | 0.55 | <0.001; <0.001 |
| Range | 3.8–29.4 | 3.1–25.6 | 1.8–6.7 | | |
| Free/total cortisol at baseline, % | 34.8 ± 31.0 | 18.3 ± 9.7 | 9.2 ± 3.9 | <0.001 | <0.001; <0.01 |
| After Cosyntropin | 38.3 ± 22.3 | 24.9 ± 12.9 | 11.5 ± 4.5 | 0.02 | <0.001; <0.001 |
| No. of subjects/total with Cosyntropin-stimulated increment in total cortisol of ≤9.0, μg/dl | 29/58 | 17/59 | 9/53 | 0.002 | <0.001; 0.02 |
| Transcortin, mg/liter | 23.5 ± 9.6 | 29.8 ± 12.9 | 35.2 ± 8.6 | 0.007 | <0.001 |

*D. Medications*

Many medications alter the baseline and/or the Cosyntropin-stimulated serum cortisol levels (Table 3). Such medications often influence binding proteins (*e.g.* the estrogen-induced increase in transcortin), directly interfere with glucocorticoid synthesis (*e.g.* ketoconazole, etomidate), or have direct inhibitory effects on CRH /ACTH secretion (*e.g.* oral, dermal, intraarticular, or inhaled glucocorticoids). Some drugs have direct antiglucocorticoid effects (*e.g.* RU486), whereas others have glucocorticoid-like activities and would therefore suppress the HPA axis just like glucocorticoids would. Examples of the latter class would include progestational agents such as medroxyprogesterone (short-acting and depo forms) and a similar agent, megestrol, used in the treatment of breast and endometrial cancers as well as in the management of anorexia. Such drugs have glucocorticoid-like activity sufficient enough to result in clinical features of Cushing's syndrome with prolonged therapy (103). Similarly, the use of such drugs before or during critical illness can alter the functional integrity of the HPA and greatly increase the likelihood for true adrenal insufficiency.

As shown in Table 3, etomidate is another drug that can influence adrenal function during critical illness. Etomidate is a carboxylated imidazole that is still used as an anesthetic agent to facilitate endotracheal intubation (104–107). The drug was shown to cause reversible inhibition of the 11-hydroxylase enzyme and result in decreased cortisol secretion (105). Initial reports showed that its prolonged use caused adrenal insufficiency with the associated increased morbidity and mortality (104). Subsequent reports indicated that when given as a single injection for induction of anesthesia or as an infusion to maintain that etomidate was associated with impaired HPA function (106, 107). Despite its known effects on the HPA function, some reports suggested that etomidate can still be used (108). Recent opinions in the critical care literature concluded that etomidate should be abandoned (109), whereas others suggested that, in light of its other properties, it can still be used as long as its effects on adrenal function are acknowledged and addressed (110). From an endocrine standpoint, it would be best to avoid the use of etomidate if possible. However, if under certain circumstances etomidate is needed for induction of anesthesia, then hydrocortisone therapy should be administered for 24–36 h.

*E. Type and severity of illness*

During the acute phase of a critical illness, serum cortisol levels are generally proportionate to the degree of stress (16). This was best demonstrated in patients with presumed normal adrenal function who had various surgical procedures of increasing complexity (16). In one study (31), serum cortisol levels after a major trauma were as elevated as those seen in patients with sepsis. Another study by Sam *et al.* (35) showed that septic patients not only have a wide range of serum cortisol levels but also that those levels do not correlate with the commonly used measure of illness severity, the score of the Acute Physiology, Age and Chronic Health Evaluation. However, the same study found that patients with the highest random total cortisol levels have the highest mortality rate (35).

A recent study examined the serum levels of macrophage-MIF in patients with sepsis and in others with trauma (60). The study demonstrated that serum total cortisol levels were similarly elevated in the two patient groups (60). In contrast, serum levels of macrophage-MIF were markedly higher in patients with sepsis, compared with those who had trauma (60). Higher levels of the same factor were also observed in the subgroup of patients who developed acute respiratory distress syndrome and in those who did not survive (60). As expected, patients with sepsis had much higher levels of serum markers of inflammation such as procalcitonin, C-reactive protein, and LPS-binding protein.

The presence or absence of glucocorticoid resistance during critical illnesses is an important factor influencing adrenal function in general and the effects of cortisol at the tissue and cellular levels. Currently there are no definitive data assessing the impact of glucocorticoid sensitivity in a variety of critical illnesses on adrenal glucocorticoid secretion. It is reasonable to suggest that patients who suffer from critical illnesses associated with glucocorticoid resistance would be expected to have higher glucocorticoid levels than patients with illnesses not associated with resistance.

A recent study investigated the reproducibility of two Cosyntropin tests (1 d apart) in critically ill patients (111). The authors found that, in the critically ill group of patients without sepsis, repeat Cosyntropin testing yielded similar and reproducible results (111). In contrast, there was no correlation between the two consecutive Cosyntropin tests in patients with septic shock such that five of eight subjects who were considered to have relative adrenal insufficiency (increment of $<9$ $\mu$g/dl) on the first test had normal responses on the following day (111). Similarly, six of 12 subjects who had normal responses ($>9$ $\mu$g/dl) had blunted responses to Cosyntropin the following day (111). Similar findings were previously reported by Bouachour *et al.* (112). The reason(s) for the discordance between the two consecutive Cosyntropin testing results in patients with septic shock are not clear. The findings raise concerns and questions about the validity of one-time testing in this group of patients. It is not known whether fluid administration to these patients during the first day of critical illness contributed to these alterations. Another confounding factor in these hypotensive patients is that they often have volume contraction that is severe enough to stimulate the release of arginine vasopressin, which enhances CRH effects on ACTH secretion by the pituitary. After iv fluids, plasma volume will no longer be as powerful of a stimulus for ACTH release.

*F. Chronicity/duration of the critical illnesses*

It is commonly believed that glucocorticoid secretion during critical illnesses is generally proportionate to the degree of stress (5, 16). Earlier studies suggested that the secretory activity of the adrenal glands is augmented during the early phase of a critical illness with subsequent diminution in glucocorticoid secretion as the illness progresses into a subacute or chronic phase. However, most of the latter studies demonstrating decreased adrenal glucocorticoid secretion

with advancing chronicity of critical illnesses were based on measurements of serum total cortisol levels. The latter measurements have serious limitations, especially during chronic illnesses in which malnutrition and hypoproteinemia are more common. This is supported by the findings that when serum free cortisol levels are measured, they continue to be elevated throughout the critical illness (45).

Similarly, plasma ACTH concentrations are reported to be high during the early phase of any critical illness (58). Such levels have been shown to be increased after major surgical procedures (Fig. 2) as well as experimental endotoxemia (77–81) and practically after most stressful events. However, over time, plasma ACTH levels decline gradually, even though serum cortisol (total and free) concentrations continue to be elevated (58). As discussed earlier, it is believed that the discordance between plasma ACTH and serum cortisol levels during prolonged critical illnesses raises the question of the presence of other factor(s) that are stimulating and regulating glucocorticoid secretion. Such factors include endothelin, ANF, arginine vasopressin, and other cytokines (58).

### *G. Effects of intravascular plasma volume/hemodilution*

Because cortisol circulates predominantly as a protein-bound steroid, its measured level is greatly influenced by the concentration of its binding proteins, transcortin, and albumin. It is well known that changes in intravascular fluid volume have a major impact on the concentration of many cells, and compounds present in the circulation, such as red blood cells, urea nitrogen, and plasma proteins, to name a few. The influence of the changes in the intravascular fluid volume on serum cortisol levels has been best illustrated in patients undergoing coronary artery open heart bypass surgery (113). In such patients, the hematocrit, albumin, and transcortin values decrease rapidly with the institution of extracorporeal circulation (113). Similarly, serum total cortisol (mostly bound) levels decrease proportionately, whereas the free cortisol concentrations remain elevated and unchanged (113). After the bypass is completed, serum total cortisol as well as transcortin concentrations increase rapidly (113).

Although the degree of acute hemodilution in patients during extracorporeal circulation is unique, it is reasonable to suggest that similar, albeit less impressive, effects occur in other instances during which hypotensive patients who are volume contracted are given large amounts of iv fluids for volume resuscitation. In a recent study by Le Roux *et al.* (90, 114), a significant decrease in serum levels of transcortin was noted in the postoperative period in patients undergoing elective surgery. The latter study showed that the decrease in serum transcortin levels, which was partly due to large amounts of fluids administered during surgery, led to a decrease in measured total serum cortisol concentrations that would have been mistakenly diagnosed as adrenal insufficiency (90). The authors reported that the latter mistake would be avoided by the use of a calculated free cortisol index, defined as the serum cortisol concentration divided by the serum transcortin levels (90). Similar conclusions were reached by other investigators studying patients with trauma and others with sepsis (31, 91). However, the latter studies did not address volume status as a contributing factor. It is likely that patients in the latter studies received large amounts of fluids because they were hypotensive and that they probably had dilutional decrease in serum albumin as well as transcortin concentrations (31). Thus, it is imperative to consider patients' volume status in the interpretation of serum cortisol concentrations. An additional confounding factor here is that volume contraction is a powerful stimulus for arginine vasopressin release, which can augment the effects of CRH on ACTH release. Fluid resuscitation can often suppress this stimulus for increased ACTH secretion and result in lower plasma levels. Similarly, fluid resuscitation will lead to lower serum protein concentrations, including that of transcortin and eventually lower serum total cortisol levels. It is important to point out that hemodilution will no longer be an issue when serum free rather than total cortisol concentrations are used to assess HPA function.

### *H. Variations among individuals*

Published studies involving evaluation of adrenal function in critically ill subjects have consistently demonstrated that there was a wide range in measured random or baseline serum cortisol concentrations. This would be true even if one looks at patients with one specific diagnosis (*e.g.* sepsis, septic shock) in any given medical center. Similar observations can be made in patients experiencing a more controlled form of stresses (*e.g.* after a specific surgical procedure). The Cortrosyn-stimulated serum cortisol levels are also very variable. The latter variability represents individual differences among subjects, different illnesses, and perhaps differences in assay methods. The wide variations in random or stimulated values limit our ability to determine or set normal ranges or appropriate levels for a given specific stress. It is not clear whether the presence of mutations in the TL receptors (65, 66), described earlier, could contribute to the reported individual variations in responding to critical illness. Similarly, the reported polymorphism in glucocorticoid receptors could also contribute to the reported variations among individuals (115, 116). It is not known whether variation in ACTH or CRH receptor activities contributes to the observed individual differences among patients. Similarly, another area that has not been investigated is the variability of the 11$\beta$-hydroxysteroid dehydrogenase enzyme.

## VI. Alternative Approaches in the Assessment of Adrenal Function

In view of the significant limitations noted above, alternative approaches were sought in the assessment of HPA function. These approaches addressed some but not all of the listed limitations and include measurements of serum free cortisol and salivary cortisol concentrations.

### *A. Serum free cortisol level as a marker of glucocorticoid secretion*

As discussed earlier, measurements of serum free cortisol concentrations appear to be the most appropriate approach for assessing glucocorticoid secretion in the critically ill. The

advantages of determining serum free cortisol over total cortisol concentrations in the assessment of adrenal function were recently demonstrated (37, 45, 117). A very recent study conducted on critically ill patients at our institution (45) demonstrated that critically ill patients have markedly increased serum free cortisol concentrations (7- to 10-fold). The latter impressive increase in glucocorticoid secretion was not discernible when only the total serum cortisol concentration was measured. Patients with low plasma proteins (albumin $< 2.5$ gm/dl) best demonstrated the discordance between the total and free hormone concentrations. In fact, even though they had normally stimulated adrenal function, nearly 40% of critically ill patients with low serum albumin had low serum total cortisol levels that would be interpreted to be consistent with adrenal insufficiency. Serum free cortisol levels were consistently increased in all of these patients.

As an alternative to measuring the free cortisol concentrations, investigators introduced two different approaches that take into account the changes in serum transcortin concentrations in many critically ill subjects. One approach was the use of a calculated free cortisol index, defined as the ratio of serum cortisol over that of serum transcortin concentrations (31, 90, 91, 114). Another approach was to use a formula introduced by Coolens *et al.* (89) that characterized the relation between total, bound, and free cortisol concentrations. A recent study used the formula to calculate serum free cortisol concentrations in a group of patients with sepsis and others with septic shock (37) and compared the calculated values with those measured using an ultrafiltration method. Surprisingly, there was a good correlation between the measured and calculated serum cortisol levels in these patients, even though some were hypoalbuminemic (37). Additional data are needed to confirm these findings before the latter method can be used.

It is clear from the above discussion that measurements of serum free cortisol represent the most ideal approach in assessing glucocorticoid secretion, especially in hypoproteinemic, critically ill subjects (117). Current assays for determining serum free cortisol concentrations are difficult, time consuming, and labor intensive. At this time, the measurement can be performed at specialty laboratories, and the results are not immediately available to clinicians. It is likely that rapid assays for measurements of serum free cortisol levels will become available in the near future, just as serum free $T_4$ assays became widely available for clinical use more than a decade ago. Until serum free cortisol assays become available for routine clinical care, alternative approaches should be explored in the assessment of glucocorticoid secretion. Such approaches include measurements of salivary cortisol concentrations and determination of other ACTH-dependent adrenal steroids such as DHEA and DHEA-S.

### *B. Salivary cortisol concentration as a marker of glucocorticoid secretion*

Several research groups have investigated the use of salivary cortisol concentration as a surrogate marker for serum free cortisol levels. Studies over the past 15–20 yr have demonstrated that cortisol concentrations in the saliva are in equilibrium with, and highly correlate with, the free or unbound plasma cortisol level (118, 119). Salivary cortisol measurements are frequently used in evaluating states of glucocorticoid excess (Cushing's syndrome). An increase in plasma free cortisol level is reflected by a change in salivary cortisol concentration within a few minutes. Thus, obtaining a salivary sample over a 2- to 3-min period accurately reflects the concentration of plasma free cortisol at that time. Although this assay is currently performed primarily at reference laboratories, it is relatively easy to do and can be performed by most hospital laboratories.

Because the salivary cortisol concentrations correlate with serum free cortisol levels, they would be superior to simple measurements of serum total cortisol levels, particularly in patients who have low binding proteins. In a recent study that was just completed (120), we examined the value of measuring salivary cortisol concentrations in 53 critically ill patients hospitalized in the ICU. Baseline and Cortrosyn-stimulated serum (total and free) and salivary cortisol concentrations were measured in patients and a matched group of healthy subjects. Salivary cortisol concentrations were elevated in critically ill patients, paralleling the noted rise in serum free hormone levels. Similarly elevated salivary cortisol concentrations were noted in hypoproteinemic patients and others with near-normal protein levels, and both correlated with measured free cortisol levels. It was concluded that salivary cortisol measurements are simple to obtain, easy to measure in most laboratories, and provide a reliable and practical measure of the serum free cortisol concentration in a timely manner. In a recent report involving a relatively small number of patients, other investigators (121) reported preliminary data confirming the value of salivary cortisol determinations in the assessment of glucocorticoid secretion in critically ill subjects. One limiting factor in determining salivary cortisol concentrations is the ability to obtain saliva from some patients, particularly those who are intubated. In our study, adequate saliva samples could not be obtained in three of the 56 patients.

It is important to emphasize that the data on salivary cortisol concentrations in critically ill patients are limited at this time. It is an important surrogate of the free cortisol in the circulation, and its measurement can provide important data until serum free cortisol assays become available for routine clinical use.

### *C. Measurements of other ACTH-dependent adrenal steroids: DHEA and DHEA-S*

Because DHEA is an ACTH-dependent steroid, we recently investigated in a prospective manner the use of serum DHEA-S measurement as a marker for the integrity of adrenal function and in establishing the diagnosis of adrenal insufficiency in noncritically ill subjects (96). Our study clearly demonstrated that a normal age- and gender-adjusted serum DHEA-S level makes the diagnosis of adrenal insufficiency untenable (96). Only limited data are available on DHEA-S levels in critically ill patients. Until recently, published reports involving a relatively small number of patients showed that serum DHEA levels tended to be elevated, whereas those of DHEA-S were more variable (122–124). However, a recent study examined baseline and Cosyn-

tropin-stimulated adrenal androgen levels in a relatively large number of patients with severe sepsis (85). The authors of the study found that baseline serum levels of DHEA were elevated and did not increase further with Cosyntropin stimulation in these patients (85). In contrast and despite elevated serum DHEA levels, the study (85) found that the concentrations of DHEA-S in the serum of these patients were low when compared with younger healthy subjects. It would be important to emphasize that serum DHEA-S levels are not only gender and age dependent but also influenced by preexisting illnesses that patients may have had before they became septic. Another limitation is that most critically ill patients studied were hypotensive and were likely receiving dopamine, which is known to lower serum prolactin as well as DHEA-S levels (124).

The findings of variable serum DHEA-S levels in critically ill subjects should be contrasted with the somewhat consistent elevation of the serum DHEA concentrations. Thus, measurement of DHEA-S levels does not often adequately reflect adrenal production of DHEA. Even though it would be tempting to postulate that the latter discrepancy between serum DHEA and DHEA-S levels suggests impairment of the sulfotransferase enzyme in patients with severe sepsis, the data are too limited to justify such a conclusion. Currently there are no definitive data characterizing adrenal androgen secretion in different groups of critically ill subjects, other than the recently reported data in patients with septic shock (85). Such data would be helpful in defining the pattern of adrenal androgen production as a surrogate for cortisol during critical illness.

As discussed earlier, experimental endotoxemia in humans is a well-characterized model of acute inflammation (77–81). It is associated with activation of the HPA axis (77–81) as demonstrated by the rise in plasma ACTH and cortisol levels within 2 h of LPS injection. The same approach was recently used to investigate changes in serum adrenal androgen levels during the stress of endotoxemia (80). In the latter study, the authors demonstrated that serum DHEA levels increase after LPS injection (80). Interestingly, the same study demonstrated that pretreatment of the normal subjects with ibuprofen blunted the endotoxin-induced rise in serum DHEA but not cortisol levels (80). The latter finding suggested different regulation of DHEA and cortisol during acute inflammatory reactions or an effect on 17, 20-desmolase activity by ibuprofen.

## VII. How Do We Define Normal Adrenal Function during Critical Illnesses?

It is important to emphasize that other factors in addition to marked stress and variation in binding proteins can potentially influence the normal serum cortisol or free cortisol concentrations during critical illnesses. Such factors include possible tissue-specific resistance to corticosteroids, which can vary according to patients' illnesses (69–73). Recent data suggest that Cosyntropin-stimulated serum cortisol and free cortisol concentrations are higher in critically ill patients, compared with those observed in healthy volunteers (22, 45). Accordingly, it is important to define normal on the basis of data from critically ill patients, rather than on criteria generated from healthy, ambulatory subjects. Many believe a serum cortisol threshold level of 15 $\mu$g/dl best identifies critically ill patients with adrenal insufficiency (17). Whereas this might be true in patients with normal binding proteins, the threshold might be lower in those with severe hypoproteinemia, in which case measurements of serum free cortisol levels would be most valuable.

Despite older (31, 90, 91, 114) and newer (37) data providing calculated and measured serum cortisol concentrations in critically ill subjects, the expected normal serum free cortisol is still difficult to define. The primary illness is one of the most important factors determining the level. Given these limitations, it would be premature to attempt to define normal serum free cortisol levels during the various critical illnesses. Table 4 shows our own data on more than 100 critically ill subjects and more than 50 healthy volunteers. The data for critically ill patients with near-normal serum albumin levels are contrasted with those obtained from hypoproteinemic subjects. The data were used to generate some guidelines on the expected serum free cortisol values during critical illness.

We reasoned that in highly stressed, critically ill patients, baseline serum free cortisol concentrations would be expected to be at least near or even exceed Cosyntropin-stimulated levels as determined in normal (Table 4), unstressed subjects ($\geq$1.8 $\mu$g/dl). We therefore recommend that a random serum free cortisol level of 1.8 $\mu$g/dl be considered as a threshold that identifies patients at risk for adrenal insufficiency during critical illness. Further testing, such as Cosyntropin stimulation, may be necessary in critically ill patients with lower levels. Because Cosyntropin-stimulated serum free cortisol concentrations in our critically ill patients was 3.1 $\mu$g/dl or more (Table 4) (45), we recommend that that level be used to define normal Cosyntropin-stimulated serum free cortisol in critically ill patients until additional data, involving larger numbers of patients, become available. Applying these criteria on more than 100 critically ill subjects, the actually measured random and Cosyntropin-stimulated serum free cortisol would fall within the outlined ranges in more than 95% of patients.

Until serum free cortisol measurements become widely available, other alternative approaches used by investigators include the use of a calculated free cortisol index (31, 90, 91, 114) and more recently calculating free cortisol concentrations using the Coolens method (37) seem reasonable. Both approaches require measurements of transcortin levels, which are not yet readily available in most laboratories. Alternatively, measurements of salivary cortisol concentrations and other ACTH-dependent steroids (DHEA, DHEA-S) represent another, yet untested, approach.

From a practical standpoint and until serum free cortisol assays become available, total cortisol levels can be used as an approximation of the circulating free hormone. In doing so, it would be important to consider all of the previously discussed limitations as well. In that respect, the concentration of plasma protein can serve as a rough guide as to whether total cortisol levels are likely to be reliable. An albumin concentration of 2.5 gm/dl or less appears to signify marked reduction in binding proteins that would influence measured total cortisol (45). In our study, the discordance

between total and free serum cortisol levels was best appreciated in patients with a serum albumin of less than 2.5 gm/dl (45). In this group of patients (albumin < 2.5 gm/dl) the percent free cortisol at baseline was 19–62% with a mean of 31%. Using conservative estimates, one can suggest that when serum albumin levels are less than 2.5 gm/dl, a baseline serum total cortisol of 9.5 μg/dl or more would be equivalent to the recommended minimum free cortisol of 1.8 μg/dl. Similar estimates in the Cosyntropin-stimulated levels (percent free 20–67%) indicate that a total cortisol of 15.5 μg/dl or more would be similar to the 3.1 μg/dl of the free hormone. As stated earlier, these are rough estimates that have not been validated yet.

Despite a large increase in glucocorticoid secretion, a subset of critically ill patients could remain hypotensive and manifest symptoms and signs suggestive of relative adrenal insufficiency, in which elevated cortisol levels are insufficient to control the inflammatory response (17, 32). Alternatively, tissue-specific resistance to corticosteroids has also been postulated, at least in some of these patients. Obviously, clinical judgment must be exercised in administering glucocorticoids to critically ill patients before or even after serum total cortisol or free cortisol levels become available in select patients with apparently normal values. This would be clinically important in patients with hypotension unresponsive to volume or pressor therapy. Such patients would include those with septic shock who might benefit from exogenous glucocorticoids as was recently demonstrated (32). In such patients, it is not clear whether the benefit from glucocorticoid therapy is related to treating the associated severe inflammatory process with glucocorticoids or there is an element of glucocorticoid resistance. It is also important for the clinician to assess critically ill patients' potential risk for adrenal insufficiency at all times and interpret biochemical data in that context. Thus, instead of long-term therapy, glucocorticoid administration should be limited for only a few days in selected patients.

## VIII. The Concept of Relative Adrenal Insufficiency

The concept of relative adrenal insufficiency was recently introduced to describe a group of patients who had no risk factors or prior evidence for adrenal dysfunction and who, during a critical illness, had serum total cortisol levels that were judged to be inadequate for the severity of their illness (17, 24, 32). Importantly, most of these patients were likely to be hypoproteinemic and had low transcortin levels; two factors that would limit the value of total cortisol measurements. The concept is poorly conceived and there are inadequate and conflicting criteria to define this controversial entity. One of the initial reports on the concept of relative adrenal insufficiency was that of Rothwell *et al.* in 1991 (24). In that report, the authors found that septic patients who had an inadequate Cosyntropin-stimulated increment (<250 nmol/liter) had a higher chance of death (13 of 13), compared with another group of patients with similar illness (six of 19) who had an adequate (>250 nmol/liter) response to ACTH stimulation (24). The authors concluded that the Cosyntropin-induced incremental rise in serum total cortisol was an important prognostic feature in these patients (24).

Rothwell *et al.* (24) did not examine the role of glucocorticoid therapy in their patients. Since then, several reports appeared in the literature in which the influence of glucocorticoid administration was examined. One of these initial reports described two critically ill, hypotensive subjects who despite vasopressor therapy had subnormal responses to Cosyntropin (125). The two patients responded to glucocorticoid therapy and subsequently recovered from their illnesses and were demonstrated to have normal pituitary adrenal function (125). A close review of the clinical data in those two subjects show that both had received etomidate, an anesthetic drug now known to inhibit 11β-hydroxylase and consequently cause cortisol deficiency (104–106). After that publication, several reports described the entity of relative adrenal insufficiency, primarily in patients with septic shock (17, 23–37), and the influence of hydrocortisone therapy was investigated in some. The prevalence of this entity among critically ill patients varies, depending on the patients' characteristics, types of illnesses, and the biochemical definition used in making the diagnosis. As shown in Tables 1 and 2, the prevalence ranged from 20 to 75% in patients with sepsis/septic shock and from 0 to more than 70% in other critically ill patients. A recent editorial in this journal raised concern about the concept as well as the definition of relative adrenal insufficiency (126).

Although there were no uniform criteria to define this controversial entity, most publications adopted the definitions used by the report that included the largest number of patients with septic shock (32). In that study, Annane *et al.* (32) examined 299 patients with septic shock and used the serum cortisol response to the standard Cosyntropin test (250 μg, iv) to characterize patients as responders (those who had an increment of >9 μg/dl in serum cortisol) and nonresponders (those who had an increment of <9 μg/dl in their serum cortisol levels), regardless of their baseline values. Although the study had a major impact in the field, it had serious limitations that became apparent a few months after its publication (127).

The most serious limitation is that 72 of the patients enrolled in that study had received etomidate within 8 h of testing (127). It has been well established that etomidate, an anesthetic, is an agent that is known to block adrenal glucocorticoid synthesis (104–106). Undoubtedly, some if not most of the patients who received this agent had impaired adrenal function. Furthermore, published data by other groups in subjects receiving etomidate demonstrated that the Cosyntropin-induced increment in serum cortisol was blunted, even 24 h after the anesthetic agent was administered (104–106). It is important to point out that of the 72 patients in the Annane study who received etomidate, 68 were, as one would predict, in the so-called nonresponders group. It is in this group that hydrocortisone showed some benefit. It is reasonable to expect that such patients could benefit from glucocorticoids because they had true adrenal insufficiency. The authors did not publish revised data excluding such patients from analysis (127). In a subsequent correspondence (128), the authors stated that etomidate-treated patients benefited from hydrocortisone and did not indicate whether those who did not receive etomidate did or did not benefit from hydrocortisone.

## IX. Glucocorticoid Therapy during Critical Illness

Most of the available published data on the use of various doses of glucocorticoids in critically ill patients have been in subjects with severe sepsis/septic shock syndrome (32, 129–132) and those with respiratory distress syndrome (133–136), as well as patients with head injuries (137). The rationale for the use of glucocorticoids in this setting of severe systemic inflammatory response has been the potent antiinflammatory properties of these drugs (5). Such effects include inhibition of cytokine production and prevention of the migration of circulating inflammatory cells into tissues (5, 54). However, other potential benefits from glucocorticoids include their effects on the cardiovascular system in which they enhance vasoactive tone and catecholamine responsiveness (18, 138–142). Decreased responsiveness to catecholamines is a common feature of septic shock, and it is postulated to be due to desensitization or down-regulation of catecholamine receptors (138–142). In this respect, the benefits from glucocorticoids are postulated to be due to their ability to prevent desensitization of the $\beta$-adrenergic receptor and to up-regulation of the down-regulated receptors (138–142). A study by Hinshaw *et al.* (138) provided supportive evidence for this mechanism because it demonstrated that adrenalectomized dogs with *Escherichia coli*-induced septic shock had impaired responsiveness to catecholamines that was restored with glucocorticoid therapy.

A very recent prospective, placebo-controlled study examined the influence of hydrocortisone therapy (50 mg iv every 6 h) on ventilator weaning in 70 critically ill, intubated patients with relative adrenal insufficiency (143). In that article, the authors defined relative adrenal insufficiency as a baseline serum total cortisol of less than 25 $\mu$g/dl associated with a Cosyntropin-stimulated increment of less than 9 $\mu$g/dl (140). The authors found that that hydrocortisone therapy to these patients resulted in improvement in the rate of successful weaning (143). The authors also found that the rate of successful ventilator weaning was higher ($P = 0.035$) in patients with adequate adrenal function (20 of 23) and those with adrenal insufficiency given hydrocortisone (32 of 35) than in those given placebo (24 of 35). Importantly, however, hydrocortisone therapy did not influence hospital stay or hospital mortality (143). The mechanism(s) involved in the reported improvement in ventilator weaning remain unknown (143). It is important to emphasize the fact that even the authors of the report acknowledged that there was no physiological explanation for their findings (143). Additional studies are needed to confirm this finding and, once confirmed, to examine mechanisms of potential benefit from hydrocortisone on ventilator weaning.

Several animal models of sepsis demonstrated beneficial effects of glucocorticoid therapy (138). However, clinical trials of glucocorticoid therapy in patients with septic shock have yielded conflicting results. Earlier clinical trials used pharmacological doses of glucocorticoids and were demonstrated to be, in metaanalysis, not only ineffective but also potentially harmful (130, 132). In recent years lower doses of glucocorticoids have been used in patients with septic shock (32, 131). Although such doses were certainly supraphysiological, they are incorrectly described as low dose. The study published by Annane *et al.* (32) included the largest number of patients. In that study of 299 patients with septic shock, 200 mg iv hydrocortisone (50 mg every 6 h) along with 0.1 mg oral fludrocortisone *vs.* placebo were given for 7 d (32). The authors divided their patients into responders (increment of $>9$ $\mu$g/dl in serum total cortisol) *vs.* nonresponders (increment of $<9$ $\mu$g/dl in serum total cortisol) in response to Cosyntropin stimulation tests (32). The authors noted that the benefit from administered steroid therapy was limited to patients who were labeled as nonresponders (*i.e.* have a $<9$ $\mu$g/dl Cosyntropin-induced increment in serum total cortisol levels). In this study, nonresponders greatly outnumbered responders, 229 to 70, limiting the ability to determine whether steroid therapy had any beneficial or adverse effects in the so-called responders. The study found that the time to withdrawal of vasopressor support was shorter in nonresponders who received steroids than in those who received placebo (32). The study also found that the median time until death was longer in the nonresponders receiving steroids, compared with those receiving placebo (32).

As outlined earlier, the latter study had significant limitations. Despite these limitations, the study had a major impact in the field. A subsequent major review on adrenal function in critical illness adopted the recommendations of that study and used their approach in defining adrenal dysfunction in other critically ill subjects (17). Relying heavily on the findings of the later study, a metaanalysis of similarly published human investigations was recently published (131). The metaanalysis in fact recommended that all patients with vasopressor-dependent septic shock should be administered low-dose glucocorticoids, regardless of their response pattern to Cosyntropin stimulation (131). An editorial published alongside the latter metaanalysis raised some concerns about its conclusions and recommendations (144).

It is worth emphasizing that in most of the studies in which glucocorticoids were administered, pretreatment serum total cortisol levels were often elevated (32). How would glucocorticoid therapy benefit septic patients whose serum cortisol levels are high, normal, or clearly elevated? The presence of disease-induced (severe sepsis) glucocorticoid resistance in these patients could explain potential benefit from steroid therapy, at least in some patients. Furthermore, it is hard to reconcile the difference between the recently reported benefit from glucocorticoid therapy in patients with septic shock (32, 131) and the earlier negative experience with such treatment when given in larger doses (130). It is important to emphasize that earlier studies used much higher doses of glucocorticoids and included more reported adverse events that might have counteracted some of the potential benefit. The pattern of response to glucocorticoids in critically ill patients given these agents is characteristically slow, occurring over several days rather than a few hours, as expected in patients with true uncomplicated adrenal insufficiency. In fact, the data published by Annane *et al.* (32) showed that glucocorticoid therapy decreased the median time for withdrawal of vasopressors from 10 to 7 d. This would suggest that the potential benefit from glucocorticoids is more likely related to their ability to treat the inflammatory disease associated with sepsis.

A study is being conducted throughout Europe that attempts to address the same question but avoids the limitations of earlier studies. The so-called CORTICUS study involves nearly 800 patients with septic shock and will test whether glucocorticoids have beneficial or adverse effects in either the responders or the nonresponders to Cosyntropin, as was described in the study of Annane *et al.* (32). Analyzing such an important study is necessary to determine whether glucocorticoids have any advantage and in which patients with septic shock they should be administered. Until such data are available, clinicians should exercise clinical judgment in administering glucocorticoids to patients with septic shock or those who have any other critical illness.

## XI. Serum Cortisol Concentrations during Hydrocortisone Therapy

It is important to emphasize that the serum total cortisol concentrations achieved by using nearly 200 mg hydrocortisone per day through a constant iv infusion are quite high, reaching more than 70–100 $\mu$g/dl, a large percentage of which is in the free or unbound form (30, 33). This would be equivalent to a serum free cortisol concentration of 20–30 $\mu$g/dl in patients with normal transcortin and albumin levels. These values would be even higher in patients with hypoproteinemia. Such values should be compared with those achieved in critically ill patients with presumed normal adrenal function in whom the mean serum free cortisol would range from 3 to 5 $\mu$g/dl (37, 45). The levels achieved after iv boluses of hydrocortisone are even more cause for concern. An example of the degree of elevation in serum total cortisol concentrations in subjects given repeated injections of 50 mg of hydrocortisone is shown in Fig. 3. In this example, patients with documented central adrenal insufficiency were given iv hydrocortisone at a dose of 50 mg every 6 h for intercurrent serious illness. It is important to point out that with frequent measurements after the iv dose, one can best appreciate the degree of elevation achieved with this regimen. Such levels (total and free) are obviously much higher than those noted in any group of critically ill patients and should call into question the practice of using such high doses that are incorrectly referred to as low dose.

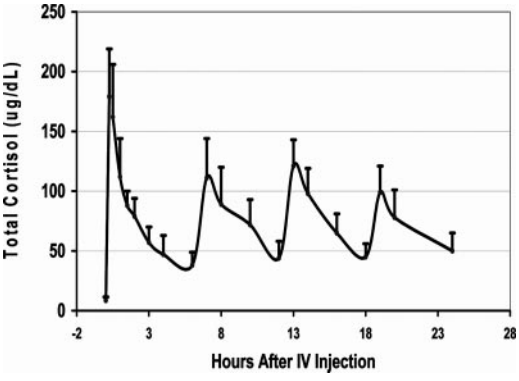


FIG. 3. Mean (± SD) of serum total cortisol concentrations in five patients with known adrenal insufficiency who developed sepsis and were given higher doses of hydrocortisone (50 mg iv bolus every 6 h) during their intercurrent illness. The first dose of hydrocortisone was given at time 0. Note that serum cortisol levels are higher when measured more frequently during the first 2 h of hydrocortisone administration. Also note that the nadir serum cortisol level 6 h after each dose was still high, near 40–50 $\mu$g/dl. To convert serum cortisol levels from micrograms per deciliter to nanomoles per liter, multiply the value by 27.59.

A major concern should therefore be raised about the indiscriminate use of hydrocortisone in the critically ill. Many of the known adverse effects of this steroid are serious and are often overlooked. These include hyperglycemia, hypokalemia, myopathy, and other neurotoxicities as well as immune suppression, especially when used for prolonged periods.

## XII. Patients at Risk for Adrenal Insufficiency

Adrenal insufficiency can be difficult to diagnose in critically ill patients unless clues from patients' prior clinical history are considered in that context. Such clinical features include prior history of unexplained fatigue, arthralgias, and the intake of medications that are known to suppress the HPA axis. Such medications include any form of oral, parenteral, inhaled, and large amounts or dermal or intraarticular glucocorticoid administration. Other drugs with potent glucocorticoid activity include progestational agents such as megestrol, which is commonly used as an anticancer therapy and in some instances to treat anorexia in patients with debilitating chronic illnesses such as cancer. Other instances include the use of drugs known to have antiglucocorticoid properties such as mifepristone (RU486) and others that can potentially inhibit glucocorticoid secretion such as antifungal agents (*e.g.* ketoconazole) and the anesthetic agent etomidate. It is important to raise similar concerns in patients with medical illnesses that are more likely associated with adrenal insufficiency such as those with known hypothalamic-pituitary disease (tumors, central nervous system irradiation, sarcoidosis), those with HIV, and others with multiple autoimmune illnesses (primary hypothyroidism, Grave's disease, type 1 diabetes mellitus, vitiligo, autoimmune arthritis, premature gray hair, pernicious anemia). In evaluating such patients for the risk of adrenal insufficiency, one can look for hyperpigmentation, clinical features of combined pituitary hormone deficiencies (hypothyroidism, hypogonadism), and features suggesting loss of adrenal androgen production such as loss of axillary and pubic body hair in women. Other biochemical features to consider include eosinophilia, hypoglycemia, and hyponatremia, even though the interpretation of such clinical data is often difficult in the critically ill patient.

## XIII. Summary and Conclusions

Evaluation of adrenal function during critical illnesses is difficult because there are many controversies and a larger number of confounding factors. In some centers, critically ill, hypotensive patients are treated with glucocorticoids routinely without any input from endocrinologists to evaluate adrenal function. In many other centers, however, endocrinologists are consulted to evaluate adrenal function in these patients. Ideally, attempts should be made to identify patients at risk for adrenal impairment. In interpreting serum total cortisol levels, one should consider the limitations of

these measurements when the binding proteins (transcortin and albumin) are increased or decreased.

Testing adrenal function in the setting of critical illness currently relies on measurements of random and Cosyntropin-stimulated serum total cortisol levels. When available, serum free cortisol or salivary cortisol can provide more conclusive answers. Plasma aldosterone and renin are valuable adjuncts when primary adrenal disease is suspected. Insufficient data are currently available on the value of measuring adrenal androgen secretion in this setting. Alternative tests for the adequacy of HPA function (*e.g.* insulin hypoglycemia, Metyrapone) are unsuitable in the setting of critical illness.

In the absence of specific guidelines on the expected serum cortisol concentrations during each type of critical illness, it would be hard to recommend a specific level as a cutoff value. Critically ill patients who have normal or near normal binding proteins generally have random serum total cortisol levels that are greater than 15 $\mu$g/dl and Cosyntropin-stimulated values of 30 $\mu$g/dl or more. However, many with hypoproteinemia might have lower levels, proportionate to the drop in plasma binding proteins. The respective values in serum free cortisol concentrations are 3 and 8 $\mu$g/dl. Patients with severe sepsis and/or septic shock generally have higher cortisol concentrations, even though most are hypotensive, hypoproteinemic, and at times unresponsive to vasopressors. It is in the latter setting that glucocorticoid resistance might be a factor and in which corticosteroids could perhaps be beneficial. Alternatively and in the absence of data demonstrating glucocorticoid resistance, such patients might have overwhelming severe illness. It is therefore important to emphasize that clinical judgment should always be exercised in deciding whether glucocorticoids should be used, irrespective of serum cortisol (total or free) levels. This would be particularly true in septic, hypotensive, critically ill patients who are unresponsive to standard supportive therapy with fluids, volume expanders, vasopressors, and antibiotics.

It is important to recognize that if glucocorticoid therapy is to be used, it should be given in a physiologically meaningful fashion as a continuous iv infusion or alternatively as frequent (every 4–6 h) iv boluses. It must be recognized in this setting that glucocorticoid therapy is not a permanent therapy and can/should be tapered quickly as clinically indicated. In the absence of definitive data, hydrocortisone with its potent glucocorticoid and mineralocorticoid activities is the preferred agent. The dose should not exceed 200 mg/d given as a continuous iv infusion (preferably) or as iv boluses every 4–6 h. With such a schedule, serum total and free cortisol levels are much higher than can be generally achieved by endogenous production even in patients with severe Cushing's syndrome. Less frequent (every 8 or 12 h) administration of hydrocortisone is not desirable or physiologically meaningful because it would lead to extreme elevations in serum total and free cortisol concentrations. In light of limited data and the known adverse effects of hydrocortisone, caution should be exercised in the indiscriminate use of this drug. Although there are no definitive data, other than those of Annane *et al.* (32), on the use of fludrocortisone in critical illness, it is unlikely that such additional therapy is necessary in light of the potent mineralocorticoid properties of hydrocortisone at these doses.

*Future studies*

It is evident from this review that there are more questions than answers in this important field. It is likely that studies will be conducted to address some of these questions. Efforts to improve biochemical measures of adrenal function will undoubtedly continue. It is likely that newer techniques for determining serum free cortisol will become widely available over time. Until serum free cortisol determination becomes widely available, additional data on the value of its surrogate marker, salivary cortisol in critically ill subjects, would be helpful. More data are needed on the value of DHEA and DHEA-S in the critically ill before they become part of the standard assessment of adrenal function in this setting. An important limitation that should be addressed is to provide disease-specific standards for normality. The current standards are based on data from healthy volunteers and often with different age and gender characteristics. Investigating polymorphism in the glucocorticoid receptor would be another interesting approach in our attempts to understand this complex system. Another area of future investigation would be to examine the optimal doses of glucocorticoids to patients who might benefit from such therapy. This is particularly important in view of the extreme elevation in serum cortisol concentrations using current doses mistakenly labeled as low-dose therapy.

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