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# Endocrine Changes in Critical Illness

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**The homeostatic corrections that have emerged in the course of human evolution to cope with catastrophic events involve a complex multisystem endeavor, of which the endocrine contribution is an integral component. Although the repertoire of endocrine changes has been probed in some detail, discerning the vulnerabilities and failure of this system is far more challenging. The ensuing endocrine topics illustrate some of the current issues reflecting attempts to gain an improved insight and clinical outcome for critical illness.**

Key words: *critical illness, cortisol, absolute hypoadrenalism, relative hypoadrenalism, cortisol replacement, stress hyperglycemia, stress metabolism, hyperglycemic therapy, nonthyroidal illness, hypothyroid, thyroid replacement, growth hormone resistance, mortality, immune effects, metabolic effects*

Appropriate adaptation in the hypothalamic-pituitary-adrenal axis is essential for survival. Although complete adrenal insufficiency is rare in intensive care unit (ICU) patients, there is an ongoing vigorous debate regarding the prevalence, diagnosis, treatment, and outcome of "relative adrenal insufficiency." Despite the renaissance in promoting the use of "physiological" doses of glucocorticoids, a conservative approach should be weighted against potential benefits of glucocorticoid and mineralocorticoid administration in selected critically ill patients.

Hyperglycemia is a common metabolic feature of severe stress and is becoming recognized as a harbinger of the severity and outcome of illness. Although there are several potential causes of stress hyperglycemia, the effects of counterregulatory hormones and proinflammatory cytokines predominate. Furthermore, enhanced oxidative stress and stress-signaling pathway activation engender a toxic metabolic milieu for all cells including the pancreatic beta cell. Studies have shown that reversing hyperglycemia and insulin resistance reduces mortality; these findings require confirmatory trials.

Adjustments in the thyroid axis in critical illness include a rapid decrease in T3, the bioactive thyroid hormone. Despite decreased T3 in peripheral tissue sites, the TSH often remain near normal and there are no compelling data to administer thyroid hormone in the so-called euthyroid sick syndrome. The clinical challenge is to uncover and treat true thyroid dysfunction in the midst of multisystem abnormalities with a concomitant hypothalamic-pituitary-thyroid setpoint adjustment.

The catabolic events associated with critical illness along with the recognition of major alterations in the growth hormone-insulin growth factor-1 axis have led to studies attempting to overcome the apparent resistance using exogenous recombinant growth hormone. Although previous studies were typically anabolically salutary, 2 recent large, randomized, placebo-controlled, multicenter trials revealed increased mortality and morbidity. The cause for this adverse outcome is not known but has curtailed the use of growth hormone to bona fide growth hormone deficient subjects and those with less than fulminant catabolic stress.

In summary, endocrine changes associated with glucocorticoids, thyroid hormones, glucose/insulin, and growth hormone have been reviewed. Each hormonal system reveals characteristic changes that can be of diagnostic and prognostic significance. In the early stages of critical illness, however, it may be inadvisable to pharmacologically intervene, most likely related to the overlapping actions between the endocrine and immune systems. Intervention in the parallel metabolic changes such as stress hyperglycemia, however, shows promise for improved outcome.

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## Steroids in Sepsis—Re-resurrection of the Last Rites?

Although there is general agreement about the dangers of absolute adrenal insufficiency, there is no such unanimity in defining putative states of hypoadrenalism such as "relative adrenal insufficiency." This is particularly the case in identifying the patients at risk who may require "supportive" cortisol replacement therapy during stress. Improved diagnostic criteria and validation by a demonstration of a survival benefit in selected, predefined patients continue to be of paramount clinical importance to avoid previous mistakes.

## Normal Hypothalamic-Pituitary-Adrenal (HPA) Physiology

The primary glucocorticoid in humans is cortisol, which is essential for life. The central nervous system senses stress from a variety of integrated inputs (e.g., neurological or hormonal signals) and sends information to the hypothalamus, which increases the release of corticotropin-releasing-hormone (CRH). CRH, probably in concert with other humoral substances (eg, vasopressin), stimulates the release of pituitary corticotropin (ACTH), which subsequently stimulates the diurnal synthesis and release of glucocorticoids. The HPA axis exerts a pivotal role for survival in stress [1]. Conversely, adrenal insufficiency accompanied with lack of cortisol is life threatening.

## HPA Axis in Critical illness

The acute adaptive adrenal response to stress is a shift away from mineralocorticoid production to an up to 6-fold increase in glucocorticoid production. In addition, in acute illness, the biological effects of cortisol increase because of a decrease in cortisol binding globulin (CBG) and an increase in receptor sensitivity [2,3]. This acute phase typically lasts for a few hours or days. During the subsequent prolonged phase, there is dissociation between high plasma cortisol and low ACTH levels, suggesting non-ACTH-mediated mechanisms for the regulation of the adrenal cortex. This hypercortisolism contrasts with the very low dehydroepiandrosterone sulphate (DHEAS) level, indicating an imbalance between the immunostimulatory (DHEA) and immunosuppressive (cortisol) adrenocortical hormones [2]. In addition, preliminary data on postmortem samples of critically ill patients reveal evidence for a tissue-specific alternative splicing of glucocorticoid receptors and a down-regulating effect of HPA activation [4]. Increased circulating cortisol levels seem to reflect an increasing severity of illness [5], and mortality of untreated adrenal insufficiency increases with the severity of the acute stress [1]. Importantly, the interindividual range of measured serum cortisol in a given stress situation is very wide. This dispersion of results complicates the differentiation of an abnormal from a normal adrenal response in the course of acute illness.

## Defining Adrenal Insufficiency

Two subgroups of adrenal insufficiency can be differentiated. In absolute adrenal insufficiency, a cortisol increase does not occur, because of malfunction in the HPA axis (eg, after autoimmune adrenalitis or glucocorticoid therapy). It is considered to be present when "basal" (or unstressed) cortisol levels are < 100 nmol/L (< 3.6 µg/dL) and "stimulated" values (eg, after ACTH-stimulation) are < 500 to 550 nmol/L (< 17.9 to 19.6 µg/dL) [6]. During severe illness, comorbidities such as head injury or adrenal hemorrhage, pharmacological agents (eg, etomidate, opioids), or inflammatory mediators (eg, tumor necrosis factor-α, interleukins) can impair the proper stress response of the HPA axis [7]. The term "relative" or "functional" adrenal insufficiency has been proposed for hypotensive, septic critically ill patients who are resistant to the administration of catecholamines, but show hemodynamic improvement to cortisol administration in the absence of factors known to impair HPA axis [8]. In these patients, the cortisol levels (despite being within the normal reference range or even elevated > 550 nmol/L [> 19.6 µg/dL]) are still considered to be inadequate for the severe stress, and the patient may be unable to respond to any additional or protracted stress [9]. Another facet of relative adrenal insufficiency may involve an inflammation-induced restraint of the HPA axis, which includes glucocorticoid resistance at target tissues that can be ameliorated by diminishing the proinflammatory milieu [10,11]. Thus, relative adrenal insufficiency, if present, represents a reversible dysfunction of the entire HPA axis, that is, the syndrome is transient and reverses with recovery from critical illness. It is important to recognize inadequate adrenal cortisol production since there is increasing evidence that relative adrenal insufficiency is associated with a worsened outcome [8] and, thus, has

potential therapeutic implications. In this respect, treatment of septic patients with corticosteroids has undergone a renaissance, although its beneficial effects remain unproven and controversial [12-14].

*Tests for adrenal dysfunction.* There is an ongoing debate concerning the identification of patients at risk of and the definition of relative adrenal insufficiency. Clinical features and laboratory findings such as vitiligo, depression, fatigue, nausea, abdominal pain, hemodynamic instability, unexplained fever, hyponatremia, hypoglycemia, and eosinophilia are nonspecific and must be placed in the clinical context by the treating physician. The diurnal pattern of cortisol secretion together with a large interindividual range of circulating cortisol levels during severe illness and stress make it impossible, and possibly even misleading, to define an absolute serum cortisol threshold level that would identify a patient with functional failure of the HPA axis in critical illness. Hence, various laboratory stimulation tests have been proposed, yet none of them offers unequivocal results. The best consensus reference standard for the diagnosis of integral failure of the HPA axis ("absolute adrenal insufficiency") is the insulin-induced hypoglycemia test (ITT = insulin tolerance test) [15]. An increase of circulating cortisol, during symptomatic hypoglycemia (ie, plasma glucose levels < 2.2 mmol/L [< 40 mg/dL]) after intravenous administration of insulin, is used as the outcome measure. An absolute cortisol increase to circulating values > 550 nmol/L (> 19.6 µg/dL) typically together with a relative increase of > 200-250 nmol/L (> 7.1-8.9 µg/dL) is considered a normal "stress-competent" response. However, in critically ill patients, circulating "basal" cortisol levels may greatly surpass these levels (exceeding 1000 nmol/L [35.7 µg/dL]). Furthermore, there are no prospective follow-up data to validate the diagnostic accuracy of the ITT. The ITT is also unpleasant for the patient, resource intensive, and potentially dangerous (and thus contraindicated in patients with ischemic heart disease and epilepsy). It is inadvisable in children and the elderly, and certainly not feasible in critically ill patients [16].

Simpler tests for the diagnosis of primary adrenal insufficiency include a basally elevated plasma ACTH with respect to cortisol levels. However, ACTH has a short half-life, and its determination is cumbersome. Furthermore, stimulation tests to evaluate pituitary ACTH-reserve (eg, using metyrapone) are not feasible in critically ill patients [17]. In children with meningococcal disease, circulating ACTH levels are high upon admission but decline rapidly within 24 hours, suggesting a pituitary exhaustion or a down-regulation of the HPA axis [18]. Another simple, and widely used, test is stimulation with synthetic ACTH1-24 (Synacthen®). In hypotensive critically ill patients, a "basal" cortisol of > 935 nmol/L (> 33.4 µg/dL) combined with an increase of cortisol < 250 nmol/l (< 8.9 µg/dL) after 250 µg ACTH stimulation has been proposed to represent relative adrenal insufficiency [5]. However, the 250 µg ACTH stimulation test induces supraphysiological ACTH concentrations, giving false-normal cortisol responses. Therefore, it has a lower sensitivity, especially in identifying acute-onset and mild secondary adrenal insufficiency [19-21]. The 1 µg synthetic ACTH1-24-test has been suggested to be more sensitive to diagnose adrenocortical insufficiency. One microgram has been found to be the lowest ACTH dose capable of inducing a maximal cortisol response [22]. The results of the 1 µg synthetic ACTH1-24-test correlate well with the ITT test results [23].

Most of the circulating cortisol is bound to CBG; only a small fraction is free for receptor binding and, hence, biologically active. In patients with septic shock, CBG levels are very low after 7 to 8 days of severe illness [9]. Since a decrease of CBG increases the biologically active fraction of cortisol, CBG levels need to be considered in the evaluation of the HPA axis [24]. In this regard, the measurement of free cortisol in the serum is now becoming available. Another confounding local factor that needs future diagnostic and therapeutic consideration is the activity of glucocorticoid metabolism by the 11-ß-hydroxysteroid dehydrogenase system.

## Cortisol Replacement

The wide range of the measured concentrations of cortisol in critical illness and the lack of controlled studies in patients with absolute adrenal insufficiency make it difficult to define what constitutes the "normal and necessary" adrenal response and cortisol production. Fortunately, absolute adrenal insufficiency is an uncommon event in the ICU. Relative adrenal insufficiency, however, has been reported to occur in as many as 55% to 75% of ICU patients with refractory septic shock; this has fueled an ongoing debate concerning the appropriate treatment. The presumed "physiological" dose of glucocorticoids of 300 mg per day, even if administered as a continuous IV infusion, leads to supraphysiological circulating cortisol levels as compared to untreated critically ill patients [25]. Notably, cortisol production in septic shock cannot

be suppressed by steroids [26]; this has led investigators to question whether a supraphysiological dose of glucocorticoid is more beneficial than what is secreted endogenously, and this highly controversial question has been debated for a half century. A historical perspective is instructive: when adrenal corticosteroids were first introduced some 50 years ago, their use in clinical infection was accompanied by rapid defervescence and improved hemodynamic parameters, but also by evidence that the underlying pathologic process had not been ameliorated and in some cases made worse [27]. Nevertheless, the clinical frustrations of dealing with severe sepsis and its high mortality rate led clinicians to use corticosteroids. In a multicenter trial, patients with life-threatening infections received cortisol in doses that were then considered very large—300 mg per day. The results were disappointing: there were more deaths among patients who received cortisol than among those who received placebo [28,29]. A significant excess of side effects occurred, particularly hemorrhage and secondary infection. With time, due to the obvious ineffectiveness of a dose of 300 mg per day, larger doses of corticosteroids began to be used. The problems of anecdotal evidence, clinical variability of the syndrome of sepsis, small sample size, and suboptimal study design were addressed sporadically and inconsistently. Fortunately, as before, the initial enthusiasm was followed by more carefully designed studies. The results of studies using large doses of corticosteroids—cumulative doses of several grams—demonstrated again the harmful effects of these drugs in systemic infections [30,31]. The increased mortality was, once again, caused by an excess of hemorrhage and secondary infections. Meta-analysis of the published evidence offered little room for continued enthusiasm [32].

Rites are prone to become resurrected; this is currently exemplified by the reemergence of the concept of "relative adrenal insufficiency" [5] and the promotion of "low-dose" (ie, 100 to 300 mg per day) corticosteroid therapy. Once again, initial trials showed promising trends in subgroups of patients with sepsis [14,25,33]. Mostly the beneficial effects were restricted to improvements in hemodynamics and a reduction in the need for vasopressor therapy. One trial found also a marginal reduction of mortality, however, only in patients with impaired response of cortisol < 250 nmol/L (< 8.9 ug/dL) 30 minutes after the administration of synthetic ACTH [14]. Unfortunately, this led some clinicians to administer hydrocortisone to a very heterogenous group of critical ill patients, mostly without HPA testing, and without co-administration of mineralocorticoids; the beneficial effect of steroids remains indeed unproven, and a conservative approach is more prudent. Notwithstanding the current enthusiasm, which often overlooks "pre-medline" literature, there is little definitive advice to offer concerning the use of pharmacologic doses of glucocorticoids in critical illness, in general, and in critically ill patients who meet some of the aforementioned contradictory basal cortisol criteria for "relative adrenal insufficiency" or the contradictory post-ACTH serum cortisol criteria for "functional hypoadrenalism." The alleged benefits should be weighted against the potential dangers of such therapy, such as hyperglycemia. The marked reduction of the harmful hyperglycemia in critically ill patients by insulin should be an additional cause for concern [34].

## Summary

It is unfortunate that no strict biochemical criteria defining a "normal" serum cortisol or ACTH levels or an adequate cortisol response to ACTH exists. It is a dilemma for which there is no recourse other than to rely on a clinical assessment of the severity of the stress, to evaluate the presence of masked or misleading clinical symptoms, and to estimate the adequacy of the measured cortisol concentration, all of which must be placed in a clinical context. In view of both the frequency of absolute and relative adrenal insufficiency and the ongoing debate about "supportive" cortisol therapy in critically ill patients with presumed relative adrenal insufficiency, this unresolved question is of paramount clinical importance and needs to be further investigated. In the interim, the clinician is advised to be ever more vigilant for cues of adrenal dysfunction, such as unexplained eosinophilia [9]. In certain conditions, such as tuberculosis, meningitis, typhoid fever, and pneumocystis pneumonia in AIDS, the use of glucocorticoids appears less controversial [35,36]. If so indicated, a limited course of physiological stress doses of glucocorticoids and mineralocorticoids [14] can be considered in selected high-risk patients, predominantly in septic shock patients, while awaiting confirmatory results of HPA testing. Steroid therapy should be stopped if results of HPA testing become available and do not indicate the presence of adrenal insufficiency.

## Stress Hyperglycemia—The Tip of the Inflammatory Iceberg

Acute hyperglycemic response to stress has been recognized since Claude Bernard's observations more than a century ago [37]; this "diabetes of injury" appears to exemplify the obligatory metabolic rearrangements required to cope with critical stress. This concept is evolving, however, as glucose is becoming identified as a potential metabolic mirror of the severity and outcome of critical illness. Importantly, as illustrated in this summary, the ongoing elucidation of the pathophysiology associated with abnormal glucose levels will buttress the clinical approach to this vexing problem.

*Prevalence.* The estimate of the prevalence of stress hyperglycemia (SH), defined as hyperglycemia in previously euglycemic patients that corrects once the acute process resolves, is highly variable. This occurs because of an inconsistently applied definition and the co-mingling of patients with new onset or unrecognized diabetes mellitus (DM). The estimated rate range varies from 3% to 70% in adults with myocardial infarction (MI) [38] (although if based on HbA1c, the rate was 4.3%) [39]. The range of SH prevalence in patients with a stroke is similarly wide (10% to 40%) (up to 50% having an elevated HgbA1c) [40]. SH may be seen in about 3% to 5% of patients in pediatric emergency room visits or admissions [41,42]. In a recent retrospective chart analysis, a 38% rate of hyperglycemia was noted upon hospital admission (fasting glucose of 6.9 mmol/L [126 mg/dL]) or random glucose of 11 mmol/L (200 mg/dL). Twenty-six percent of these patients had known DM, and 12% had no history of DM [43]. In another study, 13% among subjects with glucose > 6.1-11 mmol/L (> 110-200 mg/dL) had known diabetes [34]. In early sepsis, the prevalence of hyperglycemia approaches 50% [44].

*Severity and outcome.* Although hyperglycemia was once considered a compensatory response, it imposes a range of adverse effects including abnormal immune function [45], increased infection rate [46], and hemodynamic and electromyocardial disturbances [47]. A number of studies have shown a direct relationship between the extent of SH and severity and outcome (including mortality). For example, the severity of illness has been shown to be correlated to the degree of hyperglycemia in surgery, trauma, shock, stroke, and MI [48]. Insulin resistance also correlates to the severity of stress [49]. Outcome has been correlated with SH in MI, stroke, and head injury. In one meta-analysis, elevated glucose (mean glucose 8.0 ± 3.0 mmol/L [146 ± 54 mg/dL]) was a significant predictor of nonfatal reinfarction, hospitalization for congestive heart failure (CHF), and a major cardiovascular event [50]. Moreover, 1-year mortality (44% vs 19.3%) was significantly correlated to glucose in a multivariate analysis of post-MI patients [51]. In another meta-analysis, in-hospital mortality was 3.9-fold increased in nondiabetics with SH as compared with diabetics who had lower glucose levels [38]. A similar increased risk of adverse outcome for patients with SH as compared with diabetics was observed among admitted patients [43]. In this study, hyperglycemia was associated with an increased ICU admission rate. Burned children with hyperglycemia (> 7.7 mmol/L [> 140 mg/dL]) had an increased incidence of positive blood cultures, lower percent graft take, and higher mortality [52]. Following ischemic stroke, a glucose level of > 6.1-6.9 mmol/L (110-126 mg/dL) increased the relative risk of death by 3.28 [40].

## Causes of Hyperglycemia

It is well recognized that glucose concentration is maintained in a rather narrow range (fasting; 3.9-6.1 mmol/L [70-110 mg/dL] and postprandial < 7.7 mmol/L [< 140 mg/dL]), although the clinical importance attached to the upper range has not been considered as relevant. A multitude of factors contribute to the hyperglycemia found in ICU patients. These include lack of muscular activity, aging, the use of dextrose solutions and certain drugs (eg, catecholamines, glucocorticoids, thiazides, highly active antiretroviral therapy, phenytoin, tacrolimus, cyclosporine), underlying medical conditions (eg, obesity, pancreatitis, cirrhosis), and the debut of diabetes itself. Hypokalemia is an important overlooked source of diminished insulin release.

*Stress metabolism.* Severe stress, including injury and sepsis, initiates a neurohormonal response involving counterregulatory hormones, the response to which is dependent on both time and type of stress. Sympathetic activity raises glucose by enhanced glycogenolysis, which is correlated to the degree of trauma and level of epinephrine. A continuous 72-hour infusion of a combination of hydrocortisone, glucagon, and epinephrine resulted in hypermetabolism (catabolism of proteins and

fat), negative nitrogen balance, hyperglycemia, hyperinsulinemia, and insulin resistance [53]. In vitro, hepatocytes appear to respond to counterregulatory stress hormones by increased synthesis of certain protective acute phase proteins [54]. The regulation of carbohydrate metabolism is markedly altered such that the overall whole-body production of carbohydrates is increased and channeled toward immune-related activities of inflammation, wound-healing, and immune cell function(s). The liver becomes insensitive to autoregulation by glucose itself [55] and insulin; glucose production and lactate extraction are typically increased by 2-fold; and the glycerol contribution increases by 20% [56]. The uptake of glucose is near maximal at noninsulin sensitive immune-related sites, reflecting upregulation of glucose transporters (ie, GLUT 1). Thus, the stressed patient is characterized by fasting and postprandial hyperglycemia, insulin resistance, and stimulation of hepatic glucose production. Insulin levels, albeit elevated, are relatively low. In this regard, experimental studies suggest that insulin signaling is defective; lipopolysaccharide (LPS) exposure diminishes phosphorylation of the insulin receptor, insulin receptor substrate-1, and MAP kinase [57].

*Cytokines.* Many of the metabolic changes associated with severe stress arise from interrelated effects of proinflammatory cytokines (eg, tumor necrosis factor [TNF], interleukin-1, and interleukin-6 [IL-6]) and the counterregulatory hormones. For example, TNF-induced insulin resistance and diminished insulin release can explain many of the changes noted in stress metabolism [48,58,59]. Members of the calcitonin gene family of peptides, which are increased in systemic inflammation, can also induce insulin resistance [60]. Another way in which cytokines can promote hyperglycemia is the well-known activation of the entire hypothalamic-pituitary-adrenal axis [61]. Insulin itself may be involved as euglycemic hyperinsulinemia augmented IL-6, growth hormone, and cortisol responses following an LPS challenge to healthy subjects [62]. Nonetheless, other studies suggest that insulin has anti-inflammatory properties (see below).

On the other hand, hyperglycemia can affect cytokine expression. Raising glucose levels in healthy subjects to 14.9 mmol/L (270 mg/dL) (while suppressing endogenous insulin by octreotide) increased IL-6, TNF-a, and interleukin-8 within 2 hours, an effect which lasted for 1 hour [63]. This response was not seen when the antioxidant glutathione was co-infused. Glucose loading in fasted rabbits resulted in significant exacerbation of the metabolic and hemodynamic response to LPS; TNF release was also increased by this experimental manipulation [64]. In vitro, exposure of human monocytes to hyperglycemia for 24 hours increased IL-6 and TNF synthesis [65]. As noted in some of these studies, cytokine responses to hyperglycemia may involve changes in oxidative stress.

*Oxidative stress.* Exacerbated oxidative stress has been reported in ICU patients with systemic inflammation. These patients also have lower serum levels of antioxidative factors [66]. Oxidative stress is defined as an imbalance between the production of highly reactive oxygen and/or nitrogen species (ROS and RNS) and endogenous antioxidant defenses. This imbalance can lead to damage to DNA, protein, and lipids. Importantly, the role of oxidative stress is to engender the biochemical abnormalities thought to be associated with the complications of diabetes. In this regard, hyperglycemic exposure to endothelial and smooth muscle cells for 48 to 72 hours stimulated ROS; intervention nullified changes in several pivotal metabolic pathways abnormally expressed in diabetes [67,68]. The oxidative changes may occur more acutely, however, as pancreatic beta cells exposed to hyperglycemia in vitro for as short a time as 15 minutes resulted in increased ROS and decreased first-phase secretion of insulin [69], changes that were nullified with inhibitors of mitochondrial function. In this regard, it appears that the pancreatic beta cell expresses relatively low levels of antioxidant factors [70]. It is also noteworthy that acute hyperglycemia in vivo alters the ability of beta cells to couple insulin secretion to glucose changes [71]. The deleterious effects of acute hyperglycemia in vivo may thus be caused by the production of free radicals and the associated oxidative stress [72]. For example, a very high glucose (32.9 mmol/L [599 mg/dL]) perfusion in rat hearts for 2 hours increased nitric oxide (NO) and superoxide generation and the formation of nitrotyrosine; the subsequent apoptosis was prevented by glutathione [73].

*Stress signaling pathways.* Hyperglycemia-induced ROS can function as an acute signaling factor for stress-sensitive pathways including nuclear factor-kappa B (NF-κB), c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and mitogen-activated protein kinase (MAPK). NF-κB is a heterodimeric peptide that is normally neutralized in the cytoplasm by being bound to IκB. Following a

variety of activating stress signals, dissociation of IκB occurs, and NF-κB crosses the nuclear membrane and up-regulates a host of proinflammatory cytokines that can cause defective insulin signaling and insulin resistance [74]. As explained previously, hyperglycemia produces enhanced mitochondrial oxidative phosphorylation and increased ROS, up-regulation of NF-κB being a very proximate response. In accord with these studies, a 2-hour hyperglycemic clamp reaching 9.9 mmol/L (180 mg/dL) resulted in increased monocyte NF-κB p56-associated translocation into the nucleus [75].

## Therapeutic Implications

Clinical trials have shown that aggressive treatment of hyperglycemia in some subsets of diabetic and nondiabetic patients has a positive impact on immune recovery [76] and during the recovery from an MI [77,78]. More recently, mortality was decreased by 34% in a surgical ICU by "clamping" the glucose level between 4.4 and 6.1 mmol/L (80-110 mg/dL) with insulin [34]. This effect was most pronounced in patients with protracted illness (> 5 days). These and other reports have indicated that insulin may have anti-inflammatory properties [79-81], albeit reaching normoglycemia, rather than the insulin dose, was related to the benefits of insulin therapy [82]. Several additional approaches to SH include the observation that the use of a beta blocker ameliorates SH, thus implicating catecholamines to the disorder [83]. In a double-blind study, metformin was administered to burned patients and shown to decrease endogenous glucose production and glucose oxidation and to increase glucose clearance following a glucose challenge [84]. Metformin may be particularly useful in SH in view of its antihyperglycemic effects via suppression of glucose production of the liver as well as having antioxidant properties [85]. Metformin, however, has important limitations including the risk of developing lactic acidosis, a serious consideration. In experimental studies, the lipid-soluble thiamine agent, Benfotiamine, was shown to diminish NF-κB formation following a 6-hour hyperglycemic exposure [86].

## Summary

Acute hyperglycemia associated with severe stress is now recognized to be a potential harbinger of aggravated illness and outcome. With the emerging epidemic in insulin-resistant disorders such as aging, obesity, and the metabolic syndrome, and studies suggesting that the adverse effects of hyperglycemia can be altered, we are now challenged to consider an alternative clinical paradigm [87]. Although pancreatic beta cell function should normally be adequate to overcome insulin resistance, SH may result from a combination of the high levels of cytokines, severity of oxidative stress, beta cell dysfunction, and glucose-generating drugs (eg, steroids), as well as any underlying genetic diabetic predisposition. Indeed, pancreatic beta cells are highly sensitive to oxidative stress and NF-κB; thus, the presence of SH may be viewed as an expression of an excessive systemic inflammatory response in which efforts to modulate oxidative forces would have particular value. Certainly, glucose management in the ICU setting needs more thoughtful consideration beyond the ill-conceived and popular use of "sliding scales."

# Euthyroid Sick Syndrome—A Question of Setpoint?

In severe systemic nonthyroidal illness (NTI), profound changes occur in the hypothalamic-pituitary-thyroid (HPT) axis, also termed euthyroid sick syndrome (ESS). Typically, a normal TSH and free T4 and decreased total T3 suggest a change in HPT axis setpoint [88]. This is thought to represent a homeostatic correction by which the body diminishes the effects of the biologically active hormone T3. Since NTI occurs in most patients with systemic illness, and because the morbidity and mortality rate of NTI is high, it becomes important to determine whether thyroid hormone administration is beneficial or detrimental.

*Thyroid changes in NTI.* The most rapid and consistent finding in NTI is a fall in circulating total T3 and free T3 and an increase of the inactivate rT3 levels (ie, low T3 syndrome). As an example, the level of T3 was reported to decrease even before myocardial infarction [89]. In general, the greater the severity of disease the lower the serum T3 levels become [90,91]. Serum total T4 levels can be decreased (ie, low T4 syndrome) typically in patients with more chronic and severe systemic illness; total T4 levels below 51.6 nmol/L (4 ug/dL) are associated with increased mortality [92]. Free T4 can be determined by equilibrium dialysis, direct measurement, or ultrafiltration, and although controversial, the majority of patients have serum free

T4 either being normal or slightly decreased, but occasionally elevated [93]. A decrease in the peripheral production of T3 due to a decreased extra-thyroidal conversion of T4 into T3 by the enzyme type I iodothyronine-5'-deiodinase is a major contributing factor [94,95]. Similar changes are seen after 24 to 36 hours of food deprivation, which is reversible [96]. The critical aspect relating to thyroid hormone action is tissue concentrations, nuclear receptor occupancy, and clinical parameters of thyroid hormone action at peripheral target tissues, all difficult to determine in critically ill humans. Interestingly, tissue T3 concentrations were found to be lower in liver, kidney, and anterior pituitary obtained from NTI patients compared to control tissue [97]. Thyroid hormone receptor levels also decrease in experimental infection [98].

Circulating TSH levels might be considered as a sensitive marker of a lack of thyroid hormone since the concentrations of TSH sharply increase in primary hypothyroidism even before serum T4 and T3 fall below the normal reference range (eg, so-called subclinical hypothyroidism) [99-101]. In NTI, however, despite the decrease in serum T3 (and T4 in severe cases), the concentrations of TSH typically remain within the low to normal range [102]. Conversely, there is a blunted response of TSH to thyrotropin-releasing hormone (TRH), and low TSH levels are associated with poor prognosis [92,103,104]. Various pharmacologic agents, such as dopamine and steroids, may further decrease TSH levels. Taken together, these findings suggest that a major change in thyroid hormone setpoint regulation occurs in NTI. Since the TRH level in the hypothalamic paraventricular nucleus (PVN) is a major determinant of the setpoint of the HPT axis, it is reasonable to assume a role for the hypothalamus in NTI. Accordingly, prolonged critically ill patients show diminished TSH pulsatility, characterized by an absent nocturnal TSH surge and a decreased TSH pulse amplitude [102,105,106]. The changes in nocturnal TSH secretion in NTI resemble those found in central hypothyroidism, suggesting that hypothalamic changes are involved in the ESS. Indeed, TRH mRNA expression in PVN is reduced in patients who died after prolonged critical illness, and this decrease correlated with both serum TSH and T3 levels [107]. In addition, a continuous administration of TRH to patients with prolonged critical illness partially restored circulating levels of T3, T4, and TSH, especially when combined with growth hormone secretagogues [108].

*Is the patient with NTI euthyroid?* It is important to obtain a complete history from the medical records, from the patient and/or relatives, and to ascertain whether the patient has had thyroid disease or received surgery or radioactive iodine. Family history of thyroid disease and measurement of thyroid antibodies and thyroid function are also important. Clinically, patients with NTI may have the classic signs or symptoms of hypothyroidism [109]; for example, patients in an ICU may have unrelated hypotension, dry skin, bradycardia, and hypothermia. It is probable that in NTI the TSH level relatively accurately reflects the amount of T3 available at the pituitary and probably also indirectly reflects tissue thyroid hormone concentrations. Thus, the changes in TSH should be viewed similarly in patients with NTI and normal subjects using a sensitive third-generation assay [104]. A normal serum TSH most likely excludes primary thyrotoxicosis or hypothyroidism and suggests that the patient is euthyroid and does not require L-thyroxine therapy. Suppressed TSH levels (ie, below the limit of detection of a third-generation assay with a functional assay sensitivity of < 0.01 mU/L) are typically seen in patients with primary hyperthyroidism, and only in a small percentage of critically ill patients (eg, those receiving dopamine or glucocorticoids). In addition, circulating peripheral thyroid levels, especially T3, are not elevated, but rather in the lower reference range in NTI.

Patients with overt primary hypothyroidism almost always have TSH levels > 10 mU/l in parallel with decreased T4 and in more severe stages also of T3 [100]. TSH measurement has a very high diagnostic accuracy for the early detection of primary hypothyroidism. However, TSH is a poor measure of the clinical and metabolic severity of hypothyroidism, because TSH is maximally stimulated in the early stages of primary thyroid failure, with no further increase occurring with greater severity of hypothyroidism [99]. In addition, elevated TSH levels may also occur in NTI upon recovery [102]; however, these values rarely exceed 10 mU/L [110]. In situations of diagnostic uncertainty, low serum concentrations of rT3 (if available), a low thyroid hormone binding ratio, and especially a high ratio of serum T3 to T4 of > 100 favor the presence of hypothyroidism over NTI and vice versa [88,101]. In addition, careful clinical evaluation of the signs and symptoms of hypothyroidism is essential if the differential diagnosis and simple clinical scores are available [109]. These signs may be extremely difficult, if not impossible, to discern in a patient in the ICU who typically has multiple medical problems and may have a tracheostomy and may be receiving medication for sedation. It is particularly difficult to assess the rare patient who

may have secondary hypothyroidism; papilledema, visual fields, involvement of other pituitary hormones then become important. Frequently, these patients may have had a CT or MRI of the head without attention to the pituitary gland. One should ensure that the remainder of the pituitary gland function is normal and that there is no hypothalamic or pituitary involvement by a mass or infiltrative disease. The medications used need to be reviewed with special emphasis to dopamine and corticosteroids [111,112]. A wide variety of other medications may additionally influence the hypothalamic-pituitary axis [113].

*Assessment and treatment of patients with NTI and suppressed TSH.* Recently, increased cardiovascular mortality in subjects aged 60 years and older has been reported in patients with subclinical hyperthyroidism (ie, TSH levels of < 0.5 mU/L in the presence of T3 and T4 levels within the normal reference range) [114]. Since correlations do not prove causality, it has been argued that this is due to the higher mortality of patients suffering from NTI, which were more prevalent in the group with suppressed TSH. In view of the lack of controlled intervention studies, the treatment of patients with NTI and suppressed TSH levels with antithyroid therapy cannot be advocated.

If overt primary hyperthyroidism is postulated in a patient with NTI, the serum TSH should be undetectable (ie, < 0.01 mU/L) with a high normal or elevated free T4, and free T3 being inappropriately normal or elevated and treatment considered in the appropriate context. Again, careful clinical assessment (eg, using the Crooks-Wayne index) is essential [115]. Treatment is usually with methimazole (eg, 5-15 mg/day) or propylthiouracil (50-150 mg/day), with frequent monitoring of blood count and liver function tests. These antithyroid agents take several days to weeks to reach maximum effect, and propranolol can be added for symptomatic control [116,117]. The use of glucocorticoids has been proposed in severe cases of hyperthyroidism. Importantly, no controlled studies are available on the optimal therapeutic regimen in these patients; any recommendations are "eminence-based" rather than "evidence-based." Because of their ability to actually increase thyroid hormone secretion over time, iodine, ipodate, or iopanoic acid administration should only be used in unusual circumstances when the clinician is relatively certain that hyperthyroidism is present and needs to be controlled as rapidly as possible [118,119].

*Assessment and treatment of patients with NTI and elevated TSH and/or low T3 and/or T4.* If the TSH is greater than 10 mU/L, especially if the free T4 is decreased with reasonable clinical suspicion, one could recommend L-thyroxine therapy. Although there are several potential regimens for the use of T4 and/or T3, L-thyroxine is preferable, usually in doses of 50-100 ug/day (depending upon the level of suspicion for hypothyroidism and the general medical and cardiac condition). If the TSH is between 5 and 10 mU/L, and assuming the patient is not in the recovery phase of his or her systemic illness, repeating the values several times over the next few days is reasonable, and if the values are consistent, the patient could be treated with L-thyroxine or simply followed very closely with frequent physical examinations and repeat thyroid function tests.

*Treatment of NTI with normal TSH.* Although the therapy in patients with suspected primary hypothyroidism is straightforward, it is controversial if patients with NTI and normal TSH levels and low T4 and/or T3 levels should be treated [88,120,121]. One might argue that the down-regulation at all levels of the HPT axis in NTI is part of the neuroendocrine adaptation to disease: a "hibernation-like" attempt of the organism to save energy. In this view, attempts to increase and thereby restore serum thyroid hormone concentrations are disadvantageous and—unless randomized clinical trials demonstrate clinical benefit—should not be undertaken, in accordance with the principle *primum non nocere*. It is not, however, certain that this view can be extended to situations where critically ill patients require and get vital organ support that are beyond pathophysiological adaptation. The applicability of animal studies to clinical NTI is unfortunately problematic. There have been several studies performed in which patients with NTI have been treated with L-T4 or T3 (for an extensive review, see [88,121]). These studies, however, are of limited use since they often have a small number of patients and study only a focused patient population. The authors find the evidence far from compelling and would advise withholding thyroid hormone therapy in NTI in critically ill patients in the absence of clear clinical or laboratory evidence for abnormal thyroid function, as outlined above. Accordingly, a normal TSH suggests that the patient is euthyroid and does not require L-thyroxine therapy. A normal clinical score and normal free T4 levels would give additional

support [109]. If the free T4 was < 2.6 pmol/L (< 0.2 ng/dL) (normal 9.0-19.4 pmol/L [0.8-1.8 ng/dL]), in conjunction with a normal TSH, consideration of L-thyroxine therapy could be advocated, since only a small percentage of euthyroid patients with systemic illness would have such a low free T4. Obtaining a rT3 level may be of interest in selected instances, but its reliance has been questioned [122]. In one study, ICU patients were randomly assigned to treatment with intravenous thyroxine for 2 weeks or placebo [123]. This normalized serum T4 and free T4 levels, but the concentrations of T3 was no different from that of control patients and it did not improve survival. One might argue that serum T3 should be normalized in order to achieve a beneficial effect. The best such large-scale studies are in patients who have undergone coronary artery bypass surgery (CABG). For example, 2 controlled studies of T3 administration to CABG patients found no difference in clinical outcome despite some favorable effects on hemodynamic variables [124,125]. Although there was no prolonged or severe critical illness present as reflected by the low mortality rate and the normal T4 concentrations, numerous studies in different settings (eg, transplantations, fasting/starvation, ICU sepsis, septic shock, burns, and in AIDS patients) could not resolve the controversy due to lack of clear clinical benefit of either T3 or T4 administration [121].

## Summary

NTI is seen in multiple disorders that present with similar thyroid function tests, that is, normal free T4 and TSH in conjunction with a decreased free T3. The clinical context, including the medical history and physical examination, must be considered; however, most of these patients are euthyroid and should not be treated with thyroid hormone until further information regarding its etiology, pathophysiology, and response to treatment have been better evaluated in diverse patient populations: Thus, further large scale prospective studies still need to be performed before thyroid hormone administration can be advocated in patients with ESS.

## Growth Hormone Supplementation—A Cautionary Anabolic Tale

Reversing the protein catabolism associated with critical illness has been an important research objective and clinical goal. Despite aggressive nutritional support, critically ill patients remain catabolic with continued nitrogen loss. Although a multitude of studies have demonstrated that growth hormone (GH) supplementation has salutary anabolic effects in a number of different stressful conditions, this therapy results in an increased risk of mortality [126]. A better comprehension of this conundrum may provide insights into future strategies for anabolic treatments.

## Normal GH Physiology

GH is secreted from the anterior pituitary, which is under hypothalamic control; positive (ie, growth hormone releasing hormone) and negative (ie, somatostatin) hypothalamic factors influence the synthesis and secretion of pituitary GH. In addition, a novel class of endogenous GH-releasing peptides, which act on the pituitary, have been described: among these, ghrelin, a 28-amino peptide secreted from the oxynthic cell of the fundus, augments pituitary GH release and has orexigenic properties [127]. Anterior pituitary GH is secreted in a characteristic diurnal and pulsatile pattern. Following secretion, approximately 50% of GH is bound to the circulating portion of its own receptor, GHR. Two GHRs bind GH and initiate signal transduction by interacting with the cytoplasmic tyrosine kinase, Janus kinase 2 (JAK2).

GH itself has well-known metabolic activities such as lipolysis, enhanced amino acid transport into muscle, and anti-insulin properties. The most prominent action, however, is the mitogenic and anabolic action via increased insulin growth factor-1 (IGF-1) production. IGF-1 circulates in a ternary binding protein complex, which includes IGF binding proteins (IGFBP3 [and to a lesser extent IGFBP5] and acid labile subunit [ALS]). Importantly, IGF-1 exerts negative feedback on GH release at the level of the hypothalamus and pituitary. The main bioaction of the GH-IGF-1 axis is nitrogen retention, protein anabolism, and linear growth. However, this axis also has important metabolic effects beyond pubertal growth as attested to by studies of hypopituitary subjects in whom the loss of GH appears to result in loss of lean muscle mass, an increase in fat mass, and accelerated atherosclerosis.

## GH in Critical Illness

The mean concentration of GH is acutely increased in most stress states such as trauma, surgery, burns,

and infection. This appears to result from a sustained increase in interpulse GH levels. Nonsurvivors generally have the highest level of GH compared to survivors. Despite the increased GH, IGF-1, IGFBP3, and ALS levels are consistently low, suggesting a GH-resistant state. In contrast, in prolonged illness, mean GH levels are often slightly elevated, but with low or few pulsatile spikes [128]. Experimental studies with lipopolysaccharide (LPS) suggest that the initial abnormality in the GH-IGF-1 axis occurs at the level of post-GH receptor signaling, that is, decreased JAK and signal transduction and activators of transcription (STAT) and increased suppressors of cytokines (SOCS) while there is a decreased abundance of GHR at later stages [129,130]. In experimental abdominal sepsis, treatment with a TNF antagonist (ie, TNF-binding protein) ameliorates the reduction in IGF-1 mRNA, suggesting that proinflammatory cytokines induce GH resistance [131]. In a series of studies in humans, pulsatile secretion of anterior pituitary hormones is reduced during the chronic phase of critical illness [127,128]. This abnormal pulsatility can be corrected using the cognate GHRH or GHS peptide. Anabolism, however, is only observed with a combination of GH-releasing factors, thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH) [132]. Coadministration of GHRP-2, TRH, and GnRH reactivated the GH, TSH, and LH axes in prolonged critically ill men and evoked beneficial metabolic effects, which were absent with GHRP-2 infusion alone and only partially present with GHRP-2 + TRH. These data underline the importance of correcting the multiple hormonal deficits in patients with prolonged critical illness to counteract the hypercatabolic state [132].

## GH Replacement

Documented GH deficiency (GHD) in children and adults can be successfully treated with replacement doses of recombinant GH. Children experience accelerated linear growth, whereas adults normalize the ratio of lean and fat mass as well as increasing bone mineral density. Interestingly, proinflammatory cytokine levels and NO balance improve (eg, increased synthesis of NO) with GH replacement [133]. GH replacement in GHD appears to be safe [134], and, although not reported, hypopituitary patients with GHD would be candidates for continued GH replacement during ongoing critical illness.

## GH Supplementation

As long ago as 1961, GH was known to combat nitrogen wasting and the hypermetabolic response in burns [135]. GH given to children with burns (including double-blind placebo trials) was reported to enhance wound healing with a shortened hospital stay, and decreased cytokine levels [136-138]. In surgical patients, GH can improve muscle strength, preserve lean body mass, and decrease fatigue [139]. Patients requiring parenteral nutrition respond to GH by positive nitrogen balance by increased IGF-1 levels. Moreover, GH may shorten the time on mechanical ventilation. GH was also used in sepsis and reported to improve nitrogen balance [140,141]. Thus, it was unanticipated that GH therapy would increase mortality in 2 large European multicenter, placebo controlled randomized trials encompassing 532 critically ill patients [126]. The patient categories included trauma, respiratory failure, and postcardiac or abdominal surgery. The dose of GH was 10- to 20-fold higher than replacement levels and was continued for a maximum of 21 days. The doubling of the mortality occurred during the first 10 days due to multiple organ dysfunction and uncontrolled infection. Although a subsequent review of GH therapy in children with burns indicated that it was safe [142], its use in acutely ill adult patients has been discouraged.

## Why GH Supplementation May Be Harmful

The results of pharmacological supplementation of GH have focused mostly on its anabolic properties, although GH has a myriad of other direct and indirect multisystem effects. Certain side effects, such as edema and insulin resistance, are expected and occur with replacement doses. The adverse outcome of the anabolic trials emphasizes the lack of detailed knowledge of the complexity underlying the response to catastrophic illness. Future supplemental use of GH should only be considered subsequent to additional studies into GH pathobiology.

*Immune effects.* Although the cause of the adverse outcome in these GH trials is not known, GH has immune-related effects that may be of significance. GH is produced by immune cells and has been implicated in the regulation of several functions in the immune system. For example, non-Hodgkin

lymphoma has been reported to cause overt acromegaly [143], and acromegalics show increased phagocytic and T cell activity [144]. Both GH and IGF-1 influence the growth and function of phagocytic cells [145]. In lymphoma cells made to overexpress GH, NO production was increased due to increased inducible NO synthase (iNOS) promoter activity and iNOS protein expression. These cells also showed reduced toxicity following exposure to an alkylating agent, suggesting a role of GH in the survival of lymphocytes exposed to stressful stimuli via the production of NO [146]. Studies of intrathymic injection of GH indicate that GH can stimulate intrathymic T-cell traffic [147]. GH may also impact the human immune system via Fas-induced apoptosis; in human lymphocyte cell lines, GH rescued Fas-induced suppression of [(3)H]-thymidine incorporation, without changing Fas antigen expression. In these experiments, GH treatment increased Bcl-2 expression, down-regulated caspase-3 expression, and inhibited activation of caspase-3 [148].

In experimental sepsis (ie, cecal ligation puncture method), GH significantly increased the expression of CD11b and the circulatory neutrophil activation. GH also increased neutrophil accumulation in lungs, thus demonstrating exacerbated microvascular injury [149]. Similar cellular and tissue abnormalities have been reported to follow LPS and GH exposure. In addition, NF-κB activity in the lung and in neutrophils was increased following GH and LPS exposure [150]. LPS injected into rats primed with GH for 3 days caused more extensive abnormalities of renal and liver function as well as worsened hypoglycemia and hyperlipidemia than was observed in controls. In this model, GH potentiated the deleterious effects of LPS [151].

*Metabolic effects.* GH has well-known direct and indirect metabolic effects. In human GH trials, hyperglycemia has been noted to be more common (glucose levels were increased by 1-2.5 mmol/L [18-45 mg/dL] in the GH-treated groups) [126]. The nutritional state is of paramount importance to the evaluation of the GH-IGF-1 axis, and much of the contradictory information in critically ill patients is related to the underlying fed or fasted state (ie, treatment with GH results in much lower IGF-1 response in fasted subjects). The supply of a critical amino acid, particularly glutamine, may be of importance in GH studies [152,153]. GH-induced lipolysis and ketone body formation may lead to metabolic acidosis and detrimental response to experimental hemorrhage [154].

GH is known to stimulate hepatic protein synthesis and to induce hepatic enzymes. It is thought also that the difference in pulsatile GH secretion pattern between males and females determines the sexually dimorphic pattern of drug metabolism [155]. GH treatment of healthy elderly male subjects induces hepatic cytochrome CYP1A2 activity [156]. Interestingly, a similar protocol of GH treatment of GHD adults resulted in decreased CYP1A2 activity [157]. Thus, the pulsatile pattern of GH is an important aspect of its action with variable metabolic effects.

## Summary

Despite the plethora of studies demonstrating the salutary effects of pharmacological doses on nitrogen balance in critical illness, such supplementation is clearly hazardous. Although the mechanism is unknown, GH supplementation has been shown to have important immune and metabolic impact that may adversely affect the GH-resistant state that is characteristic of the early phase of critical illness. Since GH replacement in GHD has been shown to have beneficial immune and metabolic effects, it remains to be established whether a comparable state of GHD occurs during prolonged illness. Nevertheless, GH supplementation may have a role in less fulminant forms of catabolic states [158]. Future anabolic studies in critical illness should focus on improved diagnostic approaches to GHD in critical illness as well as alternative GH replacement strategies that reestablish the normal GH-IGF-1 feedback system.

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