

DISLODGING SACRED DOGMAS IN COMBATING SYSTEMIC STRESS: THE CASE FOR STEROIDS

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In the realm of physics, stress is defined as the resistance of an object to a strain, which is measured by force per unit area. In physiological terms, stress is defined as a state of threatened homeostasis: the precision of measurement, however, rarely exists, leaving the clinician to judge its magnitude. Our current understanding of the endocrine response to stress has evolved since the time of Bernard, who developed the concept of “the internal environment.” Cannon coined the term “homeostasis” to describe the complete bio-response necessary to maintain a steady state, and documented the role of the sympathoadrenal system. Selye described the enlargement of the adrenal cortex in response to diverse noxious agents, later termed “the general adaptation syndrome”; this shifted attention to the hypothalamic-pituitary-adrenal (HPA) axis. Later, Munck redefined the role of glucocorticoids in stress to involve the modulation of other adaptive responses, especially proinflammatory cytokines, thereby protecting the host from the effects of “overreaction.”¹

The recognition that critical illness leads to stereotypical inflammatory responses, independent of the nature of the insult, has enhanced the understanding of its pathogenesis.¹ Most of the clinical, metabolic, and humoral changes associated with critical illness stem from the unleashing of an uncontrolled inflammatory response and its modulation of the stress hormone action.² The key concept of the stress response, however, is the multidirectional immuno-neuro-endocrine interaction.³ This integrated action is reminiscent of the Hippocratic definition of health as the balance of the elements of life, and disease as disharmony of these elements. All healing forces in human history are aimed at restoring harmony and relieving stress.

Although the appreciation of the immuno-neuro-endocrine interaction has shed light on the mechanism and magnitude of the stress response and confirmed the long-held view of the integral relationship between stress and diseases, it has failed to translate into improvement in therapy. This failure is exemplified by the persistently high mortality from sepsis in spite of the use of more potent antibiotics and immune modulators and more advanced ICU support.⁴ Initially, steroids were the darling of physicians, and more recently, immunomodulatory therapy has been cherished by the pharmaceutical industry, however, the results have not been encouraging.⁵ This failure most likely highlights a misinterpretation of the pathophysiology of the HPA axis during the stress response. Recent studies demonstrated the beneficial effect of suprphysiological hydrocortisone dose in selected cases of septic shock,^{6,7} challenging the sacred

dogma of avoidance of steroids in septic shock.⁸ Furthermore, the use of steroids in certain conditions, such as tuberculosis,⁹ meningitis in pediatrics, typhoid fever, *Pneumocystis carinii* pneumonia in AIDS,¹⁰ and in acute spinal-cord injury,¹¹ is clearly beneficial and probably useful in some other infections as well.¹⁰

A reinterpretation of the HPA axis response suggests a “relative glucocorticoid resistance” during critical illness. This concept is supported by the demonstration that certain excessive immune-mediated inflammatory states are associated with glucocorticoid resistance in target tissues.¹² In rheumatoid arthritis, for example, the concentration of glucocorticoid receptors (GR) in circulating leukocytes is reduced.¹³ Glucocorticoid-resistant asthma is also associated with increased expression of GR-beta indicative of glucocorticoid insensitivity, as GR-beta antagonizes the transactivating activity of the classic GR.¹⁴ Furthermore, this GR-beta activity is inducible by cytokines.¹⁴ There is recent evidence that proinflammatory cytokines induce glucocorticoid insensitivity.^{15,16} It remains to be seen if cortisol resistance is also confirmed in other stress conditions, including critical illness. This concept is further supported by the observation that in septic shock, the salutary effect of hydrocortisone infusion was not related to adrenal insufficiency, as suggested by the short corticotropin test.⁶

Based on this revised concept, the goal should be to restore glucocorticoid balance, while avoiding immunosuppression. The first issue in achieving this goal is to identify reliable biological marker(s) of glucocorticoid sensitivity. For example, the eosinophil count (or its proximate stem-cell growth factor) or one of the many acute phase proteins could serve as surrogate markers of glucocorticoid sensitivity.^{17,18} Consideration should also be given to one of the many inflammatory mediators and their products. One approach would be to measure the decrease in C-reactive protein (CRP) in the systemic inflammatory response, as has been observed with hydrocortisone infusion.¹⁸ Since the measurement of various cytokine components has been shown to be, at best, unreliable, emerging “late” mediators and/or markers, such as calcitonin precursors, also deserve scrutiny as surrogate measures of cytokine activity.¹⁹

The second issue would be the development of a systemic inflammatory response score, or a toxic index, based on the multifaceted actions of glucocorticoids. This index, akin to the endocrine index,²⁰ would assess the state

of the inflammatory response based on the aggregate of measured mediators or their effect(s).⁴ The use of this index should lead to improved selection of cases in future trials, more judicious timing and use of glucocorticoids, and more objective assessment of steroid responsiveness. Furthermore, it may allow the use of other modalities for modulating cortisol responsiveness.

Finally, the third issue suggests that there is still an urgent need for well-designed prospective studies to establish the proper role of glucocorticoids in critical illness. Concepts such as a “relative glucocorticoid resistance” may refine the design of such trials, uncovering new and more effective approaches to conditions with high lethality. Glucocorticoids currently are used only in special circumstances. Clearly, a more rational approach to a major anti-inflammatory force is highly desirable.

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