Should we question *if* something works just because we don't know *how* it works?

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In 1687, Sir Isaac Newton observed planetary movement and (by his own account, inspired by a falling apple[1]) postulated the existence of a force between two objects that is proportional to the product of their masses and inversely proportional to the square of the distance between them.[2] Although this did not exactly accord with later observations (Einstein's theory of general relativity was required to explain inconsistencies such as the movement of the planet Mercury), Newton's theory has been used as the basis of much successful human endeavour. Despite this, humanity does not yet really *understand* gravity, having little idea of how gravitational force is transmitted. Similarly, in other branches of science, observations can be put to good use without an understanding of the mechanism underlying the observed phenomena. An obvious analogy in medicine is the use of inhaled general anaesthetics — the mechanism of which is yet to be fully explained.[3]

Gravity, anaesthesia, and many other observed but poorly understood phenomena are nonetheless the valid subject of mechanistic research. Deeper scientific understanding may lead to more technological applications. In this issue of the Journal, Venkatesh and Cohen[4] present a valuable summary of the evidence against the concept of "relative adrenal insufficiency" as the foundation for the use of corticosteroids in human septic shock (*page 301*). They note that conventional measurements of total plasma cortisol level and the response to corticotropin do not reflect disease severity, and that changes in the free fraction of circulating cortisol and cellular alterations (for example, in intracellular cortisol metabolism and receptor binding) are probably significant confounding factors in the interpretation of these tests. Previous studies of plasma cortisol levels in sepsis showing an "inadequate" response may thus be misleading, as the response may be entirely appropriate for the, as yet, ill-defined needs of the cell ("sick euadrenal syndrome" to paraphrase the term applied to the thyroid gland under similar conditions).

The argument advanced by Venkatesh and Cohen has two implications: first, that measurement of total plasma cortisol is unlikely to be helpful in patients with septic shock, and second, that pharmacological replacement of "deficient" cortisol is not warranted. Evidence from clinical trials and consensus opinion support the first of these two contentions. The landmark major trial of low-dose corticosteroids for septic shock was that of Annane et al in 2002:[5] of 299 patients randomly allocated to receive placebo or 50 mg hydrocortisone every 6 hours plus 50 µg fludrocortisone daily, mortality benefit was observed only in the subgroup of 229 patients who mounted a "subnormal" response to corticotropin. However, in a multivariable model, the interaction of corticotropin responsiveness and steroid efficacy was not significant.[6] A subsequent larger (499 patient) multicentre trial (CORTICUS)[7] found 46.7% of patients had "subnormal" responses to corticotropin, but this was not a predictor of mortality. Moreover, there was no mortality benefit associated with low-dose hydrocortisone in corticotropin responders, non-responders, or overall. Reconciling these two trials reportedly presented great difficulty to the authors of the most recent Surviving Sepsis Campaign guidelines,[6] with the eventual recommendation being that low-dose hydrocortisone is indicated for patients who are "poorly responsive to fluid resuscitation and vasopressor therapy" (ie, similar to patients in the 2002 Annane trial), but that the corticotropin test should not be used to identify patients likely to derive the greatest benefit. More recent consensus guidelines from the American College of Critical Care Medicine[8] agree that the corticotropin test should not be used, and even suggest that the term "relative adrenal insufficiency" should be abandoned in favour of "critical illness-related corticosteroid insufficiency", for many of the same reasons articulated by Venkatesh and Cohen.

In contrast, a recent meta-analysis (incorporating the CORTICUS results)[9] disagrees with the second of the implications of Venkatesh and Cohen's argument, finding that in 12 randomised placebo-controlled trials of low-dose steroids there is overall evidence for benefit in septic shock. Current recommendations[6,8] reflect this conclusion. On the best available trial evidence, steroids appear to be beneficial, even if "relative adrenal insufficiency" or the "sick adrenal state" do not exist. This begs the question: do we need to understand *how* something works to use it? Physicists using gravity in their calculations, and anaesthetists using volatile anaesthetics in their practice, would argue not.

Those who believe in the efficacy of steroid supplementation in septic shock may be disappointed that Venkatesh and Cohen find the articulated biological rationale for this approach is flawed. However, extrapolating knowledge of biological abnormalities to guide therapy has not been particularly successful in other aspects of critical care endocrinology. Levels of growth hormone and insulin-like growth factor-1 are both reduced in critical illness (reviewed by Taylor and Buchman[10]), but supplementing growth hormone in critical illness roughly doubled the risk of death.[11] Thyroid hormone

levels are also decreased in critical illness,[12] predicting mortality,[13] but, despite promising evidence in an animal model,[14] thyroxine supplementation has been unsuccessful in limited clinical trials.[15,16] Patients with sepsis have insulin resistance,[17] and, although under certain conditions intensive insulin therapy was beneficial,[18] when widely implemented this strategy was harmful.[19]

Many parameters measured in critical illness are likely to be effects of, or even appropriate compensations for, the disease process, rather than mediators of adverse outcome. Critical care physicians increasingly understand that noting something is abnormal does *not* mean that fixing it will help. When this is forgotten, much effort is expended in achieving "euboxia" (all the boxes on the pathology print-out in the normal range), but the patient still dies. A favourite example demonstrating the irrelevance of the epiphenomena of critical illness is the number of relatives gathered around a patient's bed. Having more than two relatives is generally associated with a poorer prognosis — but asking relatives to leave rarely helps. (Of course, having no relatives by the bedside when critically ill is also often a bad prognostic sign — when the number of relatives does not increase appropriately with illness severity, perhaps this could be called a "relative relative insufficiency".) The point is that our incomplete understanding of the pathogenesis of critical illness has meant that attempts to normalise what we observe have rarely been beneficial — particularly in critical care endocrinology. The finding that measured indices of corticosteroid function may not reflect the potential benefit of supplemental steroids should therefore not be too disappointing.

Current international guidelines[6,8] (admittedly lacking Australasian endorsement[20]) recommend steroids for all patients who do not respond satisfactorily to fluid and vasopressors. However, probably there is a subset of patients who do derive benefit, and another subset who do not. If we could measure the factors listed by Venkatesh and Cohen in our patients, we might be able to distinguish these two groups. A likely major advance in intensive care medicine in the next decade will be an improved ability to select the appropriate patients for our existing treatments. This selection might be based on pharmacogenomic information (for example, genetic polymorphisms that identify patients who will respond to recombinant human activated protein C[21]), but probably also on a better ability to characterise individual patients' cellular function.

The article by Venkatesh and Cohen should therefore be seen as a call to better explore abnormalities of corticosteroid function at a cellular level, as well as to develop technology that can rapidly characterise these abnormalities in individual patients. In the meantime, though, the clinical trial evidence for low-dose steroids in septic shock should be appraised on its merits, not discounted simply because the mechanism of any effect has not yet been discovered.

See also Cohen and Venkatesh (page 287).

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