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EDITORIAL I

Therapy for sepsis: Einstein once said. . .

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Severe sepsis is a deadly, under-appreciated, under-diagnosed, under-investigated yet frighteningly common syndrome.[1–3] Data now over a decade old indicate that it kills nearly a quarter of a million people in the USA each year.[3] The toll in the under-resourced world, where the few interventions that seem to work are often unavailable, is likely to be in the millions. It is increasingly appreciated that those victims who survive may be left with significant respiratory, locomotor, neurologic, and cognitive dysfunction.[4–6] While implementation of the guidelines provided by the Surviving Sepsis Campaign (SSC),[7] a concerted effort by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine to increase the use of evidence-based management approaches, has improved recovery from acute septic episodes,[8] a recent study indicates that 3-year mortality is an astonishing 70%.[6] Those of us who care for septic patients are probably entitled to occasional fits of depression.

To most clearly illustrate the origin of the frustration felt by practitioners of *Critical Care Medicine*, it is instructive to consider the chain of events that began with the March 8, 2001 issue of the *New England Journal of Medicine*. The journal contained the results of the PROWESS study, heralding a major breakthrough in the treatment of sepsis—the drug drotrecogin alpha, a recombinant, activated form of the endogenous anticoagulant protein C.[9] The accompanying editorial[10] summarized the feelings of many intensivists in noting that recent therapeutic approaches to sepsis had been unsuccessful and then stated 'At last, however, there has been progress in finding an effective new therapy for sepsis'. Protein C has both anti-coagulant and anti-inflammatory properties.[10] It was known to be deficient in septic patients[11] and was touted as the link between excessive inflammation and aberrant coagulation, both hallmarks of severe sepsis. However, concerns about the drug, marketed by Eli Lilly and Co as *Xigris*, soon became apparent. *Xigris* was conditionally approved by the US Food and Drug Administration in November of 2001 despite a 10–10 vote by the Advisory Panel reviewing the data.[12] Similar concerns led the Committee for Medicinal Products for Human Use of the European Medicines Agency to grant approval contingent on a repeat of the PROWESS trial. After a number of years and several additional publications, the new investigation, designated PROWESS-SHOCK, was initiated in 2007.[13] In October of 2011 Lilly abruptly withdrew *Xigris* from the market. Later that day release of the results of the PROWESS-SHOCK trial in essence refuted the results of the earlier trial and failed to demonstrate efficacy.[14] And clinicians who had spent decades treating sepsis with only supportive measures—mechanical ventilation, fluid administration, antibiotics to address those cases where a causative organism could be identified—were again faced with an empty feeling as a seemingly promising therapy failed.

Our sense of futility was not a new experience. A quick PubMed search reveals 117 papers detailing results of multicentred, randomized, controlled trials of therapies for sepsis. These involved ~60 different agents, each supported by some preliminary study suggesting efficacy. In the majority of the trials, results were indistinguishable from controls. Seven interventions made matters worse and eight appeared to improve outcome. However, as occurred with *Xigris*, the benefits of all eight were either called into question or refuted by later studies.

It is important to recall this tale of woe whenever we consider the results of a study designed to alter the seemingly intractable pathobiology of sepsis. In a recent issue of *BJA*, Lowes and colleagues[15] present the results of a study examining antioxidants that preferentially protect mitochondrial function in a rat model of 'acute sepsis'. The study rests on a sound physiologic foundation; data from both animal models of sepsis[16] and from septic patients[17] reveal mitochondrial dysfunction. The results of the experiments conducted by Lowes and colleagues demonstrate the anticipated improvement in the function of mitochondria isolated from the liver and an associated reduction in liver and kidney damage. These data are robust—there is no question that the use of the three mitochondrially directed antioxidants (MitoE, MitoQ, and melatonin) restore mitochondrial metabolism, reduce serum levels of cytokines and markers of hepatic and renal dysfunction in the study animals. Based on these results, it would be tempting to begin planning a human trial. So, should we?

To answer this question, it is especially important to consider why previous approaches that seemed to hold such promise ultimately failed. The most commonly invoked explanations centre on the difficulties inherent pre-clinical testing. For complex disorders like sepsis this most often involves animal models that may not properly mimic clinical conditions or time course. Human sepsis is characterized by an acute/subacute onset but severe sepsis is most often heralded by a decrease in arterial pressure. The SSC guidelines, to be fully initiated within 6 h, directly target the acute phase primarily with fluid, vasopressor drugs and early administration of broad-spectrum antibiotics.[7] In most cases, this approach will stabilize the patient. Adherence to the SSC guidelines has been shown to improve outcome[8] so that death within hours of the onset of severe sepsis or septic shock has become increasing unusual. Rather, the onset and resuscitation most often are followed by a period of several days when organ dysfunction—the acute respiratory distress syndrome, jaundice, increasing serum creatinine, myocardial depression, anergy, etc.—becomes apparent. Some patients will indeed die as organ dysfunction develops. Others will recover, often with functional deficits that are not paralleled by altered morphology or massive cell death. A substantial number, however, develop what, for lack of a better term, has been labelled 'chronic critical illness'. Death in these patients most often occurs when families decide to withdraw mechanical ventilation or not to initiate other forms of exogenous support.

It is clear that extrapolation from animals to humans requires use of the best model available. Yet, animal models of sepsis, most often conducted in mice or rats, have significant inadequacies.[18] Lowes and colleagues modelled 'acute sepsis' by administering an i.v. bolus of fluid containing lipopolysaccharide (LPS) a component of the cell wall of Gram-negative bacteria, and peptidoglycan G, derived from Gram-positive organisms. At one time, LPS was used to mimic sepsis but this approach is no longer considered an appropriate model. The defining characteristic of bolus LPS administration is a sudden, massive inflammatory insult involving release of massive amounts of pro-inflammatory cytokines—TNFα, IL-1β, IL-6, etc.—into the blood stream.[18] This inflammatory insult is accompanied by significant organ damage, a need for mechanical ventilation, a substantial increase in circulating levels of hepatic transaminases and high mortality within a very short period of time—mortality in Lowes' untreated animals was 25% within the first 5 h. This fulminant course is quite different from the description of human sepsis detailed in the last paragraph. The cytokine response in humans is variable but hugely increased plasma levels of the magnitude reported by Lowes and colleagues are distinctly unusual. In fact, recent evidence suggests the very early onset of immune depression, not of an over-exuberant inflammatory response.[19] In addition, hepatic transaminases in human severe sepsis are at most mildly elevated. Mortality for the entire spectrum of human sepsis, from septic shock to chronic critical illness, is $\sim$25%. Clearly, the LPS-peptidoglycan model does not really model human sepsis. It would be prudent to assure that any new therapeutic approach works on animal models that most closely resemble the disorder in question. Thus, the studies with MitoE, MitoQ, and melatonin should be repeated using a better murine approximation of the human condition. Examples would include the introduction of bacteria into the lungs of rodents to cause pneumonia, the most common cause of sepsis in humans, or use of cecal ligation and puncture or intra-peritoneal implantation of an infected fibrin clot to mimic intra-abdominal sepsis. These models are hardly fool-proof—rats and mice are far more robust immunologically than humans—but they are closer to 'the real thing' than i.v. injection of toxic doses of bacterial component.

But it is also essential to consider other possible explanations for the failure of therapy to extrapolate from animals to humans or from small, targeted studies to large, randomized prospective trials. Virtually every intervention tried for sepsis has been based on a common underlying hypothesis—that sepsis results from a dysfunctional immunologic response. The thinking has been that early prevention or reversal of this dysregulation will arrest the progression of sepsis to fulminant death, organ dysfunction, or chronic critical illness. But this approach has not worked. The use of *Xigris*, for example, was based on the premise that it had anti-inflammatory properties. It may be time to consider an alternate hypothesis, one that is not based on the primacy of immune dysfunction on the pathogenesis of organ failure or chronic critical illness. A characteristic of chronic critical illness is a 'disconnect' between organ systems, that is, organ systems do not act in a coordinated manner but rather function as if they had no information about the activity elsewhere in the body. For example, hepatic gluconeogenesis is increased despite the development of a metabolic state characterized by glucose intolerance and insulin resistance. Communication between organ systems is mediated by white cells to some degree but also by the endocrine and central nervous (CNS) systems. Vanhorebeek

and Van den Berghe[20] have documented the development of a profound endocrinopathy in chronic critical illness. Our own animal work,[21] and that of Chavan and colleagues,[22] suggest significant disruption of specific CNS pathways. Perhaps, it is time to more thoroughly explore these abnormalities. It would be interesting to see how MitoE, MitoQ, and melatonin effect neuronal and endocrine responses—in an appropriate animal model—before initiating a clinical trial.

Einstein is reputed to have stated that insanity is performing the same experiment again and again in the hope of getting a different result. We should consider this statement whenever we explore new approaches to the treatment of sepsis.

Declaration of interest

None declared.

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