ANSWERING REVIEWERS

January 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6885-review.doc).

Title: The Metabolic Theory of Septic Shock

Author: Jay Pravda
Name of Journal: *World Journal of Critical Care Medicine.*

ESPS Manuscript NO: 6885

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated and core tip added.

2. Revisions have been made according to the suggestions of the reviewers.

Reviewer 1 (#889)
(1) The reviewer is correct. The Theory states that H_2O_2 has a causal relationship with septic shock.
(2) The reason for N-acetylcysteine's therapeutic failure has been added to the discussion.
(3) The aim of this paper is to present a scientifically coherent evidenced based theory that supports a causal role for H_2O_2 in the pathogenesis of septic shock. It is not a general review of radical species produced in biological systems since that is not the focus of the paper. There are many fine reviews on this topic.
(4) I agree. Peroxidation is mentioned in the context of cell membrane lipids.

Reviewer 2 (#506093)
(1) The bibliography was constructed using a modified disease vector analysis (DVA) algorithm to identify biochemical reactions that fulfill the "what-if" criteria postulated by the proposed pathogenesis.
(2) Unpublished data has been removed.
(3) I have chosen to overlap the main concepts because the theory is novel and contains a fair amount of redox biochemistry which not all readers will be familiar with. I have re-introduced the discussion section with modifications to make it more clinically relevant to the reader.

Reviewer 3 (#503099)

(1) I agree with the reviewer's general assertion that credit for prior work should always be given since virtually all discoveries in science rest on the shoulders of giants that have preceded us. In acknowledgement of previous work that provided the raw data for my novel theory of septic shock I have cited 100 references. I have since read the reference cited by the reviewer and it does not "echo the conclusions" drawn in my paper. The specific article referenced by the reviewer is a descriptive review whose conclusion is outlined in the first paragraph of the paper and states that "Dysregulation of this (immune) response may occur in sepsis leading to excessive or inappropriate release of mediators and ultimately host cell and end organ damage". The author goes on to describe how sepsis associated redox abnormalities can impact immunogenic activation.

In contrast, my manuscript proposes a new theory of septic shock pathogenesis, outlines a specific (non-immune) biological pathway leading to septic shock and identifies a non-immune metabolically generated causal agent (H_2O_2) responsible for this lethal condition. Implicit in my theory is the notion that immune mediators <u>are not</u> the cause of end organ damage in septic shock. This is in contradistinction to that which is stated in the first paragraph of the review cited by the reviewer. Both papers are completely different in aim and scope. My conclusions are not echoed in the 2003 review referenced by the reviewer.

The reviewer's comment, however, does bring to mind that there is a great deal of research data being generated without integration into a broader picture of human disease. Whether this is related to time constraints on behalf of the laboratory based researcher, to the big-business self-perpetuating nature of modern medical research that has lost sight of its primary responsibility to society and/or the failure of our educational system to stimulate and encourage creative thinking are important topics for a broader debate. This underscores the urgent need for a separate discipline of theoretical medicine and biology to provide an intellectual haven for creative and innovative thinkers to study and integrate into new models of pathogenesis the immense amount of cumulative data that laboratory based researchers continue to generate.

Reviewer 4 (#68168)

(1) I have proposed a specific mechanism of disease to explain the development of septic shock which entails the hypermetabolic generation of H_2O_2 as the causal vector responsible for the microangiopathic dysfunction and end organ failure. My paper is not about the mechanism of action of H_2O_2 in sepsis. Thus, the subtitle "Mechanism of disease" is appropriate in this context.

(2) Hypermetabolic Response was chosen because it is an intuitively understandable clinical surrogate for the underlying bioenergetic abnormalities that occur during the sepsis continuum. It also correlates with the clinical parameters that are used to define SIRS (tachycardia, tachypnea, hyperthermia and leukocytosis). Hypermetabolic response is also a useful springboard from which to introduce the mechanism of increased H_2O_2 generation. When correlated with a clinical identifiable risk factor, such as a hypermetabolic response, the resultant generation of H_2O_2 becomes relevant and meaningful to clinicians, who are reading about this new mechanism for the first time.

(3) The subtitle has been re-written to clarify its intended meaning.

(4) The passage has been replaced with two shorter sentences that more succinctly convey its message and meaning.

(5) I conceived of and commissioned the figure.

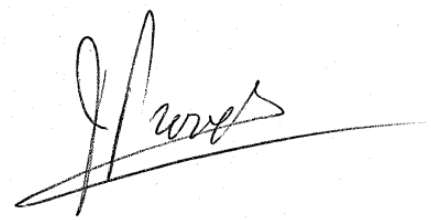
(6) "Systemic' has been replaced with "systemically elevated" to refer to the systemically elevated nature of the microangiopathic agent (H2O2) in septic shock.

(7) Septic encephalopathy refers to the specific situation in which the infection is directly invading the central nervous system. Sepsis associated encephalopathy is the more broader situation in which an infection in an area away from the brain (bacteremia, extra CNS abscess) can lead to encephalopathy without direct invasion of the central nervous system. Elevated systemic levels of H2O2 can explain encephalopathy in the absence of direct CNS infection. I have changed "sepsis encephalopathy" to "sepsis associated encephalopathy" in fig. 2 to more clearly convey this concept.

3 References and typesetting were corrected

Thank you again for publishing my manuscript in the *World Journal of Critical Care Medicine*.

Sincerely yours,



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