phylactic or therapeutic mediator blockade aimed at minimising or even counteracting the impact of second hits in surgical patients.

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Commentary

The article by Saadia and Schein on multiple organ failure (MOF) asks a fundamental question relating to its pathophysiology. In the late 1970s about 20% of trauma deaths were described as occurring "late". Nearly all of these were the result of MOF in its various guises.¹ Twenty years on the proportion of "late" deaths has not changed.² MOF remains the main cause of "late" trauma deaths.^{3,4} Despite advances in intensive care and supportive treatment for failing organs the last 20 years have been marked by no discernible reduction in MOF mortality.^{5,6} The key to improving this situation, apart from reducing the number of accidents, is to reach a better understanding of the link between trauma and the subsequent development of organ failure, often many days later.

The "two hit" concept provides just such a link. In essence though, like many other ideas in the pathophysiology of trauma, it is not a new one. The Schwartzman reaction is the classic example of a two hit process. A rabbit is prepared by an intradermal injection of endotoxin. An intravenous injection of endotoxin, given after a latent period (usually 24 hours), then results in a haemorrhagic and necrotic lesion at the site of the initial inoculation. The second insult does not have to be endotoxin: relatively innocuous substances, such as agar and starch, will also provoke the reaction. An appreciation of this reaction led Jacob Fine's team to perform experiments in the 1950s, which showed that after haemorrhagic shock dogs were unable to resist a normally non-lethal dose of *Escherichia coli*.⁷ At the time neutrophil priming and activation were unknown concepts, but it was clear that for a 48 hour period after the haemorrhagic insult there was a deficiency in the host defence mechanism. A reduction in leucocyte mobilisation was postulated.

This type of experimental model has been revisited.⁸ One group of pigs received a 30 minute *E coli* infusion two days after a four hour "Wigger's" type haemorrhagic insult and resuscitation.⁸ Pigs receiving this double insult showed greater reductions in blood pressure,

gut blood flow, gut oxygen delivery, and gut oxygen consumption, than those subjected to either haemorrhage alone or *E coli* alone. On day 5 they took biopsy specimens of mesenteric lymph nodes, liver, spleen, kidneys, and lungs. Gut derived bacteria were found in the mesenteric lymph nodes of animals from all the groups, but there was more translocation to the solid organs of animals in the haemorrhage plus *E coli* group than in the single insult groups. Translocation of gut derived bacteria to arterial blood was only seen in the haemorrhage plus *E coli* group.

Animal models seem to provide good evidence for the two hit model. However, one of the recurring themes in research into the pathophysiology of sepsis and MOF is the contrast between results from laboratory studies (using in vitro techniques or whole animal models) and clinical studies. This has been especially apparent in the case of bacterial translocation. Bacterial translocation has been demonstrated in many rodent models.⁹⁻¹² In large animal models translocation has been demonstrated by some,¹³⁻¹⁴ but not others.¹⁵⁻¹⁷ In traumatised humans several groups found no evidence of translocation from blood and lymph node cultures,¹⁸⁻¹⁹ but did find evidence from immunofluorescence,²⁰ or electron microscopy.²¹

The same appears to be happening with the two hit model.

Some of the cytokine studies have hinted that there is a second inflammatory response related to late complications in trauma patients. A secondary increase in IL-6 and IL-8, after the resolution of the immediate post-injury increase, was documented in two trauma patients developing a leucocytosis and fever.²²

Svoboda *et al* found that cytokine concentrations were initially elevated and then gradually declined after trauma.²³ In patients going on to develop MOF there was a second increase in cytokine concentrations. In the non-survivors this was unremitting, while in the survivors cytokine concentrations gradually decreased. The trigger for the secondary increase in cytokines was not determined but it might be interpreted as either the result of a "second hit" from outside or a secondary failure of endogenous anti-inflammatory mechanisms. Some supportive evidence for this comes from a study into the production of soluble tumour necrosis factor receptors (sTNF-R) after trauma.²⁴ These receptors are known to have a protective effect in models of endotoxaemia.²⁵ In the clinical study not only were sTNF-Rs present within one hour of trauma and remained raised until day 15 but also, "Daily variations in sTNF-R levels correlated with clinical situations in individual patients. In particular, receptor levels seemed to decline during critical episodes of sepsis or hypoxia".

An editorial in 1996 summarised the situation, "Sepsis, the systemic inflammatory response syndrome, and multiple organ failure

remain critical obstacles to further improvement in survival of these patients. A better understanding of multiple organ failure after injury is required: the search for a unitary theory is still on".²⁶ The search is still on. We do not know very much about the second "hit", but the circumstantial evidence for its existence is accumulating.

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