THE GUT IN SEPSIS

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In the sixties, Evans and Darin [1] demonstrated that a 90% distal enterectomy protected dogs from endotoxic shock: survival was improved from 13% in control animals to 52% in enterectomy treated animals. Accordingly, the authors suggested the gastrointestinal tract has an important role in the pathogenesis of organ failure and death in septic shock. Based on a growing body of evidence, Meakins and Marshall [2] later proposed in a review article that the gut may act as a ‘motor’ of the multiple organ dysfunction syndrome (MODS). Their original proposition was that gut mucosal dysoxia (i.e., oxygen supply insufficient to meet oxygen requirements) occurs during shock states as a consequence of an inadequate splanchnic oxygen delivery (DO₂) to oxygen uptake (VO₂) and as a cause of loss in gut mucosal barrier. Hyperpermeability would then result in bacterial or endotoxin translocation leading, ultimately, to remote organ injury and MODS. This hypothesis could explain the clinical paradoxes observed in septic MODS:

1. organs that fail frequently are not initially directly injured
2. there is a lag period of time between the initial insult and the development of MODS
3. not all patients with clinical sepsis and MODS have microbiologic evidence of infection
4. no septic focus can be identified clinically or at autopsy in more than 30% of bacteremic patients dying of clinical sepsis and MODS
5. identification and treatment of suppurative infections in patients with MODS may not improve survival.

However to date, there is no demonstrated causal relationship between increased intestinal permeability and the severity of splanchnic ischemia,
infectious complications or MODS score [3]. Bacterial translocation and changes in intestinal permeability may be independent process, and the correlation between survival and bacterial translocation is certainly related to the magnitude of the inflammatory insult [4], but the potential relationship between gut barrier failure function or injury and MODS may be more complex than initially assumed.

Experimental and clinical evidence [5-7] suggests that, during septic shock, altered blood flow distribution within the gut wall may contribute to the generation of mucosal hypoxia and hyperpermeability, despite normal or increased overall splanchnic blood flow. However, other reports [8-10] suggest that gut mucosal hyperpermeability in sepsis might not be solely due to the decrease in mucosal perfusion. Abnormal or decreased utilization of oxygen by epithelial cells has been advocated to explain observed abnormalities [11]. This chapter will review how both hypotheses are currently presented.

**CIRCULATORY SHOCK AND GUT MUCOSAL HYPOPERFUSION**

The intact mucosal barrier is thought to play an important role in defending the host from translocation of intact microorganisms or their breakdown products and toxins [12]. The mucosa is the mucous membrane that lines the digestive tract. It consists of three layers: an epithelial layer, the lamina propria, and the muscularis mucosa. The submucosa contains blood vessels, lymphatics, nerves, and in some regions glands. Mucosal blood flow in the intestine originates from the submucosal arterioles that arborise into a dense network of capillaries. These capillaries pass through the mucosa, supply the crypts and extend into the mucosal villi [13]. Venous blood from mucosal capillaries drains into the mucosal venules, which eventually re-enter the submucosa.

The mucosa vascular architecture creates a situation where the oxygenation of cells at the tips of the villi are relatively susceptible to conditions that reduce the overall oxygen supply to the mucosa. The capillaries supplying blood flow to the intestinal villi form a ‘hairpin loop’ arrangement, with arteriolar and venular ends coursing in parallel along the villus which has the potential to create a countercurrent exchange of oxygen from the inflow vessels to the outflow vessels with a base-to-tip gradient in the partial pressure of oxygen. The extensive length of the capillaries supplying the villi magnifies this gradient between the base and tips of the villi, with lower oxygen tensions at the apex of the hairpin loop [5, 14]. This