An evolving ability to support vital organ system function during a period of otherwise lethal physiologic insufficiency changed the process of hospital care over the last half of the 20th century. Over a relatively short period, the development of techniques of positive pressure ventilation, hemodialysis, and invasive monitoring and cardiovascular support transformed life-threatening illness from a rapidly lethal event to a chronic state that was, potentially, survivable. The impact has been profound; for example, the mortality of abdominal trauma on the battlefield was virtually 100% before World War I but had fallen to 2% to 3% during the Arab-Israeli conflict in 1973 (1). Necrotizing pancreatitis was uniformly lethal in the early 20th century (2); today, the majority of patients survive. Advances in the support of vital organ function gave rise to intensive care units (ICUs) as dedicated geographic venues for the administration of these technologies (3) and spawned an entirely new specialty—intensive care medicine.

The cost of this progress has been considerable. The provision of critical care services consumes more than 1% of the gross national product of many countries of the developed world (4). Moreover, the very successes of this new discipline have created an entirely unprecedented spectrum of clinical problems, arising in the wake of the profound physiologic derangements of critical illness and the heroic interventions applied to reverse them. For example, the emergence of Gram-negative organisms as significant pathogens in hospitalized patients is a phenomenon of the last half of the 20th century (5), and their subsequent replacement by relatively avirulent organisms such as coagulase-negative *Staphylococcus*, *Candida*, *Pseudomonas*, and the *Enterococcus*, is an even more recent development (6). The syndrome of acute lung injury known as acute respiratory distress syndrome was first described less than four decades ago (7), and the role of the mode of support in the syndrome’s evolution has been appreciated only in the last few years (8). Similarly, septic shock became a describable entity (9) only after resuscitation and organ system support techniques were sufficiently effective that overwhelming infection ceased to be a rapidly lethal event and was transformed into a prolonged, but survivable, process.

The ICU made possible a spectrum of disorders that are characterized by their strong association with inflammation and described by their effects on the function of individual organ systems: the acute respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation, septic shock, and stress gas-

**Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome**

*John C. Marshall, MD, FRCSC*

**Objective:** An improved understanding of the mechanisms through which infecting pathogens harm the host is leading to new formulations of the concept of sepsis. We review the roles of inflammation and coagulation in the pathogenesis of the multiple organ dysfunction syndrome, and explore the potential of new therapies to restore the fine biological balance between procoagulant and anticoagulant mechanisms that are disrupted during the life-threatening processes that lead to organ dysfunction.

**Data Sources:** Narrative review of published primary sources in the basic and clinical literature.

**Data Summary:** Traditional models of host-pathogen interactions ascribe the morbidity of infection to the direct cytotoxic effects of micro-organisms on host tissues. However, abundant experimental and clinical evidence has revealed that it is the response of the host, rather than the trigger that elicited it, that is the more potent determinant of outcome. The elucidation of a complex network of host-derived inflammatory mediators raised the possibility that targeting these individually could improve patient outcomes, and some modest successes with this approach have been achieved. More recently, it is becoming evident that the inflammatory response, in turn, mediates its deleterious effects by inducing tissue hypoxia, and cellular injury, either through tissue necrosis or through the induction of programmed cell death or apoptosis. Thus, treatment strategies that target the downstream consequences of the activation of inflammation, for example, microvascular coagulation or acute adrenal insufficiency, represent the latest, and some of the most promising approaches to attenuation of the septic response to improve survival, and minimize organ dysfunction. The maladaptive sequelae of systemic inflammation, embodied in the concept of the multiple organ dysfunction syndrome, comprise the leading obstacle to survival for patients admitted to a contemporary intensive care unit. Further insights into this intimidatingly complex process will not only provide potent new therapeutic options, but promise to transform critical illness from a biological standoff, during which the clinician merely supports failing organs, to a disease that can be successfully treated.

**Key Words:** sepsis; multiple organ dysfunction syndrome; inflammation; coagulopathy; apoptosis; complexity theory

---

*From the Department of Surgery and the Programme in Critical Care Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada.*

*Presented, in part, at the Margaux Conference on Critical Illness, Margaux, France, November 8–12, 2000.*

*Address requests for reprints to: John C. Marshall, MD, 9 Eaton North, Room 234, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada. E-mail: john.marshall@uhn.on.ca*

*Copyright © 2001 by Lippincott Williams & Wilkins*
tissue factor pathway inhibitor; TNF, tumor necrosis factor.

Dysregulated apoptosis Increased epithelial and lymphoid apoptosis, decreased
Gut-liver axis Increased infection with gut organisms, endotoxia, Kupffer
Cell activation

MODS is widely considered to be the leading cause of morbidity and mortality for patients admitted to an ICU (16–19). However, despite its immediate and infinitely recognizable manifestations in the critically ill patient, its characterization as a discrete syndrome with a common and measurable pathologic basis has been problematic. First, patients admitted to an ICU frequently have some degree of preexisting physiologic impairment, so that it may be difficult to differentiate derangements that are acute and potentially reversible from those that are chronic and irreversible. Second, the spectrum of disorders that lead to ICU admission commonly includes diseases that cause direct organ injury, for example, pneumonia or trauma producing acute lung injury, or mesenteric vascular ischemia causing liver dysfunction. Finally, the challenge in characterizing organ dysfunction in biochemical terms has been not a lack of definable abnormalities, but a surfeit (Table 1). Literally hundreds of biochemical and cellular abnormalities have been described in patients with MODS, and their very number has made it difficult, if not impossible, to define a single common underlying event or process as the pathogenic basis of the disorder. Indeed, it is not at all clear whether MODS is a single pathologic process with highly variable clinical expression or simply the limited phenotypic expression of a large number of pathologically divergent processes.

This paper will review the more prominent theories about the pathogenesis of MODS, recognizing that the mechanisms that have been proposed are by no means exclusive and are often best viewed as differing perspectives on common pathologic processes.

Uncontrolled Infection

The first descriptions of the MODS emphasized its common association with occult or poorly controlled infection (9, 13, 20), frequently either peritonitis (14) or pneumonia (21). However, more recent reports indicate that infection, although common in patients with MODS, is not necessarily present (22) and frequently follows, rather than precedes, the development of the syndrome (6). Indeed, nosocomial infection may be better considered a manifestation of MODS than a cause of it. Characteristic infecting flora include opportunistic organisms of low intrinsic virulence (notably Candida, coagulase-negative Staphylococci, Pseudomonas, and Enterococci) (6), as well as species whose emergence reflects local environmental factors (notably Acinetobacter and Stenotrophomonas) or selective antimicrobial pressures (methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and extended-spectrum β-lactamase–producing Gram-negative organisms). Indeed, the prevalence of infection with the former group of organisms is strongly associated with the severity of MODS (Fig. 1) (23).

Microbial products such as endotoxin may also be a cause of MODS. Endotoxemia is much more common in the critically ill patient than is documented infection (24) and correlates poorly with culture-proven infection (25), suggesting an important role for the absorption of endotoxin from the gastrointestinal tract (26) or lung (27).

It is generally accepted that the morbidity of bacterial infection arises indirectly, through such downstream effects as the activation of an inflammatory response or the induction of intravascular coagulation in the host. However, bacterial products can be directly toxic to cells, altering fundamental cellular processes, as in the case of cholera toxin, or inducing the apoptosis, or programmed cell death, of neutrophils (28, 29) and epithelial cells (30).

Although infection commonly triggers MODS, the evidence that infection plays an important role in the evolution of the syndrome is not compelling. Meta-analyses of the effects of infection prophylaxis using the techniques of selective digestive tract decontamination show a striking reduction in rates of such infections as pneumonia, wound infection, and bacteremia but a much more modest, albeit statistically significant, reduction in mortality (31, 32). Moreover, peritonitis and pneumonia are frequent causes of MODS, but the evidence that successful treatment of either alters outcome is far from compelling (33–36). The pathogenic role of endotoxin is equally uncertain:

Table 1. Conceptual models of multiple organ dysfunction syndrome

<table>
<thead>
<tr>
<th>Pathologic Process</th>
<th>Manifestations</th>
<th>Therapeutic Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled infection</td>
<td>Persistent infection, nosocomial ICU-acquired infection, endotoxemia</td>
<td>Aggressive use of antibiotics and source control measures</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Cytokinemia (particularly IL-6, IL-8, TNF), leukocytosis, increased capillary permeability</td>
<td>Neutralization of specific cytokines (IL-1, TNF, PAF) or of activational pathways</td>
</tr>
<tr>
<td>Immune paralysis</td>
<td>Nosocomial infection, increased anti-inflammatory cytokine levels (IL-10), decreased HLA-DR expression</td>
<td>G-CSF, interferon</td>
</tr>
<tr>
<td>Tissue hypoxia</td>
<td>Increased lactate</td>
<td>Augmentation of DO₂</td>
</tr>
<tr>
<td>Microvascular coagulopathy and endothelial activation</td>
<td>Increased procoagulant activity, decreased anticoagulant activity, increased von Willebrand factor, soluble thrombomodulin; increased capillary permeability</td>
<td>Augmentation of anticoagulant mechanisms (APC, TFPI, antithrombin)</td>
</tr>
<tr>
<td>Dysregulated apoptosis</td>
<td>Increased epithelial and lymphoid apoptosis, decreased neutrophil apoptosis</td>
<td>Caspase inhibition</td>
</tr>
<tr>
<td>Gut-liver axis</td>
<td>Increased infection with gut organisms, endotoxemia, Kupffer cell activation</td>
<td>Selective digestive tract decontamination, enteral feeding</td>
</tr>
</tbody>
</table>

APC, activated protein C; G-CSF, granulocyte colony-stimulating factor; ICU, intensive care unit; IL, interleukin; PAF, platelet activating factor; TFPI, tissue factor pathway inhibitor; TNF, tumor necrosis factor.
none of the dozen or more clinical trials that have evaluated endotoxin neutralization as a therapeutic strategy have shown unequivocal evidence of benefit, and at least one (37) raised the possibility that such an approach might be harmful.

Uncontrolled Systemic Inflammation

Clinical evidence of systemic inflammation is evident in almost all patients developing MODS (38–40); in fact, remote organ dysfunction can be considered the *functio laesa* of systemic inflammation. Although it is difficult to differentiate the clinical manifestations of inflammation from the infections that are commonly their cause, it can be shown that the severity of the clinical inflammatory response, rather than the presence or absence of infection, is the more important determinant of ICU survival (39) (Fig. 2).

An extraordinary number of proinflammatory mediator molecules have been implicated in the expression and resultant morbidity of a systemic inflammatory response. The lethality of murine endotoxemia, for example, can be prevented by specific neutralization of more than two dozen inflammatory mediators, including interleukin (IL) 1, tumor necrosis factor (TNF), high mobility group 1, interferon γ, leukemia inhibitory factor, macrophage migration inhibitory factor, IL-12, and phospholipase A2 (41), although their neutralization has variable effects in other models. Cohort studies in critically ill patients show that increased circulating levels of cytokines such as TNF and IL-6 (42–44), or markers of increased release of TNF in response to inflammatory stimuli (45, 46) are associated with organ dysfunction and an increased risk of death.

Although the synthesis and release of a panoply of biochemical mediators of inflammation is characteristic of both experimental and clinical sepsis, the mechanisms through which these molecules may induce organ injury are much less clear. The cellular receptor for tumor necrosis factor is a member of the Fas family of death receptors that are capable of initiating apoptosis or programmed cell death in their cellular targets (47). However, the same receptor delivers an inflammatory and antiapoptotic signal to cells such as neutrophils, and the extent to which the effects of TNF reflect direct cellular injury is uncertain. TNF and other proinflammatory molecules can also activate downstream effectors of acute inflammation, for example, by up-regulating the expression of inducible nitric oxide synthase (48), which results in increased release of nitric oxide and its attendant effects on microvascular resistance and capillary flow, or by augmenting neutrophil cytotoxic mechanisms by inducing the release of oxygen radicals and proteolytic enzymes (49, 50). Moreover, proinflammatory mediators can also up-regulate endothelial cell adhesion molecule expression (51) and activate endothelial procoagulant activity (52), while inhibiting the expression of thrombomodulin (53, 54), a critical factor in the activation of the protein C anticoagulant pathway.

An alternate model of the dysregulated inflammatory response that accompanies MODS suggests that the problem is not so much excessive inflammation as an acquired state of immunodeficiency or immune paralysis (55). The potential manifestations of this state of impaired immunity are many and include anergy to delayed hypersensitivity recall testing with common antigens (56), impaired de novo antibody synthesis to tetanus toxoid (57), reduced monocyte expression of human leukocyte antigen-DR (HLA-DR) (58), and increased circulating levels of counterinflammatory cytokines such as IL-10 (59) and transforming growth factor β (60).

Clinical trials of a variety of strategies designed to inhibit inflammation in critical illness have generally yielded disappointing results, with pooled data from studies of the neutralization of TNF or IL-1 in sepsis showing a small but significant absolute mortality reduction of 3.5% to 5% (61). A recently completed, unpublished North American study of afelimomab, a monoclonal antibody to TNF, suggested that this mortality benefit can be increased if patients with an exaggerated inflammatory response reflected in elevated circulating levels of IL-6 are targeted and that neutralization of TNF also reduces the severity of organ dysfunction developing subsequent to the onset of treatment. However, the rela-
Apoptosis is fundamental to such processes as embryologic development, immune maturation, aging, cell turnover at epithelial surfaces, and the resolution of inflammation. The expression of apoptosis is altered in critical illness. Apoptosis of lymphocytes and gut epithelial cells is increased (79, 80), whereas that of neutrophils is delayed (81–83). Excessive apoptosis has been implicated as a mechanism of liver (84), kidney (85), and cardiac (86) disease, and interventions that modulate the expression of apoptosis can improve outcome in a variety of experimental models of inflammation (87). Intriguingly, the induction of apoptosis by *Pseudomonas* in tracheal epithelial cells (88) or by *Escherichia coli* in lung neutrophils (89) results in improved survival in experimental pneumonia and intestinal ischemia/reperfusion injury, respectively.

Therapies targeting the expression of apoptosis are not yet clinically available; therefore, their ability to prevent organ dysfunction in the critically ill patient remains unproven.

**Microvascular Coagulopathy**

The mechanisms that regulate the expression of inflammation are intimately linked to those that control the expression of coagulation, and multiple lines of evidence point to a pivotal role for inappropriate intravascular coagulation as a final common pathway to organ dysfunction. Cohort studies demonstrate a striking association between dysregulated coagulation and the development of organ dysfunction. In a longitudinal study of 136 patients who had sustained multiple trauma, Gando and colleagues (90) showed that early evidence of disseminated intravascular coagulation was a powerful predictor of subsequent organ dysfunction and that a platelet count of less than 80,000/ml had a sensitivity of 83.3% and a specificity of 100% for the prediction of MODS (90).

The coagulopathy of critical illness is biologically complex and intertwined at multiple levels with the biological processes described earlier. Coagulation is initiated through tissue factor expressed on the cell surface activates factor VII, and the resulting complex of factor VIIa and tissue factor converts factor X to factor Xa. In concert with factor Va, factor Xa converts prothrombin to thrombin, which in turn results in the cleavage of fibrinogen to fibrin. Although fibrin deposition plays a critical role in hemostasis and in the localization of microorganisms within an abscess cavity, intravascular coagulation impedes oxygen delivery to tissues and can induce further inflammatory injury, indirectly through the response to hypoxia and directly through signals delivered to the thrombin receptor. Engagement of the thrombin receptor activates the nuclear transcription factor NFκB (95), causing the transcription of a broad array of proinflammatory gene products and resulting in the release of nitric oxide (96). Nor is the thrombin receptor unique as a mechanism through which an inflammatory response is amplified. Clustering of tissue factor has also been shown to initiate gene expression for proinflammatory cytokines, including TNF (97).

Activation of coagulation is tonically inhibited by three major endogenous anticoagulant pathways. Antithrombin III is an inhibitor of serine proteases that inactivates a number of coagulation factors. It complexes with thrombin to form thrombin-antithrombin complexes and, through its binding to endothelium, initiates the release of prostacyclin, an inhibitor of platelet aggregation (98). Tissue factor pathway inhibitor synthesized by endothelial cells inhibits factor Xa and the factor VIIa–tissue factor complex (99). Finally, protein C is synthesized primarily in the liver, although extrarenal synthesis occurs, particularly in the kidney and testis (100), and circulates as an inactive precursor. The protein C pathway is activated through the binding of thrombin to thrombomodulin on the endothelial surface, generating activated protein C, a serine protease that complexes with protein S to inhibit factors Va and VIIIa (101).

The biology of protein C exemplifies the complex interactions between coagulation and inflammation that can amplify both and hence increase the resultant tissue injury. Protein C binds to a specific receptor on endothelial cells, the endothelial cell protein C receptor (EPCR), a process that amplifies the generation of activated protein C by thrombin-thrombomodulin complexes (102). Inhibition of this interaction with a blocking antibody

**Tissue Hypoxia**

Reduced oxygen delivery or utilization would be expected to inhibit the normal physiologic functions of the cell; therefore, the assumption that cellular hypoxia is the final common pathway to organ dysfunction is attractive (65, 66). Although adequate initial resuscitation usually restores oxygen delivery at the level of the whole organism, regional hypoxia in tissues such as the gastrointestinal tract (67, 68) or brain (69) is a well-documented phenomenon. Increased circulating concentrations of lactate are also suggestive of tissue hypoxia, either global or regional, and are associated with an adverse outcome (70, 71).

Unfortunately, the initial enthusiasm for resuscitation to supranormal values to correct occult tissue hypoxia (72) has not been supported by more recent randomized trials (73); indeed, the use of transfusion (74) or large doses of dobutamine (75) to increase oxygen delivery actually worsens outcome and increases the severity of organ dysfunction. In the case of transfusion, at least, it appears that the deleterious effects arise from the failure of transfused red cells to reach the tissues, because of microvascular plugging by aged and poorly deformable red cells (76). Alternatively, tissue hypoxia may result from derangements in the intracellular utilization of oxygen, in the face of adequate delivery, a pathologic state that has been termed “cytopathic hypoxia” (77).

**Dysregulated Apoptosis**

Apoptosis describes a physiologic process through which cells activate an endogenous program that leads to the controlled death of the cell and its transformation to membrane-bound vesicles that are cleared by macrophages without evoking an inflammatory response (78). The normal expression of
The disparate biological processes that comprise inflammation are intimately interrelated, and strategies directed at one manifestation may have significant and unexpected consequences for others.

**Table 2. Coagulation abnormalities in trauma and sepsis**

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procoagulant activity/tissue factor</td>
<td>Platelets</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Thrombin-antithrombin</td>
<td>Protein C antigen</td>
</tr>
<tr>
<td>Fibrinopeptide A</td>
<td>Protein C inhibitor</td>
</tr>
<tr>
<td>Prothrombin fragment 1 + 2</td>
<td>Protein S</td>
</tr>
<tr>
<td>Plasmin α2-antiplasmin complexes</td>
<td>Factor VII</td>
</tr>
<tr>
<td>D-dimers</td>
<td>Factor XII</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td></td>
</tr>
<tr>
<td>tPA activity</td>
<td></td>
</tr>
<tr>
<td>tPA antigen</td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor propeptide</td>
<td></td>
</tr>
<tr>
<td>Platelet thrombospondin</td>
<td></td>
</tr>
</tbody>
</table>

tPA, tissue plasminogen activator.

Results in increased mortality, in association with an inflammatory cell infiltrate in the liver, kidneys, and adrenal glands, as well as elevated circulating levels of IL-6 and IL-8 (103). Proinflammatory cytokines such as TNF inhibit EPCR expression by augmenting EPCR’s shedding from the endothelial cell surface and down-regulating its transcription (93). Moreover α1-antitrypsin, an acute-phase reactant, shortens the half-life of activated protein C (APC). Thus, APC interactions in vivo are predominantly anti-inflammatory, whereas inflammation reduces APC levels and activity. As described earlier, the binding of thrombin to its receptor initiates NFκB-dependent inflammatory gene transcription; in addition, thrombin up-regulates endothelial P selectin expression and induces synthesis of platelet-activating factor (104). In addition to its role in the activation of protein C, thrombomodulin exhibits anti-inflammatory properties; its administration to rats challenged with endotoxin prevented pulmonary leukosequestration and pulmonary vascular injury (105).

Yet another example of the complex interactions between these physiologic processes is seen in the interactions between coagulation and programmed cell death. Phosphatidylserine is normally expressed asymmetrically on the inner aspect of the cell membrane. As part of the expression of apoptosis, phosphatidylserine becomes exteriorized and serves as one of the markers by which macrophages recognize and engulf apoptotic cells. However, exteriorized phosphatidylserine is also a potent stimulus for activation of the alternate pathway of complement and for induction of procoagulant activity leading to thrombin generation (106).

Alterations in levels of factors that regulate the balance between coagulation and fibrinolysis are common in critically ill patients and cause a shift toward a procoagulable state (Table 2). Changes in these parameters precede the development of organ dysfunction (107) and persist in those patients who develop organ dysfunction or die (108). Moreover, protein C levels are decreased in acute renal failure, a discrete manifestation of MODS (109), and in patients with neutropenia (110).

A variety of strategies that target the coagulation cascade improve survival in experimental models (111). In human volunteers, infusion of TNF activates coagulation and reproduces the coagulopathic profile of critical illness (112); paradoxically, neutralization of TNF may augment coagulation (113). Early studies suggesting benefit for administration of antithrombin III (114, 115) were not replicated in a recent large phase III multicenter trial (S. Opal, unpublished observations). Recombinant tissue factor pathway inhibitor has shown promise in early-phase clinical studies, and a large multicenter phase III study is in progress. The administration of protein C has been shown to improve outcome in purpura fulminans (116), and a phase II study of APC in sepsis showed a striking trend toward improved survival in a small cohort of patients (117). The as yet unpublished results of a large phase III study of APC, terminated at an interim analysis because of impressive evidence of clinical efficacy (118), should provide the most compelling evidence thus far that dysregulated coagulation is fundamental to the pathogenesis of MODS.

**Conclusions**

MODS is a prototypical exemplar of the application of complexity theory to an understanding of the pathophysiology of critical illness (119, 120). It arises through the interactions of a network of physiologic insults including infection, the host inflammatory response, tissue ischemia, injury, and the interventions used to sustain organ function during a time of otherwise lethal insufficiency. Its mediators are many and interdependent, with the activity of one inducing the expression of others that amplify, inhibit, or otherwise modify the expression of the process. The clinical syndrome that emerges reflects the state of dynamic balance that exists between each of the component mediators and can be considered an emergent system.

The implications of an understanding of the complex nature of organ dysfunction are critical to the development of rational strategies to prevent or treat the process. Strategies directed against events early in the process may be effective as prophylaxis but are unlikely to have a significant effect on a process whose expression, at least from the perspective of the element targeted, has become autonomous. For example, although the prevention of infection in critical illness may reduce morbidity and mortality (121), once such downstream events as proinflammatory mediator release have been activated, their persistence is not necessarily dependent on continuing infection. Similar consider-
ations may help to explain the relatively modest impact of neutralization of early proinflammatory mediator release in patients with sepsis (122), although the potential merits of targeting later circulating mediators such as high mobility group 1 (123) remain to be determined. In contrast, activation of coagulation is a relatively late consequence of the inflammatory response and, therefore, conceptually a more attractive therapeutic target.

In reality, the disparate biological processes that comprise inflammation are intimately intertwined, and strategies directed at one manifestation may have significant and unexpected consequences for others. Unfortunately, these processes are not demonstrated particularly well in small-animal models, and the elucidation of the richness of these interactions emerges only slowly, as data from trials of a variety of interventional strategies accumulate.

REFERENCES

1. Root HD: The way we were: 1989 presidential address, American Association for the Surgery of Trauma. J Trauma 1990; 30:1309–1315
90. Gando S, Nanzaki S, Kemmotsu O: Dissem-
nated intravascular coagulation and sus-
tained systemic inflammatory response syn-
drome predict organ dysfunctions after tra-
uma: Application of clinical decision anal-
91. Gregory SA, Morrissey JH, Edgington TS: Reg-
ulation of tissue factor gene expression in the 
monocyte procoagulant response to en-
92. Rosenthal GA, Levy GA, Rotstein OD: Induc-
tion of macrophage procoagulant activity by 
Bacteroides fragilis. Infect Immun 1989; 57: 
338–343
93. Esmon CT: Possible involvement of cyto-
kines in diffuse intravascular coagulation and 
thrombosis. Baillieres Best Pract Res Clin 
egin engagement induces monocyte pro-
coagulant activity and tumor necrosis factor 
production via induction of tyrosine phos-
95. Maruyama I: Biology of endothelium. Lupus 
1998; 7:S41–S43
275:29955–29959
97. McGivray ID, Rotstein OD: Signalling path-
ways of tissue factor expression in monocytes and 
98. Opal SM, Thijss LG: New potential therapeutic 
modalities: Antithrombin III. Sepsis 1999; 
3:153–159
99. Creasey AA: New potential therapeutic mo-
dalities: Tissue factor pathway inhibitor. Sep-
sis 1999; 3:175–182
100. Yamamoto K, Loskutoff DJ: Extraduodenal 
expression and regulation of protein C in the 
101. Esmon CT: New potential therapeutic mo-
102. Stearns-Kurosawa DJ, Kurosawa S, Mollica 
JS, et al: The endothelial cell protein C 
receptor augments protein C activation by 
thrombin-thrombomodulin complex. Proc 
Nat Acad Sci USA 1996; 93:10212–10216
103. Taylor FB Jr, Stearns-Kurosawa DJ, Kuro-
sawa S, et al: The endothelial cell protein C 
receptor aids in host defense against Esch-
erichia coli sepsis. Blood 2000; 95: 
1680–1686
104. Esmon C: The protein C pathway. Crit Care 
105. Uchiba M, Okajima K, Murakami K, et al: Re-
combiant thrombomodulin prevents endo-
toxin-induced lung injury in rats by inhibiting 
106. Test ST, Mitsuyoshi J: Activation of the al-
terative pathway of complement by calci-
um-loaded erythrocytes resulting from loss of 
membrane phospholipid asymmetry. J Lab Clin 
Med 1997; 130:169–182
107. Leithauser B, Matthias FR, Nicolai U, et al: 
Hemostatic abnormalities and the severity of 
inflammas in patients at the onset of clini-
cally defined sepsis: Possible indication of 
the degree of endothelial cell activation? 
of the hemostatic network in critically ill 
patients: is there a difference between sep-
is, trauma, and neurosurgery patients? Crit 
Care Med 2000; 28:445–450
Protein C in acute renal failure. Acta Med 
Scand 1998; 224:375–380
110. Mesters RM, Helderbrand J, Utterback BG, et 
al: Prognostic value of protein C concen-
trations in neutropenic patients at high risk of 
severe septic complications. Crit Care 
111. McGivray ID, Rotstein OD: The role of co-
agulation in systemic inflammation: a re-
view of the experimental evidence. Sepsis 
1998; 2:199–208
112. van der Poll T, Lelieveld J, Utterback BG, et 
al: Fibrinolytic response to tumor necrosis fac-
174:729–732
113. van der Poll T, Levi M, van Deventer SJ, et 
al: Differential effects of anti-tumor necro-
sis factor monoclonal antibodies on sys-
temic inflammatory responses in experi-
mental endotoxemia in chimpanzees. Blood 
1994; 83:446–451
114. Fourrier F, Chopin C, Huart JJ, et al: Dou-
ble-blind, placebo-controlled trial of anti-
thrombin III concentrates in septic shock with 
disseminated intravascular coagulation. 
Chest 1993; 104:882–888
thrombin III (ATIII) replacement ther-
apy in patients with sepsis and/or postsur-
gical complications: A controlled double-
blind, randomized, multicenter study. 
28:2373–2378
117. Bernard GR, Hartman DL, Helderbrand JD, et 
al: Recombinant human activated protein 
C (rhAPC) produces a trend toward im-
povement in morbidity and 28 day survival in 
patients with severe sepsis. Crit Care Med 
1999; 27:335
Efficacy and safety of recombinant activated 
2001; 344:699–709
119. Seely AJE, Christou NV: Multiple organ dys-
function syndrome: exploring the paradigm 
of complex nonlinear systems. Crit Care 
120. Marshall JC: Complexity, chaos, and incom-
prehensibility: Parsing the biology of criti-
cal illness. Crit Care Med 2000; 28: 
2646–2648
121. Nathens AB, Marshall JC: Selective decon-
tamination of the digestive tract in surgical 
patients: A systematic review of the evi-
122. Marshall JC: Clinical trials of mediator-
directed therapy in sepsis: What have we 
learned? Intensive Care Med 2000; 26: 
S75–S83
as a late mediator of endotoxin lethality in 

Question and Answer Session After 
Scientific Review

Benoit Vallat. You have indicated that 
activated protein C (APC) interferes primarily with coagulation rather 
than inflammation. Do you think this 
explains why APC therapy has suc-
cceeded in clinical trials, whereas anti-
cytokine treatments, which target in-
flammation, have failed? 

would disagree with the term “failure” to 
describe these trials. In many cases, 
the trial results were not truly negative, 
but inconclusive or suggestive of only 
minimal benefit. In addition, I am not 
arguing that coagulation is the be-all 
and end-all of the story. In fact, it may 
be that the final common pathway is 
related more to endocrine insufficiency 
rather than intravascular coagulopathy. 
At this stage, I think it is difficult to 
speculate on the extent to which coag-
ulation is clinically important, nor am I 
sure that we can define a direct cyto-
toxic role for inflammation.