outcome and low levels of immune globulin in their patient group. They suggest that elevated level of immune globulin neutralizes the endotoxin and thus prevents SIR. Conversely, low initial levels of immune globulin are “overwhelmed” by the endotoxin and thus allow SIR to proceed unchecked. In order to appreciate this paper properly, certain seemingly unrelated observations seem important to me.

First, there is a severe and easily demonstrable SIR associated with cardiopulmonary bypass.1 The heart-lung machine creates a milieu in which cytokines are released in quantities that produce a wide variety of physiologic events. Cardiac surgeons have noted for years the capillary leak and significant weight gain which follows even the simplest operative procedure using cardiopulmonary bypass. Another frequent event associated with SIR is the tendency towards unexplained postoperative bleeding. There is little doubt that the SIR is widespread in its effect, but it is unclear what the underlying initiating event or events are.

Second, several investigators have demonstrated “endotoxemia” following cardiopulmonary bypass.2 Importantly, others have been unable to demonstrate this endotoxemia.3,4 We felt that gut translocation was most likely the initiating event leading to SIR. We undertook a study5 attempting to demonstrate that preoperative gut cleansing would reduce SIR by reducing the preoperative gut bacterial load, and thus reducing the potential for endotoxemia. Our patients, however, did not demonstrate endotoxemia as described by others, despite using exactly the same methods.5 Our patients did demonstrate the clinical signs of weight gain and generalized capillary leak that we have associated with SIR despite not being able to demonstrate endotoxemia.

Third, we have recently embarked on “off-pump coronary bypass surgery,” or minimally invasive direct coronary artery bypass (MIDCAB). We have done these operations through limited incisions as well as full sternotomies. In our view, the only significant difference between traditional cardiac bypass graft and MIDCAB is the absence of the heart-lung machine. Despite relatively large incisions in some patients, we have uniformly seen marked reduction in the evidence of SIR that we have become so accustomed to seeing in traditional cardiac surgical patients.

Fourth, experience with aprotinin in patients undergoing cardiopulmonary bypass has reemphasized the importance of SIR associated with the use of the heart-lung machine. This drug was initially proposed as a useful adjunct to improve clotting postoperatively, but clearly has a variety of other important systemic effects. The suggestion that this drug may reduce the generalized SIR and thus translate into improved overall outcomes seems attractive.1

When I put these observations together, I would offer the following explanation for the findings of Hamilton-Davies and coauthors: cardiopulmonary bypass is associated with a significant SIR. The initiating event for SIR is unclear. It is hard for me to believe that endotoxemia secondary to gut bacteria translocation is the only factor going on in these patients. I think there are likely many factors that contribute to the initiation of SIR. I think the most likely explanation for the authors’ observations is that the immune globulin level is a preoperative marker of as yet poorly understood patient characteristics that predispose to poor outcomes. The authors have proposed additional studies to augment the immune globulin levels in their patients prior to surgery. I will be interested to see if they are able to demonstrate a reduction in SIR and postoperative complications in those patients.

This is a very puzzling area of physiology. Further work in this area may provide the physiologic model needed to dissect out the relationship between theafferent and efferent loops of the SIR.

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Host Defense Response and Outcome in ARDS

The host defense response (HDR) to an insult consists of an interactive network of simultaneously activated pathways—inflammation, coagulation (intravascular clotting and extravascular fibrin deposition), tissue repair, modulation of the immune response, and activation of the hypothalamic-pitu-
Clinical manifestations of inflammation

- Body temperature
- Mean arterial blood pressure

Laboratory manifestations of inflammation

- Blood inflammatory cytokine levels
- BAL inflammatory cytokine levels
- Blood phospholipase A2 levels
- Complement activation

Laboratory manifestations of pulmonary endothelial permeability

- BAL neutrophil percentage
- BAL albumin and protein concentration
- Gallium-67 pulmonary uptake

Clinical manifestations of systemic endothelial permeability

- Positive fluid balance

Laboratory manifestations of coagulation

- Platelet count
- BAL antifibrinolytic activity

Physiologic and radiographic manifestations of fibroproliferation

- PaO2/FIO2
- PEEP requirements
- Static compliance
- Dead space ratio
- Pulmonary artery pressure
- Alveolar infiltration

Laboratory manifestations of fibroproliferation

- BAL procollagen-III
- Serum procollagen-III

<table>
<thead>
<tr>
<th>Variable at Days 3-7 of ARDS</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>↓</td>
<td>↑</td>
<td>22</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>↑</td>
<td>↓</td>
<td>22-24</td>
</tr>
<tr>
<td>Blood inflammatory cytokine levels</td>
<td>↓</td>
<td>↑</td>
<td>10,21,25-27</td>
</tr>
<tr>
<td>BAL inflammatory cytokine levels</td>
<td>↓</td>
<td>↑</td>
<td>11,21,28</td>
</tr>
<tr>
<td>Blood phospholipase A2 levels</td>
<td>↓</td>
<td>↑</td>
<td>29,29</td>
</tr>
<tr>
<td>Complement activation</td>
<td>↓</td>
<td>NA</td>
<td>27,30</td>
</tr>
<tr>
<td>BAL neutrophil percentage</td>
<td>↓</td>
<td>↑</td>
<td>28,30-33</td>
</tr>
<tr>
<td>BAL albumin and protein concentration</td>
<td>↓</td>
<td>↑</td>
<td>11,32,33</td>
</tr>
<tr>
<td>Gallium-67 pulmonary uptake</td>
<td>↓</td>
<td></td>
<td>34,35</td>
</tr>
<tr>
<td>Positive fluid balance</td>
<td>↓</td>
<td>↑</td>
<td>22,24</td>
</tr>
<tr>
<td>Platelet count</td>
<td>↓</td>
<td>↑</td>
<td>23,27,36</td>
</tr>
<tr>
<td>BAL antifibrinolytic activity</td>
<td>NA</td>
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<td>37,38</td>
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<tr>
<td>PaO2/FIO2</td>
<td>↑</td>
<td>↓</td>
<td>11,19,21-24,27,32,37-41</td>
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<tr>
<td>PEEP requirements</td>
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<td>←</td>
<td>23,24,27</td>
</tr>
<tr>
<td>Static compliance</td>
<td>↑</td>
<td>↓</td>
<td>40</td>
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<tr>
<td>Dead space ratio</td>
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<td>↓</td>
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<tr>
<td>Pulmonary artery pressure</td>
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<tr>
<td>Alveolar infiltration</td>
<td>↓</td>
<td>↑</td>
<td>14,19,27,39</td>
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<tr>
<td>BAL procollagen-III</td>
<td>↓</td>
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<td>44</td>
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<tr>
<td>Serum procollagen-III</td>
<td>↓</td>
<td>↑</td>
<td>43-47</td>
</tr>
</tbody>
</table>

*Variables at Days 3-7 of ARDS in comparison to Day 1: ← = no change; ↑ = increased; ↓ = decreased; = no change or decreased; ↑ = no change or increased; NA = not available; PEEP = positive end-expiratory pressure.

ity-adrenal (HPA) axis with production of glucocorticoids—that act in synergy to increase the host’s chance of survival.1 Sympathetic system release of catecholamines and hepatic production of acute-phase reactants are an integral part of the HDR and are under the influence of glucocorticoids. Tissue repair consists of angiogenesis, epithelial growth, fibroblast migration and proliferation (fibroproliferation), and deposition of the extracellular matrix. In this issue of CHEST (see page 1184), Deheinzelin and collaborators provide additional evidence that tissue repair starts soon after exposure to an insult, a finding in agreement with prior clinical2-3 and experimental4 work in early acute respiratory distress syndrome (ARDS).

Cellular responses in the HDR are regulated by a complex interaction among cytokines, with final local and systemic effects not directly induced by the initiating infectious or noninfectious insult. Among the broad spectrum of proximal mediators, cytokines of the interleukin-1 (IL-1) and tumor necrosis factor (TNF) family are uniquely important in initiating all key aspects of the HDR. The cell most commonly associated with initiating the HDR cascade is the tissue macrophage or the blood monocyte.5 Once released in the lung, TNF-α and IL-1β act on epithelial cells, stromal cells (fibroblasts and endothelial cells), the extracellular matrix, and recruited circulating cells (neutrophils, platelets, lymphocytes) to cause secondary waves of cytokine release, with amplification of the HDR.5 The term “inflammatory cytokines” (as they are commonly known) is limiting, because their action extends well beyond this essential pathway of the HDR to include activation of coagulation,6 fibroproliferation,7 and HPA axis.8-9

In this editorial, I will highlight selected research findings to support a unifying pathogenetic model of ARDS and to indicate that an exaggerated and protracted HDR (a term more appropriate than inflammatory response) plays a key role in ARDS evolution and outcome. Our group10,11 previously reported that on day 1 of mechanical ventilation and over time, nonsurvivors of ARDS have significantly (p<0.0001) higher plasma and BAL fluid inflammatory cytokine (TNF-α, IL-1β, IL-6, and IL-8) levels than do survivors. As evidence of an integrated HDR, we found a strong correlation among TNF-α, IL-1β, IL-6, and IL-8 in both plasma and BAL fluid at the onset of ARDS and over time.10,12 Increased activation of transcription regulatory nuclear factor-
κB, a proximal activation mechanism for the simultaneous expression of multiple cytokines, has been demonstrated in the alveolar macrophages of patients with established ARDS.13

ARDS is characterized by acute onset in the lung parenchyma of diffuse and severe HDR to a direct or indirect insult, leading to disruption of the alveolocapillary membrane with loss of compartmentalization.1 In patients who recover, effective tissue repair restores anatomy and function, and both permeability defect and gas exchange abnormalities do improve (adaptive response). Conversely, in the absence of inhibitory signals, the continued exaggerated production of HDR mediators prevents effective restoration of lung anatomy and function (maladaptive response) by sustaining ongoing injury, coagulation, and fibroproliferation (the three act in synergy). Histology of lung tissue obtained by open-lung biopsy in patients with unresolved ARDS (8 to 22 days into ARDS and prior to glucocorticoid rescue treatment) showed that new injury to previously spared endothelial and epithelial surfaces occurs in conjunction with an amplified reparative process (coagulation and fibroproliferation with deposition of extracellular matrix) on previously damaged areas (alveoli, interstitium, respiratory bronchioles, and walls of the intra-acinar microvessels).14 Persistent endothelial and epithelial injury protracts vascular permeability in the lung and systemically. Intravascular coagulation decreases the available pulmonary vascular bed, while intra-alveolar fibrin deposition promotes cell matrix organization by fibroproliferation (granulation tissue).14 The initially fibrinous intra-alveolar exudate is transformed into myxoid connective tissue matrix and eventually into dense acellular fibrous tissue. Morphometric studies in nonsurvivors of ARDS have shown that intra-alveolar fibroproliferation rapidly increased in the second and third weeks of respiratory failure.15 Fibroproliferative obliteration of the respiratory units changes their mechanical properties (loss of inflection point in the pressure-volume curve and lack of reactivity by positive end-expiratory pressure), increases dead space ventilation, and further compromises gas exchange.16-18 Mortality reported in the literature for medical patients failing to improve gas exchange by day 7 of ARDS is in excess of 80%.19-21

Within this framework, studies that have reported clinical, laboratory, and physiological expressions of inflammation, coagulation, and fibroproliferation over time provide strong evidence that an aggressive and protracted HDR is the major factor influencing outcome in ARDS. Predictors of poor outcome in ARDS as reported in the literature are actually manifestations of a persistent and exaggerated HDR (Table 1).10,11,11,21-47 In agreement with this statement are the following findings: (1) that ARDS patients may not improve despite appropriate treatment of the precipitating insult; and (2) that effective reduction in plasma and BAL of inflammatory cytokine levels with prolonged methylprednisolone administration is associated with a parallel improvement in lung injury score and markers of pulmonary endothelial permeability (albumin and neutrophil concentration in the BAL, and gallium uptake),48 and a significant decline in ICU mortality.49 The magnitude of initial HDR appears to determine the progress of ARDS1 and may partially be influenced by genetic factors.50 Furthermore, once activated, the HDR appears to be autonomous, and the cytokine response to secondary infections is downregulated to protect the host from overwhelming cytokinemism (cytoprotection).21 In other words, ARDS patients die with, rather than of, nosocomial infections.21,49 The concept that excessive activation of the HDR may cause deterioration in organ function rather than restoring homeostasis is now appreciated as a critical determinant of patient outcome in the ICU.21,51,52

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Of Emperors, Emboli, and Echocardiography

I
n 1837, Hans Christian Anderson wrote a fairy tale about a boy who unwittingly exposed his emperor’s subjects as accomplices in the emperor’s belief that he wore beautiful and magical clothes, when in fact he toured his kingdom in his birthday suit! Similarly, in 1977 Eugene Robin challenged conventional wisdom and argued that overreliance on the perfusion lung scan had resulted in the overdiagnosis of pulmonary embolism (PE). He concluded that “judging from the current practice in American hospitals, the emperor of embolism has no clothes.” Despite advances in the noninvasive diagnosis of PE since 1977, a significant number of patients continue to require angiography for a firm diagnosis of PE. These problems are magnified with massive PE, since patients are frequently too ill for transportation to these tests.

In 1980, Kasper and colleagues reported the findings of transthoracic echocardiography (TTE) in 18 patients with angiographically confirmed PE. All 13 patients with pulmonary hypertension (mean pulmonary artery pressure >20 mm Hg) showed an increased right pulmonary arterial diameter (indexed to body mass). In 1993, this same group reported on 47 consecutive patients with confirmed PE who had TTE. In the 36 patients with PE and pulmonary hypertension (PHT), TTE showed right ventricular (RV) dilatation in 92% and paradoxical septal movement in 67%; these findings were absent in all 11 patients with minor PE. These studies show that TTE has a sensitivity of 92 to 100% in the detection of PE that is massive enough to result in PHT. However, the specificity of isolated RV dilatation for PE is low because there are many other causes of RV dilatation. Unfortunately, TTE is able to directly visualize thrombus in the pulmonary arteries in only 0 to 19% of patients with PE and PHT. Naked, the emperor walks.

In this issue of CHEST, Krivec and colleagues (see page 1310) report on the utility of transesophageal echocardiography (TEE) in diagnosing PE. They performed TEE in 24 consecutive patients with shock and distended jugular veins. The main TEE diagnoses were pericardial tamponade in two patients, left ventricular dysfunction in four patients, and RV dilatation in 18. Thirteen of the 18 patients with RV dilatation were confirmed to have massive PE by other means, and 12 of the 13 patients had direct visualization of thrombus in the main pulmonary arteries. They concluded that visualization of thrombus by TEE was 92% sensitive and 100% specific for the diagnosis of PE in their patients.

Wittlich and colleagues reported 44 patients with confirmed acute massive PE who underwent TEE to look for the presence of central PE. TEE showed central PE in 26 patients, which was independently confirmed in 24 patients, resulting in a sensitivity of 100% and specificity of 88% for detecting central PE. In another study, TEE showed unequivocal thrombus in the pulmonary arteries in 12 of 15 patients with confirmed acute PE, giving a sensitivity of 80% and specificity of 100% for detecting central PE. Patel and colleagues found a specificity of 100% in 14 patients incidentally diagnosed with thrombus in the pulmonary arteries by TEE. The study by Krivec and colleagues in this issue further supports the good sensitivity and excellent specificity of TEE in the diagnosis of massive PE. TEE offers the additional benefits of being relatively quick, not requiring contrast material or transportation out of the intensive care unit, and may be easily repeated in order to follow the response to therapy. Why Emperor, what nice clothes you’re wearing!

The current report by Krivec and colleagues confirms the impressive hemodynamic response that has been seen following thrombolysis in other studies. Krivec and colleagues report that four patients showed a dramatic decrease in total pulmonary resistance by 1 h, and all but two patients showed a decrease to less than 80% of baseline by 5 h. Although not noted by the authors, their data show that three of the five patients with the most dramatic fall in total pulmonary resistance during the first 5 h had mobile thrombus on TEE, while three of the four deaths occurred in patients with immobile thrombus. These data suggest that mobile thrombus may be more amenable to thrombolysis.

There are several caveats relevant to the study by Krivec and colleagues. First, since PE was not rigorously excluded in all patients, their estimate of sensitivity may be falsely high. Second, the diagnosis of PE was confirmed in 9 of 13 patients based on perfusion lung scanning only. This would not meet the usual definition for a diagnostic lung scan in the United States, although other studies would sug-