the case with pneumococcal pneumonia, where the spectrum includes severities from mild (e.g., “walking pneumonia”) to overwhelming. And while there may be an anticipated cadre “typical” for disease, it is well appreciated that it occurs in patients of all ages, and in those without obvious comorbidities. Also similar to pneumococcal pneumonia is the appreciation that we can often treat with shorter antibiotic courses than was generally appreciated and what has been historically recommended. The current investigation, on account of protocols not specifically aimed at therapy for legionellosis, utilized durations of treatment as little as 5 days with generally excellent outcomes, although numbers are small. Indeed, almost 20% of patients were treated with this short duration, similar to recommendations for management of uncomplicated pneumococcal pneumonia in patients with good initial response. Recently, other data have demonstrated the effectiveness of azithromycin in 25 patients hospitalized with CAP caused by L. pneumophila. Mean duration of IV plus oral therapy was < 8 days, with good outcomes. Although the pharmacokinetics and pharmacodynamics of azithromycin are dissimilar to those of the fluoroquinolones, this report adds further substance to the concept of shortened therapy for this disease.

It would have been valuable for Yu and colleagues to have analyzed pooled information about legionellosis in the control populations from the databases that were investigated. As an example in one of these studies, two thirds of a small number of patients with Legionella pneumonia had satisfactory outcomes despite receiving only cephalosporins. An analysis of larger numbers of similar patients could have helped place the results of the current study in better perspective, and perhaps provided further information about the natural history of this infection.

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Cytokines

The Tomb Markers of the ICU

A study reported that severe sepsis accounts for >215,000 deaths annually from a total population of approximately 750,000 patients, which means a mortality rate of 29%. Multiple other reports quote a range between 25% and 50%. Mortality levels may be much higher in the developing world. Such high mortality has lead to widespread research and the expenditure of billions of dollars. This has lead to a great deal of progress in the last few years in our understanding of the molecular and genetic factors that affect the pathophysiology of sepsis and severe illness. This ability to leave the whole-organism model to now study the cellular model has led to introduction of many possible treatment options.

With the release by the pharmaceutical industry of activated protein C, we now have targeted therapy toward specific cellular functions, which are modulated by the systemic inflammatory response and cytokine levels. This avenue of therapy will only expand in the next few years as multiple clinical trials come to completion.

Despite the wealth of information of cytokine
modulation of sepsis, organ failure, and severe illness, there has been no widespread introduction in clinical practice of the laboratory evaluation of these cytokines as disease markers. We routinely evaluate glucose levels, electrolyte levels, tumor markers, and hundreds of other levels to diagnosis disease and treat patients. No modern ICU would treat a patient with severe ARDS without the use of oxygen saturation and blood gases to titrate mechanical ventilation.

In this issue of CHEST, we have two reports of the use of cytokines as markers of illness: Cardier and coworkers (see page 2238), who report on the levels of tumor necrosis factor (TNF)-α/TNF receptor I (TNFRI) and Fas ligand/Fas in sepsis; and a report by Vincent and coworkers (page 2232), who report on the TNF-2 allele and survival from cardiogenic shock. These articles illustrate how these markers may have a future in clinical practice much as routine laboratory values did at the start of the last century. Both articles showed how specific levels of cytokines can play a role in patient outcome, transforming growth factor-β1 being predictive of survival in cardiogenic shock, and increased levels of TNFRI and Fas as important markers of the severity of sepsis in the other. Both articles measured and evaluated TNF-α one of the most commonly measured cytokines in research. TNF-α has been implicated in myocardial depression associated with septic shock, as well as in the pathogenesis of heart failure. The study by Vincent et al showed that the TNF-2 allele of the TNF-α promoter is a strong independent factor associated with better survival from cardiogenic shock. The clinical implication cannot be understated, in that it if we can identify patients with cardiogenic shock with the TNF-2 allele we may be able to provide them with more aggressive therapy or transfer them to university centers were they may have improved outcomes. TNF-α levels in the study by Cardier et al, as in several other studies, found no correlation in mortality in patients with severe sepsis, which suggests that although TNF-α plays an important role in the pathogenesis of sepsis, it may not be a good marker or predictor of mortality in severe sepsis. TNF-α levels can also be greatly affected by the support provided in the ICU. Our group showed how there can be a loss of compartmentalization of TNF-α in the lung and can affect systemic levels based on the mode of mechanical ventilation. This varied utility of one common cytokine marker shows how specific cytokine levels can be used in specific patient populations and why further investigation of the utility of each cytokine must be investigated in critical illness.

Cardier et al have added to our database on how specific cytokines affect the systemic inflammatory response and may lead to specific aspects of organ failure. Cell death by apoptosis may play an important role in the pathogenesis and development of multiple organ dysfunction syndrome in patients with sepsis syndrome. He showed that there are differential patterns in the circulating levels of apoptosis-associated molecules between severe sepsis and sepsis. The key marker seems to be serum levels of death-receptors TNFRI and Fas. They reported that serum levels were higher in patients who died than those who survived, which may suggest that serum Fas levels may constitute an important marker not only for severity but also for survival. This supports other reports that up-regulation of Fas has been reported in both experimental models of sepsis and in the patients. This may support a future avenue of investigation: the genetic mapping of these patients to see if some patients are genetically primed to be high cytokine releasers.

The investigations in this issue and the many others published investigations are creating the markers and guideposts to unlock the physiology of sepsis and organ dysfunction. As we move forward in our understanding of these important cellular modulators, we believe we will utilize specific laboratory tests to classify patients and use them as markers to modulate therapy and predict outcome. It is important that other investigators begin to study these and other cytokines and measure their levels in patient populations. The genetic variation in the expression of these cytokines must also be expanded. This wide spread use of this basic science data will in the future lead us to further investigations of cell dysfunction. With these data in large homogeneous groups of patients, investigators may be able to develop specific therapies to target increases of cytokines that may be unique to a disease or trigger. They may be also able to identify patients with genetic phenotypes that place them at risk for activation of cytokine cascades, much as patients with specific genetic phenotypes are at risk for specific diseases.

We believe that this may be a fruitful pathway to investigate therapies instead of the current pattern of large multicentered studies over varied ICU patient populations. Many of these studies failed to have overall positive outcomes, but did have small groups of patients who were responders. This ability to measure levels and titrate therapy to specific end points seems like a logical avenue to treat illness. A basic example of this has been the control of glucose levels in patients both with chronic diabetes and in patients with low levels of insulin with sepsis. With tight control of glucose levels, we have improved both morbidity and mortality. This time-tested way to evaluate and treat patients may hold true in this new century as we explore the cellular response of
illness and trauma. Evidence-based medicine is highly suited in the practice of ICU if we use these cytokine markers to develop protocols and treatments that will modulate specific cellular dysfunction. This will tell us if elevations of some cytokines are destructive or protective. We most develop easy, economical assays for cytokines and introduce them to widespread clinical practice. Once they are used in such widespread practice, there will be exponential growth in our ability to care for patients. The field of cellular medicine will only grow as more and more investigation and physicians in clinical practice add to our growing understanding of how specific patients react to specific stimuli and how these physiologic responses are regulated.

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SARS, Pneumothorax, and Our Response to Epidemics

In late 2002, the severe acute respiratory syndrome (SARS) coronavirus (CoV) jumped from feral animals to humans in the Guangdong province of China. This CoV strain had the capacity to spread from person to person, and many of the infected people became severely ill with SARS. The official toll from the multifocal epidemic that ensued was 8,422 cases and 816 deaths on five continents.1 This startling epidemic demonstrated the continuing risk of zoonotic diseases for humans and the awesome potential for emerging diseases to wreak havoc around the globe. SARS brought several ethical issues associated with new, severe epidemic diseases into sharp focus.

In this issue of CHEST (see page 2345), Sihoe et al describe an important clinical feature of SARS, and they raise an important ethical issue that faces clinicians caring for patients with new infectious diseases. Clinical details were reported for six cases of spontaneous pneumothorax that occurred among 356 patients with SARS at two Hong Kong hospitals, an incidence of 1.7%. Secondary pneumothorax developed in other patients who were receiving mechanical ventilation or who had catheters inserted into veins near the pleura. Two of the six patients had pneumomediastinum, an uncommon but characteristic sign of SARS.2

In these six cases, pneumothoraces were bilateral in three patients, mechanical ventilation was indicated in three patients, and two patients died. Air leaks or recurrences occurred in all four patients who accepted chest tubes; the other two patients refused chest tubes. These air leaks took 14 to 31 days (mean of 23.5 days) to resolve. The concentrations of peripheral leukocytes and serum lactate dehydrogenase in patients with SARS and pneumothorax were greater than in other patients with SARS in Hong Kong, which supported the clinical perception that pneumothorax was associated with more severe disease. These complications reflected the severe pathologic changes in lung tissues and strong pulmonary and systemic inflammatory responses that accompany SARS.3

All six patients reported in this issue had received glucocorticoids. This reflected the opinions of several clinicians around the world who believed that early treatment with glucocorticoids improves outcomes from SARS.3 Glucocorticoid therapy may have interfered with lung healing in ways that predisposed to pneumothorax in these patients. The risk of this complication may be acceptable if in fact glucocorticoids improve outcomes in most patients,