present study, Held and colleagues made use of C3H/HeJ mice to demonstrate that the mediator release due to overstretch of the lung occurs in these mice via translocation of NF-κB, despite the fact that there is no release of cytokines in response to LPS alone, thus demonstrating that the upstream events for signaling by LPS are different from those that initiate biotrauma.

Why is this result so exciting? This finding suggests the possibility that it will be possible to treat and/or prevent biotrauma without necessarily affecting other relevant host defense mechanisms. Held and others have shown that corticosteroids can attenuate release of mediators due to lung stretch (2, 5). However, steroids represent a sledgehammer approach to the problem and block many pathways we don't want blocked; clinically, this is manifested as an increased risk of infection in patients treated with corticosteroids. The findings of the current study suggest an approach to circumvent this problem. If we think of the LPS signaling pathway as a major pathway for innate immunity, it may be possible to target the biotrauma signaling pathway without affecting the innate immunity pathway. If this is correct, then one could potentially limit biotrauma by targeting specific signal transduction pathways proximal to NF-κB that are important in ventilation-induced release of mediators, but that play no role in LPS signaling. In this way, the basic findings of Held and colleagues could have tremendous implications at the bedside.

But why should this anticytokine approach be effective when most anticytokine trials have been ineffective in the context of sepsis? First, most sepsis trials have blocked a single cytokine, despite the fact that there are multiple cytokines and multiple pathways. Blocking the biotrauma pathway proximal to NF-κB would block the signal transduction pathway relatively proximally, and hence would theoretically affect multiple cytokines. Second, most anticytokine therapies are effective in animal models when given *before* the septic insult; this is impossible to do in most cases of sepsis because the diagnosis is made by recognition of signs, symptoms, and laboratory data related to the host's response to the stimulus, implying that therapy can only begin *after* the initiating stimulus. Biotrauma associated with ventilator-induced lung injury is noteworthy in that we know exactly when the stimulus will begin (when mechanical ventilation is initiated), and more importantly, we can thus begin therapy before initiation of this insult. A number of studies of different animal models suggest that this approach may have merit (8, 9).

Furthermore, future studies that more specifically elucidate a specific patient's susceptibility to biotrauma, perhaps on the basis of the signal transduction pathways, may suggest which patients are more likely to benefit from antimediator therapy. There are now a number of studies that have demonstrated that a patient's genetic make-up may predict his/her response to sepsis (10). Specifically, septic patients who are homozygous for a specific polymorphism in the tumor necrosis factor α (TNF-α) gene have an increased risk of death, presumably because of increased TNF-α levels. Another example of genetic susceptibility was recently provided by Arbour and colleagues, who demonstrated that differences in responsiveness to inhaled LPS in humans may be due to differences in common mutations in TLR4 (11). If similar types of polymorphisms are important in the context of biotrauma, then intensivists in the future may decide whether to use antimediator therapy in a ventilated patient on the basis of the patient's particular genotype profile. Within the context of this model, patients who are genetically susceptible to biotrauma would be the ones who receive this therapy (12). Basic studies, such as the present one by Held and colleagues, are critical if approaches such as this are to become a reality in the intensive care unit of the future.

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Reinfection Tuberculosis
How Important Is It?

How often does exogenous reinfection with *Mycobacterium tuberculosis* occur among immunocompetent persons who have been treated and cured of tuberculosis? Does exogenous reinfection occur among healthy persons who are tuberculin skin test positive and have latent tuberculosis infection? Are there host genetic factors that come into play in this equation—are some healthy or cured subjects more resistant to challenge by *M. tuberculosis* as a result of genetic mechanisms

that control native immunity? Are some strains of *M. tuberculosis* more virulent or more likely for other reasons to infect subjects who have native or acquired immunity? These questions have been raised over and over by investigators, clinicians, and tuberculosis controllers because of their importance to those who seek to understand immunity/resistance to tuberculosis, and to those working toward the development of an effective vaccine. It is also of interest to those who prepare prediction models for tuberculosis control and eradication in geographic areas with widely varying tuberculosis case rates. In this issue of *AJRCCM* (pp. 717–720), the article entitled "Exogenous Reinfection with Tuberculosis on a European Island with a Moderate Incidence of Disease" by Caminero and coworkers provides valuable information on these questions (1). Caminero and colleagues evaluated persons with recurrent tuberculosis living on the Spanish Island of Gran Canaria between 1991 and 1996. The island population of almost 714,000 persons had a case rate that varied from 28 to 32 per 100,000 during the study period. This rate is about five times higher than in the United States and about 15–20 times less than in countries where tuberculosis is out of control. Among 912 patients with positive cultures during the study period, 23 (2.4%) became culture positive again after being culture negative for at least 12 mo postchemotherapy. Cultures obtained before therapy and 12 mo or more after ending therapy were available for 18 patients. For all 18 patients DNA fingerprints of the pretreatment and recurrent isolates were obtained and for eight of them the genotype of the recurrent isolate showed a different pattern as compared with the pretreatment isolate. The authors conclude that these 8 patients are examples of exogenous reinfection. Thus about half the patients in this population who experienced a second episode of tuberculosis were apparently infected exogenously. And this occurred in a setting where the case rate is modestly low, meaning that chance inhalation of viable tubercle bacilli would be infrequent as compared with an area with a much higher case rate. This observation runs counter to commonly held concepts and must be scrutinized carefully.

The first step is to examine how each reinfection was documented. Did laboratory error such as mislabeling or laboratory cross-contamination of specimens occur? I think not. At least two isolates each from the pre- and posttreatment period were genotyped in each instance and the cases were evaluated clinically as well for signs and symptoms of recurrent disease. In every case there seemed to be no other explanation except exogenous reinfection. However, there is one troubling point: three of the exogenous reinfecting isolates were of the same genotype, a finding that seems unlikely to occur by chance alone. Could laboratory cross-contamination explain it? The authors state, without giving any data, that this particular genotype is "frequently isolated on the island" and no epidemiological links were found among these patients. The authors state that they are not surprised to find multiple isolates of this genotype in this set. This is a concern that remains unresolved. Two of the eight patients with exogenous reinfection had acquired immunodeficiency syndrome (AIDS) and it is well known that these patients are easily reinfected.

In my view, reinfection of individuals who have been cured of tuberculosis remains an uncommon explanation for recurrent tuberculosis among immunocompetent patients living in geographic areas of low incidence. The chance of anyone inhaling viable tubercle bacilli in these areas is growing increasingly less likely. In addition, these episodes of recurrent tuberculosis after an effective therapy regimen has been completed are clustered in the first 2 yr after ending treatment. One would expect exogenous reinfection to be a more random event and thus should occur sporadically over the remaining lifetime of the subject.

Caminero and colleagues cite a number of prior publications that show strong evidence of exogenous reinfection and give emphasis to a report by van Rie and coworkers, who studied this question among persons living in a very high incidence area of Cape Town, South Africa (2). In this setting it was found that exogenous reinfection is the major cause of recurrent disease. I have serious reservations about this particular report and advise caution about extending these observations as being true and applicable to other high incidence areas. Laboratory cross-contamination as an explanation for some of their observations was not effectively excluded by van Rie and associates, nor was the clinical evidence of relapse convincingly set out. More details about these concerns are published in another journal (3).

Cured patients who live in high incidence areas are at risk of inhaling tubercle bacilli on a relatively frequent basis and if their native and acquired immunity to tuberculosis is inadequate, recurrent disease with a new infecting strain will result. No doubt this does occur. The larger question is how often. More studies of this question are needed, not only to help those planning for tuberculosis control, but for those interested in tuberculosis immunity and variation in virulence among isolates of *M. tuberculosis.* Human subjects who have firmly demonstrated reinfection should be studied for genetic markers of resistance to tuberculosis (as these markers become known) and the infecting isolates should be evaluated for any features they might exhibit that promote their ability to cause disease in a subject with presumed acquired immunity.

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