also provides very valuable information for the design of future studies, such as field testing inclusion/exclusion criteria and study endpoints, as well as injecting some increased confidence into the process of estimating the effect size that steroid treatment might provide to SARS patients, thus allowing more rigorous power calculations to determine prospective sample size. Ho and coworkers are wise to be circumspect in the conclusions they draw—namely, that this report helps guide SARS therapy but only until data from randomized trials become available (6).

Twenty-five years ago (1978) Craddock wrote about the "hypercortisolism" of severe acute illness suggesting that the immunologic response to self-antigens exposed by disease or trauma may be suppressed by corticosteroids to offset the likelihood of autoimmune attack (15). This kind of thinking has provided support for the notion of corticosteroid supplementation as treatment for acute, critical illness, and additional support can be drawn from the report of Annane and coworkers (16). No doubt, with the next outbreak of SARS, studies of its pathophysiology will continue, as will well controlled clinical trials comparing treatments and combinations of treatments, including corticosteroids. Until those results are available, the medical community will have very limited information with which to determine whether steroids are an appropriate treatment for SARS, but will have some important decisions to make if SARS returns. Once SARS pathophysiology becomes better understood and we accumulate the results of clinical trials that are consistent and reproducible, we may have the answer to the corticosteroid question. If not, we may still be debating the use of steroids in SARS for another 25 years.

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Gordon R. Bernard, M.D.
Vanderbilt University School of Medicine
Nashville, Tennessee

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Competing Benefits of Tumor Necrosis Factor-α for Bacteria and for Host Defense

The cytokine tumor necrosis factor-α (TNF-α) functions as an endogenous alarm signal that coordinates gene expression and cellular activity, driving inflammatory responses to infection, injury, or irritation. In addition to stimulating host cell responses, TNF-α causes some bacteria to increase their net growth in culture (1). This observation suggests the hypothesis that TNF-α could exacerbate bacterial infection, which was tested by Lee and coworkers (2) and reported in this issue of the *Journal* (pp. 1462–1470).

Lee and coworkers studied the *in vitro* and *in vivo* effects of TNF-α on two gram-negative bacteria that cause pneumonia in patients with compromised host defenses, *Escherichia coli* and *Pseudomonas aeruginosa* (2). *E. coli* responded to recombinant soluble TNF-α with increased growth *in vitro*. This effect of TNF-α on bacterial growth was dose-dependent and inhibited by blocking antibodies against TNF-α. In contrast, the *in vitro* growth of *P. aeruginosa* was not affected by either TNF-α or anti–TNF-α antibodies. That is, recombinant TNF-α *in vitro* stimulated the growth of *E. coli* but not *P. aeruginosa*.

To study the effects of endogenous TNF-α *in vivo* on bacterial growth in the lungs, Lee and coworkers used mice with a gene-targeted deficiency of TNF-α (2). They rendered both wild type and TNF-α–deficient mice neutropenic by injecting them with cyclophosphamide, and they infected mice by intranasal inoculation with bacteria. When neutropenic mice were infected with *E. coli* (which grew in response to TNF-α *in vitro*), there were significantly more living bacteria in the lungs of wild-type mice compared with TNF-α–deficient mice (2). In contrast, when mice were infected with *P. aeruginosa* (which was not responsive to TNF-α *in vitro*), the number of living *P. aeruginosa* per lung was not affected by

TNF-α deficiency (2). Thus, in neutropenic mice, the endogenous host cytokine TNF-α promoted the growth of responsive bacteria and worsened the infectious burden in the lungs.

These data from experimental pneumonias in mice suggest that, for some immunocompromised patients, the end result of TNF-α may be an exacerbated bacterial infection. Such a contention encourages new directions for research. For example, it will be important to determine whether acute interruption of TNF-α, such as with soluble receptors or blocking antibodies, can ameliorate bacterial growth in immunocompromised lungs. Additional settings of immunosuppression should be considered to determine how broadly applicable the findings with cyclophosphamide-treated mice are to immunocompromised lungs. Finally, elucidating the mechanisms by which some bacteria sense and respond to TNF-α, likely involving surface receptors on the bacteria (3), may identify rational targets for potential adjunctive antibacterial therapies. Selectively interrupting the responses of bacteria to TNF-α could limit bacterial multiplication and thereby benefit immunocompromised patients, especially if they are treated to augment TNF-α (4).

For mice that had not been rendered neutropenic with cyclophosphamide, the effect of TNF-α deficiency during infection was markedly different. During pneumonia caused by either *E. coli* or *P. aeruginosa*, TNF-α deficiency significantly increased bacterial burdens in the lungs and increased mortality (2). Decreased recruitment and activation of neutrophils was likely responsible for the increased bacterial burden (2). These data indicate that, when neutrophils were available, the role of TNF-α in coordinating inflammatory responses to bacteria in the lungs was more important than its stimulation of bacterial growth.

The magnitude of these effects of TNF-α deficiency in mice without neutropenia was remarkable. After 24 hours of infection, TNF-α deficiency increased the bacterial burden in the lungs by an astonishing 5–7 logs, or 100,000- to 10,000,000-fold. In previous studies, soluble inhibitors of TNF-α (5–8) or the genetic ablation of TNF-α receptors (9, 10) have been found to affect bacterial clearance in the lungs by 1 log (10-fold) or less. Moreover, whereas interruption of the gene for TNF-α prevented approximately 90% of neutrophil recruitment in response to either *E. coli* or *P. aeruginosa* (2), interruption of the genes for both known receptors for TNF-α does not decrease neutrophil recruitment during pneumonia caused by either bacteria (9, 10). Thus, these studies of bacterial pneumonia in mice with a genetic deficiency of TNF-α suggest far greater roles for TNF-α than observed in previous reports. These results may reflect differences among study designs, but they also raise the provocative hypothesis that the lifelong deficiency of TNF-α ligand may increase neutrophil recruitment and bacterial killing by mechanisms not inhibited either by the acute disruption of TNF-α ligand–receptor interactions or by the lifelong deficiency of TNF-α receptors.

In addition to killing bacteria, inflammation driven by TNF-α can disrupt and compromise respiratory and circulatory physiology. Excessive proinflammatory cytokines contribute to acute lung injury and systemic shock (11–14). When not absolutely essential for eradicating a microbe, interrupting signaling from proinflammatory cytokines, including TNF-α, may diminish inflammation and preserve pulmonary and cardiovascular function during pneumonia (15, 16).

Thus, diverse effects of TNF-α determine the outcome of bacterial pneumonia. TNF-α promotes bacterial killing, but compromises pulmonary and cardiovascular performance. Interestingly, the genetic deficiency of TNF-α may have more substantial effects on inflammation and bacterial killing than does the acute interruption of ligand–receptor interactions or the genetic deficiency of TNF-α receptors for reasons that remain to be determined. In addition to these effects on host cells, TNF-α stimulates the multiplication of some bacteria. In neutropenic mice, this effect of TNF-α on bacteria can exacerbate respiratory infection. These novel findings highlight important research directions relevant to immunocompromised patients with or at risk for bacterial pneumonia.

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Joseph P. Mizgerd, Sc.D.
Harvard School of Public Health
Boston, Massachusetts

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