is the crucial mechanism of low vascular resistance or vasoplegia. Again, our emphatic statements about the NO pathway and endothelium function may have led to this interpretation. We agree that cardiac surgery vasoplegia has multiple mechanisms, including drug interactions, as Poullis discussed in his excellent letter, which was motivated by the article of Argenziano et al on vasodilatory shock after cardiac surgery.

Their third comment rejects the notion that low systemic vascular resistance is “the main problem with protamine administration.” In our opinion, this is really the main hemodynamic protamine effect. These effects are closely related to infusion rate. Pulmonary hypertension and systemic hypotension routinely occur in most animal models when protamine or any other polycation is given by rapid injection. Many reports have suggested that there may be advantages to the intra-aortic (IA) administration vs the IV administration of protamine due to the reversal of heparin at the end of cardiopulmonary bypass. The cardiac surgical practice is consistent in presenting similar good results if protamine is infused by the IV or IA route. However, there is significant hypotension when protamine is infused by the IA route. NO release is mainly responsible for this effect, because the arterial endothelium is more adapted to this function than is the venous endothelium.

Their fourth comment focuses on the unpredictability of the endothelium function of different organs and animal species, and the unpredictability of NO donors and blockers effects. We completely agree with this comment. We did not emphasize these points, but they are relevant. When low systemic vascular resistance occurs during or after protamine infusion, NO release is a transitory consequence of the constitutive NO-synthase expression. However, if protamine evokes an anaphylactoid or inflammatory reaction, it causes massive overproduction of NO as consequence of inducible NO-synthase isoform expression.

We agree that isolated pulmonary vasodilatation may increase cardiac output and BP by increasing left ventricular filling. This is true and happens when using inhaled NO to treat patients with pulmonary hypertension. However, even in the setting of pulmonary hypertension, and considering the possibility of hypovolemia, isolated pulmonary vasodilatation may cause systemic hypotension by volume redistribution. Finally, we would like to emphasize the three known vasodilatation mechanisms, as follows: guanosine monophosphate-cyclic-dependent, adenosine monophosphate cyclic-dependent, and hyperpolarization-dependent. These three mechanisms are synergistic. Beside these three mechanisms, an arginine vasopressin deficiency also has been reported. From our point of view, a better understanding of this synergism is mandatory. If the vasoplectic hypotension is unresponsive to catecholamines (adenosine monophosphate cyclic), methylene blue (guanosine monophosphate cyclic) infusion would be logical. In our opinion, this synergism is strongly suggested by the faster decrease of catecholamines after methylene blue infusion. Arginine vasopressin deficiency is a particular and individual possibility, because, in general, vasopressin levels remain increased until 48 to 72 h after cardiopulmonary bypass.

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Restoration of Antigen-Specific CD4 T-Cell Response Against Mycobacterium tuberculosis in HIV-Infected People

To the Editor:

In a recent issue of CHEST, Schluger et al (August 2002) reported on a very interesting study of the immune response against tuberculosis in HIV-infected patients who were receiving antiretroviral therapy. This finding is crucial in order to predict the relapse of tuberculosis infection and to develop new therapeutic approaches for HIV-infected people. However, there are some points in the study on which we would like to comment.

(1) The proliferative response and amount of interferon-γ secretion when peripheral-blood mononuclear cells were stimulated with H37Ra were not different, based on previous tuberculin skin test results. In this respect, it is possible that live and heat-killed Mycobacterium tuberculosis H37Ra might not be specific. Thus, the results concerning immune reconstitution after antiretroviral therapy cannot be attributed to the restoration of the immune response against M tuberculosis. In order to clarify this question, it would also be interesting to know the results obtained when peripheral-blood mononuclear cells were stimulated with the other tested antigens (Mycobacterium bovis bacillus Calmette-Guerin-expressing strain and purified protein derivative). (2) The authors considered that all HIV-positive subjects were latently infected by M tuberculosis, because they were born outside the United States or they had risk factors for tuberculosis infection. However, the authors were not able to affirm the definitive diagnosis of latent M tuberculosis infection. Taking into consideration all these facts, we believe that the conclusions of Schluger et al should be considered cautiously since there is no evidence that the antigen used was a specific one. In the future, it would probably be useful to perform a new study using more specific antigens and to include patients with documented active and latent M tuberculosis infection.

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To the Editor:

We agree with Dr. Soriano that the T-cell responses we described in our article may not be specific for Mycobacterium tuberculosis. However, we made no claim in the article that in fact they were specific. The article points out that there is a certain time course that describes the reconstitution of immune recognition of tuberculosis, and it is certainly reasonable to think, as Dr. Soriano suggests, that this description might apply to immune recognition of other pathogens as well.

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Effects of Tumor Necrosis Factor-α Inhibitors on Lung Lesions With Rheumatoid Arthritis

To the Editor:

Recently in CHEST, Vassallo and colleagues1 (September 2002) reported on a 71-year-old man with a 3-year history of rheumatoid arthritis (RA) whose damaged pulmonary function, associated with RA, was ameliorated by treatment with the tumor necrosis factor (TNF)-α inhibitor infliximab. More recently, Peno-Green and coworkers2 (November 2002) reported the first case of lung injury to occur while the patient was receiving etanercept. Although the molecular players in RA are still poorly understood, representative proinflammatory cytokines, such as TNF-α and interleukin (IL)-1, have proven to be major contributors to this disease. However, there are few studies elucidating the role of TNF-α in the pulmonary lesions of RA. The contrary effects of TNF-α inhibitors on the pulmonary lesions of RA in the published case reports in CHEST might have depended on the severity of the disease affecting the lung parenchyma.

Over a decade ago, Gosset et al3 elucidated the roles of the release of TNF-α and IL-1 from alveolar macrophages in patients with RA and compared the contributions of these proinflammatory cytokines between RA patients who had or did not have lung involvement. In the study, Gosset et al3 showed that the spontaneous production of TNF-α was significantly increased in RA patients with or without pulmonary manifestations compared with production in control subjects, but patients with interstitial lung disease had a markedly increased rate of local immune complex reactions to albumin in BAL fluid compared with patients without lung disease. However, Elias4 claimed that the interaction of TNF with IL-1 or interferon-γ modulated fibroblast proliferation. Therefore, TNF-α inhibition may alter the interaction, resulting in an increased proinflammatory effect for IL-1 or interferon-γ in the patient reported by Peno-Green et al.2

The histopathologic findings of the patient by Peno-Green et al2 also require some discussion. Transbronchial lung biopsy specimens obtained from the patient demonstrated noncaseating granulomas, and Mycobacterium avium-intracellulare complex was isolated in the BAL fluid specimens. A pivotal role for TNF-α in the defense against mycobacteria has been implicated, and causative mechanisms of anti-TNF-α agents have been reported to impair the tuberculosis immune response.5 Transgenic mice lacking TNF receptors developed lethal mycobacterial infections due to widespread inflammatory cell apoptosis within disintegrating granulomas, which was mediated by an excess of T cells.6 Granuloma formation may be elicited through the reduced immunity to mycobacteria, which is caused by TNF-α blocking.7 Additionally, we would like to introduce an interesting study by Campbell et al.8 The investigators examined the direct role of TNF in two representative animal models of arthritis using TNF-deficient (TNF−/−) mice. Two RA models (ie, collagen-induced arthritis and acute monoarticular arthritis) in TNF−/− mice generally had some reduction in the clinical parameters and histology when compared with those in wild-type mice, but some mice exhibited severe disease. Campbell and colleagues8 concluded that TNF is important but not essential for these types of inflammatory arthritis. This excellent work illustrates that TNF-α inhibition may be harmful as well as beneficial for RA patients.

The further accumulation of similar case reports is needed to clarify the contribution of TNF-α inhibitors on RA patients.

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