patients will still be complaining of upper airway side effects resulting from their use of inhaled corticosteroids.

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Diagnosing Tubercular Pleural Effusions

To the Editor:

We read with interest the article by Hikari et al (March 2004) comparing the markers of tuberculosis in pleural effusions. We wish to express our disagreement with their statement that interferon (IFN)-γ should be measured routinely in all suspected cases of pleural tuberculosis. They have based their conclusion on the basis of a perfect area under the curve of 1.000 on receiver operator characteristic analysis for IFN-γ as compared to 0.958 for adenosine deaminase (ADA). The authors have failed to adequately review the fairly large body of literature on biological markers of tubercular pleural effusion.

ADA has been reported with perfect values in the literature (100% sensitivity,2–4 and also 100% specificity, positive predictive value, and negative predictive value5) in studies with larger sample sizes (n = 221, 48 tuberculosis; n = 405, 91 tuberculous; n = 350, 76 tuberculous; and n = 138, and 61 tuberculous) than the present study (n = 55, 20 tuberculosis).1 Valdes et al,3 using simultaneous measurement in the same set of patients (n = 405), reported a higher sensitivity for ADA (100%) than IFN-γ (94.2%) and a higher specificity (95%) for ADA and 91.5% for IFN-γ. Villegas et al6 compared ADA and IFN-γ (along with polymerase chain reaction [PCR]) simultaneously in 140 patients with 42 confirmed TB cases and reported a higher sensitivity (88.1% for ADA vs 85.7% for IFN-γ) and better negative predictive value than IFN in the whole prevalence range. Valdes et al7 reported that 253 of a total of 254 tuberculous pleuritis patients had ADA levels > 40 IU/mL, and in the 82 patients in whom both ADA and IFN-γ were done, the sensitivity of IFN was 89% (73 of 82 patients) against at least 98.78% (81 of 82 patients) for ADA.

Studies comparing ADA and IFN-γ simultaneously in the same set of patients have reported both ADA better than IFN-γ,8–11 and IFN-γ better than ADA,9,10 as diagnostic markers. In fact, a meta-analysis by Greco et al10 regarding the diagnostic accuracy of ADA vs IFN-γ included 31 studies in favor of ADA (total, n = 4,738) and 13 studies in favor of IFN-γ (total, n = 1,189). Using summary receiver operating characteristic curve, they found only a marginal difference in overall sensitivity and specificity: 93% for ADA, and 96% for IFN-γ. Using Bayes theorem, the posttest probability of a negative test result was calculated. The minute difference in posttest probabilities (ADA vs IFN-γ, 0.4% vs 0.2%, 2.4% vs 1.2%, and 24% vs 17%) was maintained over a wide prevalence range of 5 to 85%. The authors concluded that "ADA and IFN-γ appear to be reasonably accurate at detecting TB pleurisy." Virtually similar sensitivity and specificity coupled with lower cost should favor the use of ADA as a diagnostic tool compared to IFN-γ.

Lastly, the authors suggest that PCR should be compared with IFN, etc. Such a study comparing PCR, IFN, and ADA simultaneously in pleural effusion patients has already been published in CHEST.8

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To the Editor:

We are confused by the comments by Drs. Gupta and Chhabra concerning our article.1 Indeed, high concentrations of adenosine deaminase (ADA) in the pleural fluid of patients with tuberculosis pleuritis have already been confirmed by many studies. However, the statement that the use of ADA has been reported with perfect values for sensitivity and specificity in the literature is overstated. Perez-Rodriguez and Castro2 summarized the results of 11 studies and reported the sensitivity and specificity for ADA were 77 to 100% (average, 93.3%) and 81 to 97% (average, 91.3%), respectively. Chen et al3 summarized the results of eight studies and reported the sensitivity and specificity for ADA as 79 to 100% (average, 85.6%) and 80.5 to 96% (average, 85.4%), respectively. A meta-analysis including 40 articles conducted by Goto et al4 showed that the sensitivity of ADA ranged from 47.1 to 100% and the specificity from 50.0 to 100%. However, these studies5–7 also showed that the false-positive rate is relatively high. In a meta-

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To the Editor:

We are confused by the comments by Drs. Gupta and Chhabra concerning our article.1 Indeed, high concentrations of adenosine deaminase (ADA) in the pleural fluid of patients with tuberculosis pleuritis have already been confirmed by many studies. However, the statement that the use of ADA has been reported with perfect values for sensitivity and specificity in the literature is overstated. Perez-Rodriguez and Castro2 summarized the results of 11 studies and reported the sensitivity and specificity for ADA were 77 to 100% (average, 93.3%) and 81 to 97% (average, 91.3%), respectively. Chen et al3 summarized the results of eight studies and reported the sensitivity and specificity for ADA as 79 to 100% (average, 85.6%) and 80.5 to 96% (average, 85.4%), respectively. A meta-analysis including 40 articles conducted by Goto et al4 showed that the sensitivity of ADA ranged from 47.1 to 100% and the specificity from 50.0 to 100%. However, these studies5–7 also showed that the false-positive rate is relatively high. In a meta-
Apoptosis of Circulating Neutrophils and Alveolar Macrophages in COPD

To the Editor:

In a recent issue of CHEST (May 2004),1 Noguera and coworkers reported that in vitro neutrophil apoptosis in patients with COPD occurred at a rate similar to that found in healthy individuals and smokers with normal lung function. Further, increased surface expression of Mac-1 (CD11b) and decreased surface expression of L-selectin (CD62L) were observed in the apoptotic neutrophils of patients with COPD.

It has been reported that neutrophil granulocytes show a reduced spontaneous apoptosis during acute exacerbations of COPD, but that increases progressively after treatment and clinical remission.2 This raises the question of the importance of neutrophil apoptosis in the development and resolution of exacerbations of COPD. Thus, the current study may provide some scientific background to address the dynamics of apoptosis in vivo lung neutrophils. However, a number of questions remain to be solved.

First, apoptosis is induced by both oxidant production and the depletion of antioxidant in cells. Inversely, supplementation of antioxidant prevents apoptosis in lung-derived cells.3 Thus, isolated circulating neutrophils from the blood stream that are not fully occupied with blood antioxidant are not a good candidate for the analysis of cell fate in the various inflammatory diseases.

Second, cigarette smoke (CS) contains approximately 4,000 various constituents, including numerous chemicals that result in the production of reactive oxygen species. CS causes apoptosis and necrosis in airway cells including alveolar macrophages (AMs).4,5 CS-mediated depletion of lung glutathione is thought to lead to increased lipid peroxidation, neutrophil sequestration, and transcription of proinflammatory cytokine genes.6 We have reported that CS extract (CSE) induced apoptosis at lower concentrations (10 to 25%) and necrosis at higher concentrations (50 to 100%).6 We also examined the effects of glutathione S-transferase P1, one of the xenobiotic and antioxidant enzymes in the lung, against the cytotoxicity of CSE. Thus, the antioxidant status and antioxidant gene expression levels may have effects against CS in the airway cells.6,7 Third, although apoptosis is a universal process in the cells, the mechanism of apoptosis is not simple. In in vitro studies,8 human AMs cultured with aqueous CSE undergo apoptosis. This apoptosis is associated with increased oxidative stress, Bax protein accumulation, mitochondrial dysfunction, and mitochondrial cytochrome c release, but is independent of p53, Fas, and caspase activation. These results may provide information to explain macrophage dysfunction and lung diseases in cigarette smokers.

Fourth, patients with bronchiectasis had a lower percentage of neutrophils that were neither apoptotic nor necrotic than in healthy control subjects.8 The low levels of apoptosis observed in the patients may be associated with inhibition of apoptosis by inflammatory mediators such as interleukin (IL)-8 and tumor necrosis factor (TNF)-α.9 High levels of TNF-α and IL-8 have consistently been found in the bronchial secretions of the patients. Because these cytokines have been known to be increased in patients with COPD, a similar mechanism may work in patients with COPD. Acute exposure to CS induces infiltration of neutrophils into the airways through nuclear factor-κB and IL-8 gene expression.10

Fifth, in COPD, plasma soluble Fas ligand (sFas) was within normal levels. Plasma soluble Fas/Apo-1 receptor (sFas) levels were similar among healthy control subjects, disease control subjects, and patients with mild-to-moderate COPD, but were significantly increased in severe COPD.11 The increased plasma sFas is independent of hypoxemia, and increases in Paco2, TNF-α, IL-6, and inflammation may be associated with progression of COPD. Thus, the measurement of apoptosis of AMs and neutrophils in lungs in relation to the different pathologic stages of COPD may offer further information for the role of apoptosis of lung cells in the pathogenesis of COPD.

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