Our results show that the development of severe postoperative neurologic events in all but the first clusters was statistically related to at least one coexistent complication. The interrelationship of these events makes the identification of the relative contribution of each single variable difficult. It is reported that the development of neurologic complications can be the result of low cardiac output syndrome (ie, severe arrhythmias).10,11 Vice versa, cardiac injury can develop as a result of brain damage.7,8 Therefore, further studies are necessary to elucidate the relationship of these complications.

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Vascular Permeability in Active Pulmonary Tuberculosis

To the Editor:

We read with great interest the recent prospective clinical study by Alatas et al1 (June 2004). We would like to add a few comments to their work. First of all, we are interested in the wide variance of the serum vascular endothelial growth factor (VEGF) levels in patients with active pulmonary tuberculosis as compared with those in patients with inactive pulmonary tuberculosis or in healthy subjects. In particular, we want to be informed of the detailed profiles of patients with > 1,000 pg/mL of VEGF levels. Were there any correlative factors such as clinical symptoms or laboratory data with the high levels of VEGF? As Alatas and colleagues describe in the discussion, larger clinical studies are needed to find the factors in close association with VEGF titters.

We also want to introduce another candidate for an indicator of active pulmonary tuberculosis. Metallothionein is a highly conserved, low-molecular-weight, cysteine-rich protein. Metallothionein has been proposed to play an important role in homeostasis and detoxication of heavy metals. Metallothionein can serve as a sacrificial scavenger for hydroxyl radicals in vitro and protects against free radical-induced DNA damage.3–5 Since proinflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ, induce hepatic metallothionein gene expression, the role of metallothionein in inflammatory diseases has been focused. We recently have demonstrated that metallothionein-null (-/-) mice were more susceptible than corresponding wild-type mice to lung inflammation, especially to lung edema, which were induced by intratracheal challenge with bacterial endotoxin.6 We confirmed that metallothionein proteins in the lungs were detected in endothelial cells and alveolar epithelial cells of wild-type mice, whereas they were not detected in those of metallothionein (-/-) mice by immunohistochemistry. After endotoxin challenge, metallothionein deficiency enhanced vascular degeneration of pulmonary endothelial cells and type I alveolar epithelial cells, and caused focal loss of the basement membrane without any significant differences in the enhanced local (lung) expression of proinflammatory cytokines and chemokines or in the activation of nuclear factor-κB pathway in the lung between the two genotypes. We concluded that endogenous metallothionein is defensive against acute lung injury related to bacterial endotoxin, possibly via the protection of pulmonary vascular integrity.6 Additional researches targeting metallothionein in pulmonary tuberculosis might throw new therapeutic strategies to this persistent infectious disease.

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To the Editor:

We thank Dr. Inoue and colleagues for their comments on our recently published article.1 Indeed, the active tuberculosis pa-
patients have a wide range of vascular endothelial growth factor (VEGF) levels in our study. The lowest and highest levels that we observed were 202 pg/mL and 1,538 pg/mL, respectively. We have five patients with VEGF levels > 1,000 pg/mL. All of these patients have bilateral infiltration in their chest radiographs. A significant correlation (p < 0.05) was observed between VEGF levels and fever in active pulmonary tuberculosis patients. However, there was not any other correlation between VEGF levels and clinical or laboratory data.

Metallothionein may be an interesting marker since the imbalance between oxidants and the antioxidant defense system is an important issue in both tuberculosis and other inflammatory diseases. The investigations to determine a marker for the active form of tuberculosis will continue in the future.

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What About Add-On Second-Line Controller Therapy?

To the Editor:

The review by Roland et al (July 2004)1 in CHEST has provided a timely reminder of the local adverse consequences of the use of inhaled corticosteroids in treating asthma. However, while playing an integral role in the management of inflammatory airways disease, inhaled corticosteroids are effective when used in smaller doses in combination with additional second-line controller therapy. This is especially pertinent, and indeed is advised, in patients with mild-to-moderate disease whose conditions are suboptimally controlled with low-dose inhaled corticosteroids.

In their article, the authors do not mention the use of concomitant nonsteroidal antiinflammatory therapy with leukotriene receptor antagonists or long-acting β2-agonists. Using these agents would obviously permit a lower inhaled corticosteroid dose to be used, while maintaining or even improving asthma control. In turn, this would reduce the dose of corticosteroid delivered to the oropharynx and endobronchial tree, minimizing the risk of both troublesome local and serious systemic sequelae. Common sense tells us that we should continue to advise patients to use a spacer device, rinse their mouths, and gargle after using an inhaled corticosteroid. Moreover, clinicians should be aware that the addition of second-line controller therapy with a concomitant reduction of inhaled corticosteroid dose should be considered when dealing with a patient with oropharyngeal candidiasis and dysphonia. Indeed, encountering an asthmatic patient with such problems provides an ideal opportunity to consider adjusting the burden of inhaled antiinflammatory therapy.

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To the Editor:

We read the letter from Dr. Currie with interest, and we agree with the issues raised in the letter.

Our article was primarily written to bring to everyone’s attention the side effects of corticosteroids in the upper airway. We think that these quite distressing symptoms are often ignored.

The basic thrust of the article was to describe the side effects and to discuss what can be done for those patients who need therapy with inhaled steroids to control their symptoms. The assumption was that there are a large number of patients who are receiving full asthma treatment according to the guidelines, including long-acting β2-antagonists and leukotriene antagonists, who still require large doses of inhaled steroids.

We fully accept that all patients would be treated according to the various guidelines, which clearly state that long-acting β-blockers are an integral part of asthma management when the dose of inhaled steroids is getting above 800 µg/d (British Thoracic Society guidelines). The latest British Thoracic Society guidelines also have introduced add-on therapy at an earlier stage on the basic assumption that this provides better control and will have some steroid-sparing effect. In addition, there is now increasing evidence that doubling the dose of inhaled corticosteroids during an exacerbation is probably not very effective.

Leukotriene antagonists do seem to have some steroid-sparing effect for inhaled steroids (the effect for oral steroids is much more controversial). However, there is still considerable debate about the stage at which they should be used.

Thus, we agree with Dr. Currie that everything possible should be done to provide good asthma control, including the case of add-on therapies. However, even when all this is done, many