To the Editor:

I am very pleased to comment upon Dr. Daniell’s very scholarly response to our article. His work on prostate cancer and smoking was referenced in our article. I appreciate his bringing to my attention his earlier, related work examining the relationship between smoking and the natural histories of breast and colon cancers. Those studies provide further evidence of an effect of smoking upon the biological behavior of malignancies for which a causal association with smoking has not been established. I agree with Dr. Daniell that systemic effects of smoking, particularly but not limited to immunologic effects, may explain the relationship between smoking and a greater propensity to metastasis. However, I also believe a direct effect of smoking upon the lung to be another, very plausible, contributing factor. In our study, we found that the relationship between smoking and metastatic disease was strongest, in fact, for the subgroup of patients with known metastases limited only to the lung. We have recently validated an animal model of the effects of smoking upon breast cancer metastasis to the lung, and we look forward to employing this model to help clarify the mechanisms involved. As for the issue of hormonal effects of smoking, I agree with Dr. Daniell that, while smoking does have minor hormonal effects, those effects are unlikely to explain the effects of smoking upon metastasis. This possibility was included at the request of the reviewers of the manuscript.

In answer to his one specific question about our work, we employed a matched, case-control study design, and auxiliary lymph node status was one of the factors for which we matched cases and controls. Thus, it is not possible to compare the nodal status for smokers and nonsmokers in our database, which was, by design, the same for both groups.

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To the Editor:

We read with interest the article in CHEST by Barst et al (June 2002) concerning endothelin antagonism with sitaxsentan in patients with pulmonary arterial hypertension (PAH). In contrast with previous studies with epoprostenol and as well as bosentan showing improved cardiac index in patients with PAH, the authors report significant decrease in pulmonary artery pressure and resistance without improved cardiac index. The hypothesis that sitaxsentan may have a unique mode of action in patients with PAH may not be the only explanation for these findings. Approximately 30% decrease in pulmonary artery resistance accompanied with a less pronounced but almost 20% decrease in pulmonary artery pressure with stable pulmonary capillary wedge pressure, as reported in this study, should be connected with increased systemic cardiac index in patients without possibility of shunting between the pulmonary and systemic circulation. According to the text though, this study population included 10 patients with congenital systemic to pulmonary shunts, while at least two of these patients had possibly unresectable shunts at ventricular level. Patients with PAH due to congenital mixing between systemic and pulmonary circulation have relatively preserved systemic cardiac index at the expense of significant cyanosis. In these patients, a decrease in pulmonary vascular resistance leading to increased pulmonary cardiac index may result in decreased systemic cardiac index, albeit decreased right-to-left shunt and improved cyanosis. The results presented in Figure 4 showing individuals with significant increases as well as decreases in systemic cardiac index with sitaxsentan would be consistent with this explanation, especially if some of the patients with relatively normal but failing systemic cardiac indexes belong to the group with systemic to pulmonary mixing. Presentation of detailed hemodynamic data and analysis according to the presence or not of mixing in this population may help in explaining the absence of systemic cardiac index improvement. A detailed analysis of the hemodynamic effect of endothelin antagonism in patients with PAH with data analysis according to the etiology of PAH may help in elucidating the pathobiology and mechanisms involved in this patient population.

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REFERENCES

To the Editor:

It is a pleasure to see how carefully Drs. Apostolopoulou and Rammos read our article. Unfortunately, due to space issues in CHEST as well as virtually all other peer-reviewed journals, we were unable to elaborate on the hemodynamic changes observed with this pilot open-label, uncontrolled sitaxsentan trial in patients with pulmonary arterial hypertension.

Although several patients did have systemic-to-pulmonary communications, as well as right-to-left shunting resulting in systemic arterial oxygen desaturation prior to receiving sitaxsentan therapy, when sitaxsentan was administered over a long period, systemic arterial oxygen saturation either increased or remained unchanged, i.e., no patients had worsening of their right-to-left shunting and all patients maintained a normal resting cardiac index. In the several patients in whom cardiac index decreased after 12 weeks of therapy with sitaxsentan, despite the decrease that occurred in these patients, particularly those with a high resting cardiac index (which was partly due to right-to-left intracardiac shunting), cardiac index remained within a normal resting range for all patients at 12 weeks and, as expected, increased in those patients in whom the baseline cardiac index was low.