established our program. One barrier concerned the attitude of our doctors toward associate clinicians. We had to assure them that their patients would not be cared for exclusively by nonphysician associate clinicians. Next, we had to dispel the perception that the Heart Failure Program represented a threat or competition to their practice. Rather, the program is a resource available to appropriate patients and clinicians. We work with primary physicians, and our program has been well received. Working with the primary physician is important in addressing all comorbidities including diabetes mellitus, renal failure, pulmonary disease, and others that have impact on the overall morbidity and mortality of the patient.

Rozzini and colleagues present their data in the subset of 149 patients discharged from the hospital with New York Heart Association class III and IV heart failure. In this group, mortality at 6 months was 33.6%, which they call less impressive compared to our results. However, this is being modest because these results are not easily comparable for two reasons. First, their patients were much older, with mean age of 51 years, compared to 68 years for our group. One would expect a higher rate of death based on age alone. Second, most of their patients had diastolic heart failure with a mean left ventricular ejection fraction of 60.6%. I am not aware of survival rates for octogenarians with diastolic heart failure. Perhaps outcome measures other than survival may be more realistic in the very elderly, as mortality at this age is strongly linked with average life expectancy. Such measures may include quality of life and impact of program on resource utilization.

Kwame O. Akojah, MD
Gundersen Lutheran Heart Institute
La Crosse, WI

Breast Cancer in Smokers

To the Editor:

The observation by Murin and Inciardi (June 2001) of increased pulmonary metastases from breast cancer among smokers is supported by more evidence than they included in their article. This evidence also helps to discount the possibility of coincidence as posed by Lillington and Sachs (June 2001) and answers some of the questions posed by the authors of both publications.

In a study of 485 postmenopausal women, we found more frequent axillary metastases among smokers than among nonsmokers after control for age, estrogen receptor status, primary tumor size, and obesity. In a separate series of 176 women with axillary metastases, we found that metastases were larger in smokers (p < 0.01) after control for primary tumor size, obesity, the number of positive nodes, and host age. Primary tumors were slightly smaller in smokers, evidence against delayed tumor diagnosis among them. These observations are most compatible with earlier and more frequent metastasis by breast cancer cells in smokers, and they are also compatible with more rapid growth of breast cancer metastases among them.

Murin and Inciardi did not report whether smokers in their study demonstrated more axillary nodes than otherwise similar nonsmokers, but this data would be of interest. The phenomenon of more frequent metastases from primary tumors in smokers, or of more rapid progression of primary or metastatic tumor tissue in them, was referenced by Murin and Inciardi in patients with myelogenous leukemia, prostate cancer, and malignant melanoma. This phenomenon is not restricted to these tumor types, having also been documented in patients with carcinomas of the endometrium, cervix, bladder, lung, and colon as well as those with breast cancer. Most metastases from these tumors are nonpulmonary, indicating the presence of smoking-related systemic factors, which either directly stimulate malignant cells or inhibit host antitumor defense mechanisms, resulting in accelerated growth, invasion, or metastasis by these cells. The probability of smoking-induced inhibition of host antitumor immune defenses was recognized by Murin and Inciardi and is supported by evidence documenting widespread impairment of immune responses in smokers, including the easily measured responses to vaccines against influenza and hepatitis B. Most tumor types with smoking-associated worse prognosis are not hormone sensitive, suggesting that smoking-induced endocrine abnormalities cannot explain this general pattern. The possibility of increased pulmonary metastases having resulted from direct influence on pulmonary tissue by tobacco smoke seems remote.

Harry W. Daniell, MD
University of California, Davis, Medical School
Redding, CA

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Correspondence to: Harry W. Daniell, MD, Clinical Professor of Family Practice, University of California Davis Medical School, 2626 Edith Ave, Redding, CA 96001

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www.chestjournal.org CHEST / 123/5 / MAY, 2003 1771
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 axillary 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.

Susan Murin, MD, MSc, FCCP
University of California, Davis, School of Medicine
Sacramento, CA

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Correspondence to: Susan Murin, MD, MSc, FCCP, Associate Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, UC Davis School of Medicine, 4150 V St 3400, Sacramento, CA 95817

Sitaxsentan in Pulmonary Arterial Hypertension

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 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 this observation. An almost 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 test though, this study population included 10 patients with congenital systemic to pulmonary shunts, while at least two of these patients had possibly unrestrictive 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 falling systemic cardiac index levels 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 pathophysiology and mechanisms involved in this patient population.

Sotiria C. Apostolopoulou, MD
Spyridon Rammos, MD
Onassis Cardiac Surgery Center
Athens, Greece

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.

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Sotiria C. Apostolopoulou, MD
Spyridon Rammos, MD
Onassis Cardiac Surgery Center
Athens, Greece

to the Editor:...