Neoplasias associated with a state of immunodepression are an accepted fact and could explain low levels of ADA. In our patient, cellular immunity was conserved because the Mantoux reaction was positive. Perhaps this could explain the elevated ADA levels. The lack of response to treatment discards a mixed etiology. Another explanation could lie in the impressive metabolic activity of the pleural fluid, manifested by LDH levels greater than 2,000 IU/L and glucose levels less than 10 mg/dL.

The specificity of ADA in the differential diagnosis of pleural effusions is 0.97; thus, this false positive does not contradict the results of various prior studies.19 However, we present this patient in the light of his special characteristics.

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Pulmonary Hypertension,
Right Ventricular Failure, and
Vasodilator Therapy
Making Pathophysiologic Sense

To the Editor:

Clinical investigations in pulmonary hypertension, associated right ventricular failure, and vasodilator therapy that do not differentiate the underlying pathophysiology continue to be reported.1 Delineating the various stages of the underlying pathophysiology may help explain the variable findings.14

The rationale for using vasodilator therapy in pulmonary hypertension is its success in systemic arterial hypertension and left ventricular failure.5 But, unlike systemic arterial hypertension, the small pulmonary arteries in adults with pulmonary hypertension lack medial hypertrophy.44 Pulmonary hypertension in adults is due to intraluminal narrowing or occlusion caused by cardiac output (CO), and only small decreases in mean pulmonary artery pressures (mPAP).5 Since vasodilators are unlikely to effect intraluminal narrowing or occlusions, the observed decreases in PVR must be due to vasodilation of the remaining unarowered and unoccluded pulmonary vessels. This vasodilation causes decreased PVR, and the reduced right ventricular afterload results in increased CO.4 If there are many unarowered and unoccluded pulmonary vessels, then a significant decrease in mPAP may also be observed. This is more likely the case in early and subclinical pulmonary hypertension, especially as seen in infants with congenital heart disease.7 On the other hand, if there are few or no unarowered and unoccluded pulmonary vessels, as seen in severe pulmonary hypertension,7,4 then vasodilator therapy would drop SVR only which, without increased CO, would result in deleterious effects.15 The decreased PVR and increased CO, suggestive of less diffuse intraluminal pulmonary vascular disease, result in increased oxygen transport and increased "mixed venous" oxygen tensions, which have been shown to correlate with survival.8 Thus, the clinical response to vasodilator therapy should be at least partially dependent on the number of pulmonary vessels remaining unarowered and unoccluded.

Right ventricular failure appears to be due to right ventricular (RV) pressure overload coupled with decreases in right coronary artery flow.10 Whether decreases in mPAP (and RV load) achieved by limiting CO response to vasodilator therapy can improve survival remains unproven (and possibly too hazardous to try). This can be shown by the following manipulations of the PVR equation:

\[
PVR = \frac{mPAP - PAWP}{CO} \\
PVR \times CO = (mPAP - PAWP) \times 80
\]

Since PAWP is small and 80 is a constant, then:

\[
PVR \times CO = mPAP \\
PVR \times SV \times HR = mPAP
\]

Generally, PVR decreases and, depending on the vasodilator drug employed, either SV or HR increases, resulting in little or no decreases in mPAP. Combination vasodilator-cardiodepressive therapy (eg, beta-blocker or verapamil and vasodilator; diltiazem) could also limit CO, which would result in a decrease in mPAP. As noted, the lack of increased CO may be deleterious due to the decrease in SVR. RV can be unloaded without changing the mPAP.

In conclusion, clinical investigations should be directed at identifying the degree of remaining unarowered and unoccluded vessels and addressing the vasodilator effects on these and on the RV. Patients with pulmonary hypertension could then be grouped, studied, and reported according to the degree of pathophysiology found. Whether anything short of a heart-lung transplant43 can improve those with far advanced pulmonary vascular occlusive disease remains to be proven.

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1 Rubin LJ, Moser KM. Long-term effects of nitrendipine or hemodynamics and oxygen transport in patients with cor pulmonale. Chest 1986; 89-141-45

To the Editor:

Several points raised by Dr. Davila warrant comment. The statement that pulmonary hypertension, either primary pulmonary hypertension or that due to chronic obstructive pulmonary disease, is solely the result of irreversible obstruction and destruction of the pulmonary vasculature is incorrect. Chronic obstructive pulmonary disease, both clinical and experimental, is characterized by muscularization of the small pulmonary arterioles. The earliest and most consistent pathologic finding in primary pulmonary hypertension is medial hypertrophy. These observations, coupled with physiologic responses to the infusion of acetylcholine, prompted Dr. Paul Wood to postulate a vasoconstrictive factor in the pathogenesis of pulmonary hypertension.

There are no data to substantiate the statement that significant reductions in pulmonary artery pressure for prolonged periods of time are necessary to improve cor pulmonale. Kawakami et al. demonstrated that pulmonary and right ventricular hemodynamics do not differentiate surviving and non-surviving patients with chronic obstructive pulmonary disease. In their study, however, the mixed venous oxygen tension, an index of tissue oxygen delivery, was significantly higher in the survivors, suggesting that interventions which improve oxygen delivery may have an important influence on survival.

Several studies have demonstrated that cor pulmonale exerts an independent influence on survival from COPD. Traver et al. reported that the presence of cor pulmonale adversely affected survival at all levels of forced expiratory volume in one second. Burrows et al. found that no patient in their study with a pulmonary vascular resistance greater than 550 dyne/sec/cm² survived three years, and that respiratory survival correlated more closely with pulmonary vascular resistance than with any other hemodynamic or spirometric parameter, including pulmonary artery pressure. The Nocturnal Oxygen Therapy Trial Group reported that patients with higher pulmonary vascular resistances at baseline had an increased mortality.

Pulmonary vascular resistance is a calculated value which relates pressure to flow, and as such is only one of several hemodynamic variables which should be monitored to determine responsiveness to interventions. Nevertheless, there is evidence to support the importance of changes in pulmonary vascular resistance in the setting of pulmonary hypertension: mortality from primary pulmonary hypertension correlates not with the pulmonary artery pressure but with the pulmonary vascular resistance. Increases in right ventricular ejection fraction in response to the administration of hydralazine and nifedipine correlate closely with changes in pulmonary vascular resistance and decreases in ventricular end diastolic pressure in patients with right ventricular failure correlated to changes in pulmonary vascular resistance, even when pulmonary artery pressure falls minimally or not at all."

Demonstration that vasodilator therapy may potentiate the reduction in pulmonary vascular resistance and increases in oxygen delivery produced by breathing low flow supplemental oxygen further suggest the utility of this approach to therapy. However, as noted in our article, several issues remain unresolved. Will this form of therapy influence survival from cor pulmonale, and how can patients be identified who are most likely to respond beneficially? The answer to these questions will ultimately determine the role of this form of therapy.

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3 Wood P. The vasoconstrictive factor in pulmonary hypertension. Br Heart J 1958; 20:357-70

Erratum

To the Editor:

Although it has been several months since the publication of the October, 1985 supplement to Chest, I would still like to have mistakes in my paper corrected. The first mistake is on page 2085. The last sentence in the first column reads, "Endothelium is not required for the relaxation induced by sodium nitroprusside, however, and nitroprusside does not stimulate the production of cyclic GMP." Nitroprusside does, in fact, stimulate the production of cyclic GMP. The second mistake is in reference 12; the third line should read, ... cyclic GMP (not "cyclic AMP") dependent."

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