experiments, both animal and clinical. In the lung, Dauber and colleagues showed that increased vascular permeability to protein occurred in association with elevated levels of tumour necrosis factor and the appearance of circulating levels of endotoxin during pump-oxygenator bypass in dogs. The take home messages from the study by Dauber et al was that pulmonary vascular injury in a model of cardiac surgery is independent of blood flow diversion, ie, pulmonary ischemia. The positive correlation that Sinclair noted between increased lung microvascular permeability and serum myeloperoxidase activity is consistent with general tenants of the causes of acute lung injury. Neutrophil activation with cardiopulmonary bypass or reperfusion or both may injure the alveolar-capillary membrane through the release of intracellular constituents in the lung’s microvessels.9

The findings by Sinclair and colleagues that the gut is injured after cardiopulmonary bypass could also be explained by a microvascular injury complicating the intraoperative management of the patient. Ohri and colleagues showed that an increase in gut permeability after cardiopulmonary bypass was temporally associated with mucosal hypoperfusion. In the gut, mucosal hypoperfusion despite maintenance of mesenteric blood flows in cardiopulmonary bypass could be the consequence of “shunting” of blood away from the villus. Even in the absence of shock, a majority now support this concept of microcirculatory dysfunction as a fundamental problem in critical illness.10 Causes of microvascular hypoperfusion in organs represented in the MODS include a depression in myocardial performance (limiting appropriate increases in systemic blood flows), a depression in arterial vasoreactivity (leading to a maldistribution in systemic blood flows between individual organs) and abnormalities in the endothelium and neutrophil (causing capillary RBC flow abnormalities). It is therefore probable that the increased endotoxin level after cardiopulmonary bypass shown in the study by Dauber et al was the consequence of mucosal ischemia due to microvascular dysfunction in the gut. More importantly, it is microvascular dysfunction that ultimately causes increases in permeability of both the alveolar-capillary membrane and the mucosal barrier of the gut.

What Can the Clinician Learn From This Study?2

The study by Sinclair and colleagues highlights a number of important issues for the clinician. First, is the reaffirmation that cardiopulmonary bypass is not without consequence. This procedure is accompanied by widespread microvascular injury, and organ dysfunction is the demonstrable outcome. It is indeed surprising that the incidence of clinically apparent organ dysfunction is generally so infrequent in this patient population.1 Second, the clinician must be tentative to optimizing a patient’s hemodynamic status in the postcardiopulmonary bypass. In the presence of pump-induced microvascular injury, postoperative complications such as hypotension could only be expected to amplify the lesion. Finally, we need to better understand characteristics of that component of the cardiopulmonary bypass population, which progress to manifest clinically significant organ dysfunction—SIRS and MODS—which result in prolonged postoperative recovery and increased mortality. We now have a better understanding of the cause of organ dysfunction in these patients, so predicting what patients are most likely at risk of this problem could lead to investigations of approaches that “protect” the microcirculation from cardiopulmonary bypass-induced multiple organ injury.

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Amphotericin B Aerosol for Transiently Immunocompromised Hosts

Reasonably Safe, but Does it Matter?

The list of drugs delivered to the lung by inhalation and which may be of benefit to patients is contin-
usually growing. In addition to those drugs being designed for systemic absorption (eg, polypeptides, heparin) and a number of newer antiasthmatic agents, such therapies include antibiotics,1 modifiers of airway fluid and electrolyte balance2 and DNAase,3 which have been shown to be efficacious in selected cystic fibrosis populations, recombinant genes,4 vaccines,5 surfactants and surfactant proteins,6 antiproteases,7 antitoxins,8,9 and cyclosporin.10 A principal attraction of delivering drugs as aerosols, powders11 and liposomes9 for the treatment of lung conditions is that the drugs are delivered directly to the site of intended action, thus reducing the possibility of systemic side effects. Although a number of previous studies have reported uses of amphotericin B (AMPH B) in aerosol form,12-14 there are only a few systematic documentations of possible respiratory tract toxicities after rigorous nebulization administration protocols; to date, AMPH B has failed to join the list of aerosol therapies which have been shown to be clearly beneficial and cost-effective (when considering alternative measures) in targeted patient populations.

In this issue of the CHEST, Dubois et al (see page 750) have examined the physiologic effects of aerosolized AMPH B administrations to 18 patients expected to have a period of granulocytopenia (<500/mm3) secondary to induction for leukemia (2 patients) or to bone marrow transplantation (16 patients). End points studied included heart rate, oxygen saturation (oximetry), peak flow rates, and indexes of both cough and dyspnea. Although patients with a history of "severe" asthma were excluded as a group, neither the asthmatics (n=3) nor the nonasthmatics (n=15), exhibited significant drops in peak flows after AMPH B treatments, although several individuals had significant drops in FEV1 and almost half of the instances where peak flow dropped ≥20% occurred in the 3 asthmatics. About one of five AMPH B treatments given to asthmatics developed reductions in peak flow ≥20% compared with ≤5% in nonasthmatics. Importantly, there were no instances in which AMPH B administrations had to be discontinued because of the observed respiratory tract effects.

It is postulated that if AMPH B could be delivered effectively to the lung in aerosol form, increased antifungal protection could take place at the entry site, accompanied by a reduction in the frequently observed undesirable systemic side effects and without a concomitant increase in renal toxicity. While delivery of inhaled AMPH B to the lung appears simple, there are several complex issues yet to be addressed. Aerosol administration to respiratory tract surfaces pose a number of challenges which theoretically affect aerosol delivery, regional deposition, drug retention, and organ pharmacokinetics.15,16 In spite of utilizations of an efficient reproducible nebulizer system, a great deal of variability of regional drug distribution can be expected to occur. In contrast to other patient groups (eg, such as cystic fibrosis), most bone marrow transplant recipients would be expected to present fairly uniform aerosol depositions; thus, effective prophylaxis could be expected to occur on all respiratory tract surfaces. However, it may be necessary to modify treatment strategies in patients with significant pulmonary disorders associated with severe inhomogeneities of ventilation and where heterogeneous patterns of aerosol deposition have been shown to occur.10,17

Dubois and colleagues aerosolized 30 mg AMPH B, and based on estimates extrapolated from studies of pentamidine inhalation, calculate that 5% of this dose (1.5 mg) could have been deposited in the lungs utilizing a nebulizer configuration system designed to generate particles between 1 to 3 μm and which would predictably reach the lower airways and lung parenchymal surfaces. This important and critical assumption is validated in a recent study by Diot and colleagues18 who bench tested particle size and aerosol distribution of a noncommercially available form of AMPH B in the same nebulizer system used by Dubois et al using isotopic techniques previously validated.10,15 Using a smaller dose of aerosolized AMPH B (5 mg), Diot's group also found that the Respirgard II delivered approximately 5% of the nebulized dose to the lung periphery in three patients being treated for pulmonary mycetoma. Like the Dubois et al study, they found no untoward pulmonary effects of the AMPH B in daily aerosol administrations over 4 weeks.

However, it is important to recognize that neither study was designed to examine the important issues of appropriate dosage and optimal schedule of treatment. Neither study determined AMPH B levels in the respiratory tract lining fluids, nor attempted to compare these levels with minimum inhibitory concentrations that would provide for adequate antifungal effects. Before designing more clinical efficacy studies of the role of aerosolized AMPH B in the chemoprevention of fungal infections, it will be particularly important to resolve optimal dosage and timing issues. These considerations will provide for additional insights on AMPH B stability and retention in the pulmonary milieu. In this regard, liposome encapsulation, which can extend the half-life of entrapped drugs by an order of magnitude, may offer the advantage of decreasing wide swings of AMPH B respiratory tract concentrations (thus theoretically minimizing complications of mucosal "irritations") while increasing its residence time in the lung.9,19 Although theoretically this would have the effect of opening up more practical and efficient opportunities for using aerosols for prophylactic applications to respiratory tract surfaces, to date the efficacy of liposomal preparations of AMPH B have been less than anticipated.14 Important, techniques for
examining all of these issues are technically available.

Of the number of important questions that remain unanswered, the most vexed question is: does it work? Can AMPH B aerosol administration substantively decrease the incidence of lung fungal infections in transiently and severely immunocompromised hosts? The answer to this last question is of significant practical importance because without effective prophylactic antifungal strategies these patients have a high incidence of fungal infections. Measures such as controlled ventilation, reverse isolation, antifungal lavages, oral azole administrations, and even prophylactic low-dose IV AMPH B administration and aerosolized intranasally administered AMPH B have proved helpful in decreasing this incidence. In fact, a pilot study using historic controls has already shown convincing evidence that the combination of high efficiency particulate air filtration and AMPH B aerosol (5 mg via a "cirrus" nebulizer [Inter-Surgical]) provided excellent prophylaxis against invasive aspergillosis in granulocytopenic patients. It is hoped that clinicians will not have to fret much longer over this issue . . . and that, given more pilot dose ranging data, AMPH B aerosol studies can quickly move from the toxicity testing (phase 1) to efficacy testing (phase 2).

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Treatment of IPF
What Does the Future Hold?

In this issue of CHEST (see page 948), Goldstein and Fine present a well-conceived and thoughtful review of new approaches to the treatment of fibrotic lung diseases, primarily idiopathic pulmonary fibrosis (IPF). Last summer, a workshop sponsored by the Division of Lung Diseases, National Heart, Lung and Blood Institute was convened to consider novel approaches for the treatment of IPF. The impetus for these two publications is the acknowledged ineffectiveness of present therapeutic regimens for a uniformly fatal disease as well as the accumulation, over the past 25 years, of experimental data detailing the potential inflammatory pathways resulting from various lung injuries which in turn could progress to irreversible fibrosis.

Although there is no question that new modifying therapies are needed for IPF and other diseases which result in lung fibrosis, it seems unlikely that there is a common fibrotic pathway that follows dissimilar inflammatory responses. Consider the distinct histologic