sure in patients with sickle cell disease, ignores the multiple humoral mechanisms that regulate blood pressure; we recently reported on the importance of mediators other than nitric oxide in these patients.[8] Our discussion of pathology focused on hemolysis, but we agree with Dr. Pawloski about septic shock, which (as we noted in our article) is generally characterized by very high levels of nitric oxide synthase activity.

Dr. Singel's defense of the S-nitrosohemoglobin hypothesis raises the more general question of how to extrapolate from experiments in vitro or experiments in animals to explanatory paradigms relevant to the human circulation. Results of laboratory experiments from many different groups have led to multiple models to describe how nitric oxide can be preserved, destroyed, or delivered by the circulatory system. Only studies in human subjects will ultimately sort out these issues and show whether a robust pharmacology based on nitric oxide delivery will be possible.

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Management of Drug and Alcohol Withdrawal

TO THE EDITOR: In their informative and practical review of the management of drug and alcohol withdrawal, Kosten and O'Connor (May 1 issue)[1] advocate the use of diazepam at a dose of 5 to 10 mg every two to four hours for the management of delirium tremens and withdrawal seizures. They note that longer-acting benzodiazepines have been found to be more effective than placebo in reducing the incidence of seizures and delirium. However, lorazepam may be more effective than diazepam for treating alcohol-withdrawal seizures and status epilepticus. In one study, lorazepam terminated 59.1 percent of episodes of status epilepticus (10 percent caused by alcohol withdrawal), as compared with 42.6 percent for diazepam.[2] Intravenous lorazepam treatment is associated with fewer recurrences of seizure than diazepam and with less need for repeated doses, since its efficacy is higher (82 to 100 percent) than that of diazepam (54 to 100 percent).[3,4]

Although all benzodiazepines enter the cerebral tissue quickly, lorazepam has a longer antiseizure effect (12 to 24 hours) than diazepam (15 to 30 minutes) and a higher affinity for benzodiazepine receptors in the brain.[5] However, the systemic half-life of diazepam is nearly 100 hours, as compared with 30 hours for lorazepam. Treatment with diazepam may lead to peripheral accumulation without anticonvulsant efficacy and with an increased likelihood of sedation, making the assessment of mental status difficult.

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1. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med 2003;348:1786-95.
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TO THE EDITOR: Kosten and O'Connor suggest propanolol as an alternative for severe cocaine-withdrawal symptoms. The use of beta-blockers in patients who have ingested cocaine is not free of hazards. Because of an unopposed alpha effect, the use of beta-blockers may be associated with decreased coronary blood flow and increased coronary vascular resistance, may predispose patients to arrhythmias, and may trigger a hypertensive crisis.[1,2] Cocaine is associated with potentially lethal cardiac toxicity. The broad spectrum of adverse events ranges from chronic cardiomyopathy to syncope and sudden cardiac death.[3] Delayed toxic effects due to the presence of active metabolites with long half-lives are possible.[4] Any use of beta-blockers in this setting requires careful monitoring and caution.

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TO THE EDITOR: Kosten and O'Connor describe the treatment of alcohol-withdrawal symptoms with symptom-triggered therapy, rather than with medication given on a fixed scale. However, our clinical experience with patients who have head and neck cancer, among whom the prevalence of alcohol abuse is greater than 60 percent, is that the prevention of alcohol-withdrawal symptoms is even more important. This idea is supported by the literature.[1] All of our patients who have a history of alcohol abuse receive 150 μg of clonidine before surgery and 300 μg per day, intravenously or orally, for the next five days in combination with benzodiazepines. We advise not waiting to provide treatment until withdrawal symptoms start. The symptoms may mimic cardiovascular, neurologic, or infectious problems. By the time those major complications have been ruled out, most patients have had full-blown withdrawal symptoms, and their treatment has become much more difficult.

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THE AUTHORS REPLY: The correspondents emphasize the complexity of withdrawal treatments. As Dr. Devi indicates, in a study of lorazepam and diazepam, either of these medications was better than placebo in terminating seizures.[1] However, the two medications did not differ (relative hazard for the persistence of status epilepticus, 0.65; 95 percent confidence interval, 0.36 to 1.17) when adjusted for covariates, such as the 15 percent higher rate of previous seizures in the diazepam group than in the lorazepam group. One limitation of lorazepam, but not diazepam, is the need for refrigeration. In addition, the brain levels of diazepam rise more quickly because it is more lipid-soluble than lorazepam. Dr. Devi mentions that the antiseizure effects of lorazepam last 50 times as long as those of diazepam, but this appears to have been an inaccuracy in the original 1993 report[2] that was then carried over into the cited 1998 review.[3] It is correct, however, that the duration of activity of diazepam is three times that of lorazepam; it is for this reason that diazepam is used, because a very-long-acting agent is better than a short-acting agent for minimizing withdrawal symptoms.

Drs. Huitink and Buitelaar suggest that because some patients undergoing surgery are at high risk for alcohol withdrawal, preemptive treatment, rather than symptom-triggered use of medication, may be appropriate. We caution that benzodiazepines given after anesthesia can lead to acute respiratory arrest because of intensified sensitivity of the γ-aminobutyric acid neurotransmitter receptors. Furthermore, their use of clonidine seems poorly considered. Clonidine will not stop seizures, which constitute the most severe complication, and will simply add to the hypotension and potential respiratory suppression induced by the benzodiazepines. We caution against the combined use of these medications in patients who may have respiratory complications due to preemptive use of benzodiazepines. If benzodiazepines are used, we suggest short-acting agents, rather than diazepam, to minimize the duration of any respiratory compromise.

Dr. Castro wisely cautions about the use of propranolol in cocaine withdrawal because of the potential for outpatients to use cocaine while taking propranolol. The medical safety and potential efficacy of carvedilol, an alpha- and beta-blocker, for reducing cocaine reinforcement has recently been

shown in laboratory studies in humans, and we agree that it would be a better medication to relieve withdrawal symptoms in outpatients.[4] However, the clinical efficacy of carvedilol has not yet been tested in outpatients in a placebo-controlled trial.

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CD8+ T Lymphocytes in Bronchiolitis Obliterans, Paraneoplastic Pemphigus, and Solitary Castleman's Disease

TO THE EDITOR: Paraneoplastic pemphigus has been reported in patients with Castleman's disease, and bronchiolitis obliterans in association with paraneoplastic pemphigus can eventuate in respiratory failure and death.[1-4] Anatomically, there is a diffuse segmental constrictive bronchiolitis of small bronchioles.[5] The cause of the bronchiolitis is obscure. Acantholysis of bronchial epithelium and linear deposition of IgG and complement along the lamina propria were observed on transbronchial biopsy in two patients,[2] suggesting that autoantibodies may have a role.

A 52-year-old man presented with abdominal discomfort in December 1999. Computed tomography (CT) of the abdomen revealed a retroperitoneal mass, 12×8×6 cm, adjacent to the left kidney. A biopsy showed Castleman's disease of the hyaline vascular type. The tumor was unresectable because of its juxtaposition to the kidney and the aorta. The patient was treated with radiotherapy (3000 cGy), and follow-up CT revealed a 50 percent reduction in the size of the mass. In January 2001, oral, conjunctival, and penile erosions developed, cicatricial pemphigoid was diagnosed, and the patient was treated for this condition. Shortly thereafter, a dry cough and exertional dyspnea developed. The dyspnea rapidly worsened, necessitating 24-hour use of supplemental oxygen.

In September 2002, the diagnosis of paraneoplastic pemphigus and bronchiolitis obliterans, in association with solitary Castleman's disease, was made. Despite aggressive treatment with cyclosporine and two cycles of rituximab, cyclophosphamide, and dexamethasone, the patient died of hypercapneic respiratory failure in December 2002.

Autopsy revealed a spectrum of pathological changes in the small bronchioles, from detachment of columnar epithelial cells to panmural cellular infiltration, partial or complete obliteration of the bronchiolar lumen by fibrolymphocytic tissue, and replacement of the entire bronchiole by fibrosis. Immunohistochemical analysis revealed that the panmural infiltrate invading the bronchiolar walls consisted almost exclusively of CD8+ T lymphocytes (Fig. 1). B cells and natural killer cells were absent. Immunoglobulin and complement deposits were not detected in the bronchiolar lesions. Studies of

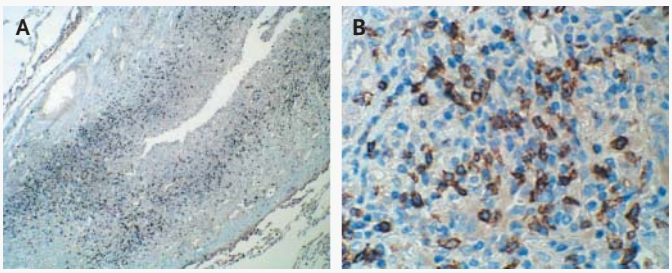

Figure 1. Section from a Small Bronchiole with Immunohistochemical Staining with Anti-CD8 Antibody (Panel A, ×100; Panel B, ×400), Showing Constrictive Bronchiolitis with Panmural Infiltration by CD8+ T Lymphocytes and the Partially Obliterated Bronchiolar Lumen.