that both artemether and the closely related compound arteether induce a selective pattern of damage principally to the brain-stem nuclei involved in auditory processing. If the prolongation of coma observed in our study and in the accompanying study from the Gambia was caused by neurotoxicity, then it was reversible. There was no associated neurologic deficit in survivors, and no evidence of auditory abnormalities. The incidence of neurologic sequelae in the Gambian trial was also similar in the two treatment groups. We believe that a definitive statement regarding the relative merits of artemether and quinine should await a systematic overview of many randomized, controlled trials. If this confirms that artemether treatment is associated with a lower mortality rate than quinine, and there is no associated increase in neurologic sequelae, then any effect on the duration of coma will have secondary importance.

Dr. Newmark is correct; an error crept into the manuscript. The line should have read, “the correlated QT interval was prolonged to more than 0.5 second.”

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Efficacy of Granulocyte–Macrophage Colony-Stimulating Factor in Acquired Alveolar Proteinosis

To the Editor: Acquired alveolar proteinosis is a rare lung disease of adults characterized by excessive accumulation of surfactant. Standard therapy is whole-lung lavage, which usually provides temporary symptomatic benefit. In mice lacking the hematopoietic regulator granulocyte–macrophage colony-stimulating factor (GM-CSF), a pulmonary abnormality develops that resembles alveolar proteinosis. Therefore, we initiated a trial of recombinant human GM-CSF therapy in a patient with this disease after obtaining the approval of the institutional ethics committee and written informed consent from the patient.

A 49-year-old man was given a diagnosis of alveolar proteinosis after open-lung biopsy in 1993. He subsequently underwent three therapeutic lavages, with transient improvement each time. When GM-CSF therapy began, he had extensive alveolar infiltrates and could walk only 400 m on level ground or climb one flight of stairs. There was no evidence of pulmonary infection. During treatment with GM-CSF, his exercise capacity progressively increased and arterial oxygenation improved (Fig. 1). By day 35 he could walk an unlimited distance on level ground or climb four flights of stairs without resting. Treatment with GM-CSF was discontinued on day 70, at which time his activity was not limited and the alveolar infiltrates had partially cleared. However, by day 84 exertional dyspnea had recurred. Resumption of GM-CSF therapy on day 252 was followed by a similar pattern of improvement. There was no deterioration in oxygenation after GM-CSF was resumed, but vomiting and fever developed on day 1. Thereafter, the only side effects were mild erythema at injection sites and headache, which was relieved by acetaminophen. The patient’s maximal neutrophil count was $6.6 \times 10^9$ per liter.

Although the condition of some patients with alveolar proteinosis improves spontaneously, this patient’s previous pattern of disease and the clinical, physiologic, and radiographic changes in response to the initiation, withdrawal, and reintroduction of GM-CSF therapy all support a causal role for GM-CSF in the response and are consistent with an underlying impairment of GM-CSF production or responsiveness in the pathogenesis of this patient’s disease. On the basis of the pulmonary changes that characterize GM-CSF-deficient mice and the demonstrated impairment of surfactant clearance in these animals, it is likely that administered GM-CSF activates alveolar macrophages and increases their rate of surfactant clearance.

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Figure 1. Serial Measurements of the Alveolar–Arterial Oxygen Gradient in a Patient with Acquired Alveolar Proteinosis during GM-CSF Therapy.

The partial pressure of arterial oxygen was measured while the patient was breathing room air (fraction of inspired oxygen, 0.21). Alveolar oxygen pressure was calculated with the alveolar-gas equation under assumed steady-state conditions and used to determine the alveolar–arterial oxygen gradient. The upper limit of the predicted normal range for the alveolar–arterial oxygen gradient is 23.5 mm Hg. The initial dose of GM-CSF was 3.0 mg per kilogram of body weight per day subcutaneously; the dose was gradually increased to 5.0 to 6.0 mg per kilogram per day. As of day 32, the patient was still receiving GM-CSF (6.0 mg per kilogram per day).
Anaphylaxis and Coronary Disease

To the Editor: In the Clinical Problem-Solving article entitled “The Domino Principle” (Aug. 1 issue), Jaffe and Zahger describe an assumed anaphylactic reaction that produced shock and subsequent myocardial ischemia. What is unusual in this case is the presence of sinus rhythm of 90 beats per minute in a patient who is assumed to be in anaphylactic shock and who is not receiving beta-adrenergic blockers. By virtue of the clinical presentation of shock, normal sinus rhythm without tachycardia is extremely unusual, especially in anaphylactic reactions. The release of histamine during anaphylaxis causes marked increases in sympathoadrenergic tone and directly stimulates histamine H1 receptors, producing positive chronotropic effects. Multiple other mediators also produce direct and indirect reflex effects, all of which consistently produce tachycardia. The fact that this patient had a sinus rhythm of 90 beats per minute suggests she may not have had an anaphylactic reaction. Furthermore, the diagnosis of anaphylaxis is usually reserved for patients with immunospecific antibodies. The assumed reaction to diclofenac, a nonsteroidal antiinflammatory drug, is actually an anaphylactoid reaction caused by nonspecific activation of the inflammatory pathway, perhaps produced by the shunting of cyclooxygenase by-products into lipoxygenase pathways. Echo-cardiography performed in patients in acute anaphylactic shock can reveal evidence of low left ventricular end-diastolic volumes with ventricular obliteration during systole, changes suggestive of profound intravascular hypovolemia, low systemic vascular resistance, and normal ventricular function. The description of the echocardiogram did not discuss ventricular volumes. Finally, the patient’s temperature of 35.5°C was never adequately explained.

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The authors reply:

To the Editor: Dr. Roth suggests that the finding of an elevated tryptase level might have facilitated the diagnosis of anaphylaxis. The assay is unfortunately not routinely available at our center and was therefore not performed.

Drs. Levy and Shanewise suggest that the absence of tachycardia and of hypercontraction and underfilling of the left ventricle argues strongly against the diagnosis of anaphylaxis. As discussed in our paper, the finding of normal ventricular function, rather than hypercontraction with cavity obliteration, should have raised the suspicion that factors other than anaphylaxis were operative. Our discussion focused on the interaction of the anaphylactic reaction and cardiac ischemia, and we believe that both the echocardiographic findings and the relative bradycardia may be explained by concomitant ischemia in a patient with severe triple-vessel disease. Myocardial ischemia was evident electrocardiographically on admission and could certainly have led to increased ventricular volumes and reduced contractility. Finally, the reaction may indeed have been an anaphylactoid rather than an anaphylactic one, although mast-cell degranulation and histamine release occur in both.

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Medicare Hospice Programs

To the Editor: In their analysis of hospice enrollment patterns, Drs. Christakis and Escare (July 18 issue) analyzed Medicare-certified hospice providers as independent agen-