placebo-controlled trial in partially acclimated trekkers has clearly shown that *Ginkgo biloba* is ineffective in the prevention of AMS. Recently, ibuprofen (600 mg three times daily) was shown to be beneficial in the prevention of AMS, but more definitive studies and proper gastrointestinal-bleeding risk assessment need to be conducted before ibuprofen can be routinely recommended for AMS prevention. Many drugs, including spironolactone, medroxyprogesterone, magnesium, calcium channel blockers, and antacids, confer no benefit in the prevention of AMS. Similarly, no efficacy studies are available for coca leaves (a weak form of cocaine), which are offered to high-altitude travelers in the Andes, or for *soroche* pills, which contain aspirin, caffeine, and acetaminophen and are sold over the counter in Bolivia and Peru. Finally, a word of caution applies in the pharmacologic prevention of altitude illness. A fast-growing population of climbers in pursuit of a summit are using prophylactic drugs such as glucocorticoids in an attempt to improve their performance; the outcome can be tragic because of potentially severe side effects of these drugs.

For the treatment of mild AMS, rest alone with analgesic use may be adequate. Descent and the use of acetazolamide and (if available) oxygen are sufficient to treat most cases of moderate AMS. Even a minor descent (400–500 m) may be adequate for symptom relief. For moderate AMS or early HACE, dexamethasone (4 mg orally or parenterally) is highly effective. For HACE, immediate descent is mandatory. When descent is not possible because of poor weather conditions or darkness, a simulation of descent in a portable hyperbaric chamber is effective and, like dexamethasone administration, "buys time." Thus, in certain high-altitude locations (e.g., remote pilgrimage sites), the decision to bring along the light-weight hyperbaric chamber may prove lifesaving. Like nifedipine, phosphodiesterase-5 inhibitors have no role in the treatment of AMS or HACE.

HIGH-ALTITUDE PULMONARY EDEMA

Risk Factors and Manifestations Unlike HACE (a neurologic disorder), HAPE is primarily a pulmonary problem and therefore is not necessarily preceded by AMS. HAPE develops within 2–4 days after arrival at high altitude; it rarely occurs after more than 4 or 5 days at the same altitude, probably because of remodeling and adaptation that render the pulmonary vasculature less susceptible to the effects of hypoxia. A rapid rate of ascent, a history of HAPE, respiratory tract infections, and cold environmental temperatures are risk factors. Men are more susceptible than women. People with abnormalities of the cardiopulmonary circulation leading to pulmonary hypertension—e.g., large patent foramen ovale, mitral stenosis, primary pulmonary hypertension, and unilateral absence of the pulmonary artery—are at increased risk of HAPE, even at moderate altitudes. For example, patent foramen ovale is four times more common among HAPE-susceptible individuals than in the general population. Echocardiography is recommended when HAPE develops at relatively low altitudes (<3000 m) and whenever cardiopulmonary abnormalities predisposing to HAPE are suspected.

The initial manifestation of HAPE may be a reduction in exercise tolerance greater than that expected at the given altitude. Although a dry, persistent cough may presage HAPE and may be followed by the production of blood-tinged sputum, cough in the mountains is almost universal and the mechanism is poorly understood. Tachypnea and tachycardia, even at rest, are important markers as illness progresses. Crackles may be heard on auscultation but are not diagnostic. HAPE may be accompanied by signs of HACE. Patchy or localized opacities (Fig. 476e-2) or streaky interstitial edema may be noted on chest radiography. In the past, HAPE was mistaken for pneumonia due to the cold or for heart failure due to hypoxia and exertion. Kerley B lines or a bat-wing appearance are not seen on radiography. Electrocardiography may reveal right ventricular strain or even hypertrophy. Hypoxemia and respiratory alkalosis are consistently present unless the patient is taking acetazolamide, in which case metabolic acidosis may supervene. Assessment of arterial blood gases is not necessary in the evaluation of HAPE; an oxygen saturation reading with a pulse oximeter is generally adequate. The existence of a subclinical form of HAPE has been suggested by an increased alveolar-arterial oxygen gradient in Everest climbers near the summit, but hard evidence correlating this abnormality with the development of clinically relevant HAPE is lacking.

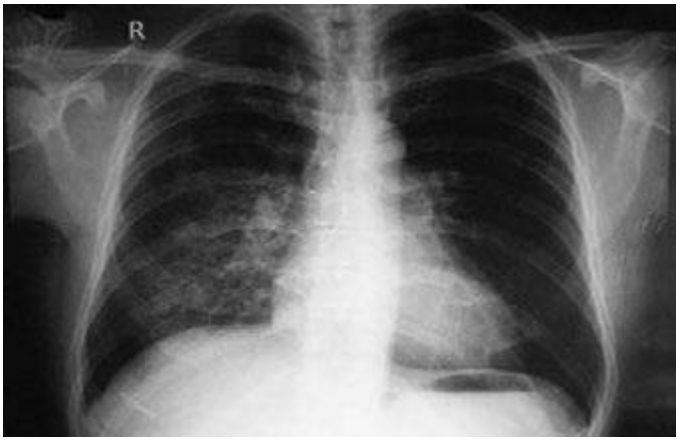

FIGURE 476e-2 Chest radiograph of a patient with high-altitude pulmonary edema shows opacity in the right middle and lower zones simulating pneumonic consolidation. The opacity cleared almost completely in 2 days with descent and supplemental oxygen.

Pathophysiology HAPE is a noncardiogenic pulmonary edema characterized by patchy pulmonary vasoconstriction that leads to overperfusion in some areas. This abnormality leads in turn to increased pulmonary capillary pressure (>18 mmHg) and capillary "stress" failure. The exact mechanism for the vasoconstriction is unknown. Endothelial dysfunction due to hypoxia may play a role by impairing the release of nitric oxide, an endothelium-derived vasodilator. At high altitude, HAPE-prone persons have reduced levels of exhaled nitric oxide. The effectiveness of phosphodiesterase-5 inhibitors in alleviating altitude-induced pulmonary hypertension, decreased exercise tolerance, and hypoxemia supports the role of nitric oxide in the pathogenesis of HAPE. One study demonstrated that prophylactic use of tadalafil, a phosphodiesterase-5 inhibitor, decreases the risk of HAPE by 65%. In contrast, the endothelium also synthesizes endothelin-1, a potent vasoconstrictor whose concentrations are higher than average in HAPE-prone mountaineers. Bosentan, an endothelin receptor antagonist, attenuates hypoxia-induced pulmonary hypertension, but further field studies with this drug are necessary.

Exercise and cold lead to increased pulmonary intravascular pressure and may predispose to HAPE. In addition, hypoxia-triggered increases in sympathetic drive may lead to pulmonary venoconstriction and extravasation into the alveoli from the pulmonary capillaries. Consistent with this concept, phentolamine, which elicits α-adrenergic blockade, improves hemodynamics and oxygenation in HAPE more than do other vasodilators. The study of tadalafil cited above also investigated dexamethasone in the prevention of HAPE. Surprisingly, dexamethasone reduced the incidence of HAPE by 78%—a greater decrease than with tadalafil. Besides possibly increasing the availability of endothelial nitric oxide, dexamethasone may have altered the excessive sympathetic activity associated with HAPE: the heart rate of participants in the dexamethasone arm of the study was significantly lowered. Finally, people susceptible to HAPE also display enhanced sympathetic activity during short-term hypoxic breathing at low altitudes.

Because many patients with HAPE have fever, peripheral leukocytosis, and an increased erythrocyte sedimentation rate, inflammation has been considered an etiologic factor in HAPE. However, strong evidence suggests that inflammation in HAPE is an epiphenomenon rather than the primary cause. Nevertheless, inflammatory processes (e.g., those elicited by viral respiratory tract infections) do predispose persons to HAPE—even those who are constitutionally resistant to its development.

Another proposed mechanism for HAPE is impaired transepithelial clearance of sodium and water from the alveoli. β-Adrenergic agonists