

use of a new drug (troglitazone, bromfenac, tolcapone, felbamate, ticrynafen, benoxaprofen). Furthermore, although the rate of serious injury has in some cases been unacceptable and has led to withdrawal or removal as a first-line therapy, in most cases the rate of serious injury has been relatively low. Other idiosyncratic events sufficient to lead to a black box warning or withdrawal have been uncommon. In some cases, discovery of a new toxicity has been quite delayed (eg, marked hypotension with clozapine, pulmonary fibrosis and marrow toxicity with tocainide). The delayed discovery of valvulopathy associated with fenfluramine hydrochloride, of subarachnoid hemorrhage associated with phenylpropanolamine, and of various toxicities of quinidine provide further evidence that even long-marketed drugs sometimes are shown to have unexpected toxic effects. Thus, there is no duration of use that allows a physician complete assurance that additional toxicity will not emerge.

A physician contemplating prescribing a new drug should consider carefully the reason for the choice, particularly when an equally effective alternative is available, as there is always some risk of an undiscovered ADR. But it is incorrect to describe the introduction of unsafe drugs as frequent; the analysis of drugs by Lasser et al actually demonstrates that ADRs of sufficient importance to change the role of a drug in practice are uncommon. If there is sound reason to use a recently approved drug, the physician need not deny the patient this treatment. The Food and Drug Administration (FDA) recently proposed a rule that would include the date of approval on the package insert.⁴

Lasser et al suggest that the FDA should "raise its threshold" for approving new drugs when safe, effective alternatives already exist; but this idea is not developed further and it is not clear whether the authors believe superiority of a new drug, as opposed to equivalence, should be established, more data should be required, or something else is

needed. It is worth observing that existing therapy does not always prove to be completely safe and fully satisfactory and that there is value in having alternatives. Terfenadine, after all, appeared to be entirely safe until its QT effects were discovered, whereupon the availability of another non-sedating antihistamine seemed fortunate. A major point of Lasser et al is that even drugs that have been on the market for some years can have ADRs that have gone undetected.

Recent changes in drug development should help protect against some of the most important past causes of drug withdrawal. Drugs are now evaluated in both animals and humans for their effect on cardiac repolarization (ability to prolong the QT interval) and drugs that do so are not approved or are approved with labeling that points to the need for close monitoring or attention to concomitant therapy. Similarly, the ability of drugs to inhibit hepatic metabolizing enzymes and interact with other drugs is now thoroughly examined. In addition, early signals of hepatotoxicity are better assessed. Thus, there is reason to believe that some of the more common causes of significant toxicity will be less likely in the future. However, no improvements will completely eliminate the risk of unexpected events. The FDA continues to rely on reporting of ADRs by physicians, other health care professionals, and others to help uncover these risks as rapidly as possible.

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High-Altitude Pulmonary Edema

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HIGH-ALTITUDE PULMONARY EDEMA (HAPE) IS A potentially fatal condition that typically starts after ascent in people ascending too quickly. When first described, HAPE was assumed to be due to acute left ventricular failure, but it has been known for 40 years that HAPE is associated with an excessive hypoxic pulmonary vasoconstriction and pulmonary hypertension. This by itself cannot be the sole cause, however, because not all in-

dividuals who develop pulmonary hypertension develop HAPE at altitude.

In 1986, THE JOURNAL published an important advance in the understanding of HAPE.¹ Schoene et al showed that climbers who had HAPE and underwent bronchoalveolar lavage (BAL) at a camp set up at 4400 m on Denali (Mount McKinley, 6194 m) had lavage fluid with a high concentration of protein compared with lavage fluid from 3 healthy investigators. In addition, the presence of complement activation and lipoxigenase metabolites indicated a degree of

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inflammation, but the white blood cell differential revealed alveolar macrophages, not polymorphonuclear leukocytes. The researchers concluded that “the early events in HAPE involve a change in permeability, without major activation of inflammatory mechanisms. . . .” In the same issue of *THE JOURNAL*, Hackett et al² showed that the total protein content of pulmonary edema fluid in a skier who had HAPE and was brought down to 1285 m was the same as that in the serum.

These 2 reports seemed to show that HAPE was a transient high-protein permeability edema,³ but unlike adult respiratory distress syndrome, without significant inflammation. HAPE, then, represented a new type of noncardiac pulmonary edema. However, the idea of an important role for inflammation has persisted. Subsequent investigators found strong evidence for inflammation in persons severely ill with HAPE,⁴ including more BAL data⁵ and an association of HAPE with viral infection.^{4,6}

In this issue of *THE JOURNAL*, Swenson et al⁷ report the results of studies done to elucidate this question, carried out at the Capanna Regina Margherita, perched on the Punta Gnifetti (4559 m), one of the summits of Monte Rosa on the Italian-Swiss border.

This mountain hut has a distinguished record in the annals of high-altitude research. The great Italian physiologist Angelo Mosso (1846-1910) made Turin a center for exercise physiologists at the end of the 19th century. Mosso was greatly interested in the effects of altitude on the body and made an early winter ascent of Monte Rosa in 1885.⁸ He drew up plans for the Regina Margherita observatory, named after his patron, Queen Margherita of Savoy, and it was built on the solid rock of the Gnifetti peak in 2 phases in 1899 and 1902. The laboratory fell into disuse but was rebuilt and greatly enlarged between 1978 and 1980, and an active research program started again under the direction of the Swiss researchers Oswald Oelz, Marco Maggiorini, and Peter Bärtsch.

Mosso used soldiers as his experimental subjects, and 4 of them appear in a photograph in Mosso's book⁸ following their descent from the original hut. Standing at the back is Pietro Ramella, described by Mosso's coinvestigator, Dr V. Abelli, as being at the start, “a mountaineer aged 22 . . . in excellent condition” but in the photograph as “recovering from an attack of inflammation of the lungs.” At low altitude, before ascent, Ramella's pulse had been 50/min and his respiration, 14/min. He had climbed swiftly from the valley floor, spending a night en route and carrying 20 kg of bread to the hut. When he arrived, he felt well, but throughout the next 6 hours his condition became rapidly alarming; he complained of a headache (which became violent), nausea, and vomiting and was leaden-colored and had tachycardia (110 to 124/min). His pulse was difficult to palpate, and he showed rapid respirations (20-32/min) with striking periodicity during sleep and when awake. He was noted to be markedly cyanotic. Although his rectal temperature

rose to 39.9°C on the evening of his arrival, it soon fell, and after the first 24 hours, it never rose above 38.8°C. A debate concerning evacuation to a lower altitude became moot when “a terrible storm burst . . . over the Alps rendering it impossible to leave the hut, much less transport” him down. Over the next few days, although he had little cough and no pleuritic pain, rales were repeatedly heard and he produced rusty sputum. Ramella recovered steadily with rest throughout the next few days.

Abelli considered that this was a case of pneumococcal pneumonia, although he could not examine the sputum under the microscope, so they took aseptic precautions. He noted that they had an effective disinfectant, discarding sputum through the south window down onto the Vigne glacier 1500 m directly below. Although Abelli was impressed enough by the case to present it to a learned society, it was Mosso's genius to realize that Ramella's case presented an important anomaly. Mosso was struck by the disparity between the tachycardia and the moderate elevation in temperature. Mosso thought, from his experiments, that this was all due to “paralysis of the vagus nerve.”

We now know that what Ramella experienced was HAPE. Indeed, Abelli's case report is the most detailed early clinical description of HAPE, although fatal attacks of breathlessness in the mountains had been recorded since a Chinese monk died, foaming at the mouth, in AD 403 while ascending a pass near Afghanistan.³ The question remains whether inflammation, as Abelli supposed, might be a significant factor in HAPE. An answer to this question is particularly important, given that if this proved to be the case, all sorts of specific preventive and therapeutic possibilities would be worth trying in an attempt to prevent and treat a disabling and potentially fatal disease of otherwise healthy individuals.

The study by Swenson et al⁷ advances our knowledge of HAPE considerably. Previous BAL studies clearly demonstrating inflammation in HAPE had been performed only after the edema was well established, sometimes 24 to 48 hours after onset of clinical HAPE. Swenson et al reasoned that if no inflammation was detected by BAL early in the course of HAPE, then inflammation could not be a cause but rather was a consequence of alveolar flooding. Their findings suggest that inflammation is indeed not an essential ingredient in the origin of HAPE.

The study has several limitations. One can only assume that evidence of inflammation would have developed as HAPE progressed; serial lavage was not undertaken in this study because of logistical considerations and because lavage itself causes transient inflammation. Another limitation was that only 3 subjects actually had HAPE close to the time of lavage, while 6 of the 7 remaining HAPE-susceptible subjects developed HAPE the next day. The 3 with HAPE, however, had a consistent and striking 100-fold increase in lavage fluid protein concentration compared with that at low altitude and 10-fold increase com-

pared with that of HAPE-resistant subjects at altitude. The increase in lavage red blood cells was even greater. Simultaneously, total leukocyte count and differential were unchanged in all subjects, strongly arguing against inflammation and confirming the data of Schoene et al.¹ The lavage protein values were lower than those in the study by Schoene et al, consistent with BAL performed earlier in the course of the illness, and with the idea that, later in the illness, alveolar reabsorption of fluid would probably increase protein concentration. Finally, although the small numbers are a limitation, there is no clear pattern suggesting more of an increase in cytokines in those with HAPE.

Supporting the notion that the HAPE-susceptible subjects who developed clinical HAPE the next day already had a minor pulmonary leak are the increased red blood cells and protein levels in this group, with values between those found in the people resistant to HAPE and those ill with HAPE, as well as their greater hypoxemia and slightly elevated chest radiograph scores. Whether this represents subclinical HAPE, as recently discussed by Cremona et al,⁹ or whether this is entirely different, as the beginning of an inevitable progression to full-blown clinical HAPE, is a matter for further study. Since the subjects went on to develop HAPE overnight despite resting, we favor the view that the inevitable process of HAPE had been set in motion.

The role of endothelial dysfunction to explain the excessive pulmonary hypertension in HAPE is of burgeoning interest. Swenson et al add the important finding of decreased nitrites and nitrates in the HAPE lavage fluid, reinforcing the notion of decreased nitric oxide production, possibly because of reduced pulmonary nitric oxide synthase.^{10,11} This finding should encourage future study of reasons for nitric oxide differences, such as evaluation of nitric oxide synthase polymorphisms in HAPE-susceptible persons, as well as other evidence for endothelial dysfunction, such as augmented endothelin 1 activity¹² and decreased neprilysin activity.¹³

Do these findings mean there is never a role for inflammation? These subjects were identified as HAPE susceptible because they had had HAPE in the past and thus had an increased likelihood of developing HAPE on this ascent. Although Swenson et al show that such individuals have no evidence of inflammation in early HAPE, data from endotoxin-primed animals exposed to hypoxia¹⁴ and an association between HAPE and viral infection^{4,6,15} suggest that constitutionally less-susceptible persons might develop HAPE if factors favoring increased permeability, such as inflammation, are present. In such circumstances, microvascular lung pressures would not need to be markedly elevated, which could explain the sporadic occurrence of HAPE in generally resistant individuals. Inflammation, at least in the form of viral infection, may thus play an important role in the general population. Whether other inflammatory conditions also predispose to HAPE is unknown; the question merits study.

If inflammation is not the missing ingredient in the pathophysiology of HAPE, what is? New evidence suggests that it may be elevated capillary pressure in combination with pulmonary hypertension. Maggiorini et al,¹⁶ using a similar protocol at the same laboratory high in the Alps, recently showed that a critical value for capillary pressure of 19 mm Hg is the apparent threshold for clinical HAPE. Reasons for elevated capillary pressure include pulmonary venous constriction, which is supported by the data of Maggiorini et al as well as that of other studies,^{17,18} and uneven perfusion of the pulmonary vascular bed, for which there is also experimental evidence.¹⁹ Swenson et al add the interesting finding of a relationship of pulmonary artery pressure to BAL protein content and red blood cell quantity, also suggesting that a critical arterial and capillary pressure disrupts the integrity of the pulmonary endothelial-epithelial barrier. Taken together, these 2 studies performed at Capanna Regina Margherita provide compelling evidence that HAPE is a hydrostatic-induced permeability leak with mild alveolar hemorrhage, followed only later by inflammation. This conclusion also fits with earlier observations that abnormalities of the pulmonary circulation,²⁰ intracardiac shunts,²¹ and preexisting pulmonary hypertension^{21,22} are all associated with HAPE on ascent to altitude.²³ No evidence suggests that these conditions are associated with inflammation.

What does the present study imply for treatment and prevention? Given this conclusion, some approaches for prevention and treatment previously thought possibly useful, such as anti-inflammatory and immune modulating therapies, can be eliminated. The focus must be on preventing or reversing increased hydrostatic pressure in the pulmonary circulation. Slow ascent and exercise in moderation are still effective prevention measures, apparently allowing the pulmonary circulation time for remodeling and conferring resistance to HAPE. Attenuating pulmonary hypertension with nifedipine is effective prevention²⁴ and carries little risk. Nifedipine has been less successful therapeutically in individuals with established HAPE.²⁵ Oxygen is clearly a superior treatment; as of course is hyperbaric treatment or descent to a lower altitude.²³

Newer, more selective vasodilating agents are being explored physiologically, and their role in treatment remains to be defined. These include nitric oxide,^{26,27} prostacyclin,²⁸ and sildenafil.²⁹ Oral and inhaled agents might be advantageous in remote settings where oxygen is unavailable and when descent is impractical. Inhaled β -agonists, which increase alveolar fluid clearance and might also reduce pulmonary artery pressure, reduce the incidence of illness by 50% in HAPE-susceptible individuals and require study for treatment of HAPE.³⁰ β -Agonist agents are safe and easily available. Untested approaches to pulmonary vasodilation for preventing or treating HAPE might include the use of dietary L-arginine or other nitric oxide donors to increase nitric oxide production, natriuretic peptides to increase

cyclic guanine monophosphate, and bosentan or other endothelin blockers.^{12,31} However, no therapy is ever likely to be as effective as increasing oxygenation, which in addition to reducing pulmonary artery pressure has the crucial advantage of reversing the extreme arterial hypoxemia of HAPE (arterial oxygen pressure of 30-40 mm Hg), thus protecting the brain and other organs. Whether a pulmonary vasodilating agent with oxygen is clinically more effective than oxygen alone remains to be determined.²⁶

If the susceptible person can be identified, would pharmacological prophylaxis be appropriate? For now, only a history of HAPE is useful in identifying such individuals. Hypoxic challenge tests assessing hypoxic ventilatory response and pulmonary pressor response have not been sufficiently sensitive or specific enough to reliably predict who will develop HAPE. Perhaps some other test will more accurately identify susceptible persons.

A problem with this approach is that most persons may be susceptible, given certain circumstances such as a rapid ascent to a high altitude, considerable physical exertion, or perhaps a viral upper respiratory tract infection. Indeed, Cremona et al⁹ have suggested that the majority of persons can develop subclinical HAPE, although whether this claim represents true predisposition to clinical HAPE is uncertain to us.

We congratulate Swenson et al and their willing research partners, the participants. Between them, they have advanced our knowledge of HAPE, which we anticipate will translate to saving lives. Angelo Mosso would have been delighted that what he started on Monte Rosa should have had such extraordinarily useful results.

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