effect of aspirin on platelet aggregation was due to interference with the ability of platelets to synthesize prostaglandin, presumably thromboxane A_2.[2]

Vane's discovery gave a huge boost to the study of the physiology of prostaglandins. Knowledge of their biologic functions, which is still growing, rekindled interest in aspirin. In addition to affecting platelet function, aspirin and other nonsteroidal inhibitors of prostaglandin synthesis have been found to delay premature labor, control preeclampsia, and reduce proteinuria in the nephrotic syndrome.

Vane found that nonacetylated salicylates were 10 times less effective than aspirin as inhibitors of prostaglandin synthesis; in addition, it was soon recognized that the antiplatelet effect of other nonsteroidal antiinflammatory drugs, unlike that of aspirin, was reversible. In 1975 Roth, Stanford, and Majerus showed that the unique property of aspirin was a consequence of the irreversible acetylation of a serine residue on the platelet prostaglandin synthase enzyme.[3] Since platelets lack the ability to synthesize new protein, the inhibition lasts for the life of the cell. It is important to note that aspirin does not influence thrombotic events in progress, in which the local thrombin concentration can circumvent the effect of the drug.

The prostaglandin products whose synthesis is blocked by aspirin include prostacyclin, an important vasodilator and inhibitor of platelet adhesion that is made by endothelial cells. The effect of blocking the synthesis of prostacyclin by aspirin therapy is an obvious concern. Small doses of aspirin may affect the synthesis of thromboxane by platelets and of prostacyclin by endothelial cells differently.[4] The difference is possible because the short serum half-life of acetylsalicylate before it is hydrolyzed may allow permanent inactivation of the platelet enzyme, whereas the effect on endothelial cells is limited because they are able to synthesize new protein. It is therefore important to know how low a dose of aspirin would remain clinically effective as an antithrombotic agent, especially since some of aspirin's side effects, particularly gastric irritation, might also be avoided.

In this issue of the *Journal*, van Gijn and colleagues report that a dose of 30 mg of aspirin per day was as effective as a dose of 283 mg in preventing death from vascular disease, nonfatal stroke, and nonfatal myocardial infarction in a group of patients who had previously had a transient ischemic attack or minor stroke.[5] Although the incidence of hemorrhagic complications was lower in those treated with the smaller dose of aspirin, it is conspicuous that there were 40 episodes of major bleeding in the group of 1555 patients receiving this dose. These bleeding episodes included both gastrointestinal hemorrhage and hemorrhagic stroke. A similar problem was encountered in the Physicians' Health Study, in which aspirin therapy failed to reduce the rate of death as an end point, possibly because a lower rate of coronary occlusion was offset by an increase in that of fatal stroke.[6] Furthermore, even low-dose aspirin therapy has been shown to increase the risk of hemorrhagic complications in patients who require emergency surgery, including coronary-artery bypass grafting.[7] Although bleeding from aneurysms or cerebral arteries cannot currently be prevented, measures can be taken to reduce gastrointestinal erosion, even with low-dose aspirin therapy. Another rare but potentially serious adverse effect that cannot be prevented by reducing the dose is angioedema or asthma due to aspirin allergy. More widespread use of aspirin to prevent arterial thrombosis could increase the frequency of serious allergic events.

In spite of legitimate concern about the consequences of its wider use, aspirin is still a remarkably safe drug when used circumspectly. To an extent, its bad press is a function of its common and careless use. Whatever new benefits of low-dose therapy are found, aspirin should not be considered a drug to be taken lightly.

The Reverend Stone turned out to be remarkably prescient.

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TOWARD A CURE FOR MULTIPLE MYELOMA?

THERE has been little progress in the treatment of multiple myeloma since the introduction of the melphalan–prednisone regimen about 25 years ago (for review, see Barlogie et al.[1]). The lack of benefit from the addition of alkylating agents and anthracyclines has been well documented in multidrug trials and probably reflects the low level of activity of the individual drugs involved.[2] Such regimens are designed to minimize myelosuppression, because of the immunodeficiency caused by the disease in what are typically elderly patients. Unfortunately, the marked efficacy of the VAD (vincristine–doxorubicin [Adriamycin]–dexamethasone) regimen in melphalan-resistant myeloma did not translate into extended survival when

tested in previously untreated patients.[3,4] In fact, recent data indicate that high doses of dexamethasone alone may be as effective as VAD,[5] so that much of the palliation produced by standard treatments may result from the glucocorticoids that are usually a component of myeloma therapy.

The late Tim McElwain and his colleagues at the Royal Marsden Hospital first addressed the issue of the intensity of the dose of cytotoxic agents.[6] Doses of intravenously administered melphalan at marrow-ablative levels, such as those used with total-body irradiation requiring hematopoietic stem-cell support, have consistently produced an incidence of complete remission in the range of 20 to 30 percent.[7-9] The collective experience in more than 350 reported cases of autologous bone marrow transplantation, mainly with unpurged bone marrow, indicates that the greatest clinical benefit occurs when the disease is still responsive to standard doses of therapy, the tumor burden is low, and the patient's clinical performance is adequate.[10] Under these conditions, treatment-related mortality is less than 5 percent and more than 30 percent of patients have complete remission, with four-year progression-free and overall survival of about 50 and 70 percent, respectively. There has thus been growing enthusiasm for autologous marrow transplantation because of its relative safety, even in elderly patients with myeloma. However, formal comparisons with standard-dose regimens have not been conducted.

Allogeneic bone marrow transplantation, pioneered by Nobel laureate E. Donnall Thomas in acute leukemia, has been investigated sporadically in younger patients with multiple myeloma.[11] The report in this issue of the *Journal* by Gahrton and colleagues of a study involving 90 patients represents the first large-scale investigation of this approach in multiple myeloma, a currently incurable cancer in which the median survival does not exceed three years.[12] The median age of the study patients (42 years) is more than 10 years less than that in most reported trials of autologous transplantation and 20 years less than the median age of typical patients who receive standard therapy. The other characteristics of the patients were more representative. More than half had advanced disease at the time of transplantation, almost two thirds had followed two or more previous regimens, and less than one half were in remission (usually partial) at the time of transplantation. The conditioning regimen before transplantation consisted of total-body irradiation in 90 percent of the patients, and prophylaxis against graft-versus-host disease (GVHD) varied. Almost 40 percent of the patients died of treatment-related complications within the first three to four months after transplantation. But 40 percent are projected to be alive after five years, and the median duration of relapse-free survival among those with a complete response was four years. As expected, a lower tumor burden and less previous therapy favored a higher incidence of complete remission, which was in turn associated with longer survival. The causes of death included the recurrence of disease in about one fifth of the patients, and severe GVHD (grade III or IV) was fatal in six of eight patients.

The authors conclude appropriately that allogeneic transplantation should be considered in patients up to the age of 55, especially since treatment-associated mortality was not significantly associated with the patients' ages. Given the relatively limited benefit of maintenance therapy with interferon after standard-dose chemotherapy,[13] marrow transplantation should be considered in all patients with symptomatic myeloma. With both autologous and allogeneic transplantation, the rate of long-term success seems to be greater when they are used not as a last resort but for the consolidation of a remission or as early salvage therapy for refractory myeloma. Concerning the choice of allogeneic or autologous transplantation, longer follow-up will be required to determine whether the significantly higher rate of early mortality in allogeneic transplantation (40 percent vs. less than 5 percent during the first 6 to 12 months) is offset by more durable control of the disease and possibly by cures resulting from a graft-versus-myeloma effect. Gahrton et al. should examine whether a true complete remission (as assessed by sensitive immunofixation or molecular techniques) is a prerequisite for extended progression-free survival. Alternatively, a benign monoclonal gammopathy (MGUS, or "monoclonal gammopathy of undetermined significance") may persist without reducing longevity.[1]

The ages of patients and the availability of donors are important variables in recruitment for transplantation trials. For allogeneic transplants, an upper age limit of 55 years is imposed by concern over the steeply increasing mortality from acute GVHD, and this limit excludes 75 percent of the typical population with myeloma. Assuming in addition that an HLA-matched sibling donor can be identified only for every fourth patient, no more than 7 percent of those with myeloma can be offered allogeneic marrow transplants. In contrast, about 70 percent of all patients with myeloma are candidates for autologous marrow transplantation, since up to the age of 70, treatment-related mortality does not increase with age.[9]

Primary physicians should be aware of these new treatment approaches to myeloma, so that excessive damage to normal hematopoietic stem cells and secondary leukemia from long-term melphalan and nitrosourea therapy can be avoided in potential candidates for autologous transplantation. Because of the relative rarity of myeloma, formal clinical trials to compare standard approaches with marrow transplantation will be possible only in the framework of cooperative groups.

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WHEN LUNGS ON MOUNTAINS LEAK

Studying Pulmonary Edema at High Altitudes

On August 10, 1894, Pietro Ramella, a young Italian soldier taking part in physiological experiments, ascended rapidly to the Capanna Regina Margherita hut on Monte Rosa (4559 m), an Alpine peak bordering Italy and Switzerland. Within a day he had severe headache, cyanosis, dyspnea, rales, and pink, frothy sputum. He was thought to have pneumonia. A storm prevented his descent, but luckily he recovered spontaneously within a few days. An Italian physiologist, Angelo Mosso, suspected that heavy exertion at high altitude had contributed to Ramella's illness.[1] In retrospect, Ramella probably had high-altitude pulmonary edema.

More than 60 years later, in 1960, Houston's authoritative report in the *Journal* of noncardiogenic pulmonary edema after ascent to high altitude[2] triggered three decades of research, often conducted in remote mountain laboratories. In the current issue of the *Journal*, Bärtsch and his colleagues[3] report on their return to the Margherita hut to conduct an important study of high-altitude pulmonary edema that provides new insight into this mysterious disorder.

The mystery surrounding high-altitude pulmonary edema primarily concerns its pathogenesis. We understand that it occurs soon after rapid ascent to altitudes above 2500 to 3000 m, particularly in subjects who exercise in the cold. As with other forms of pulmonary edema, the symptoms are dyspnea, cough, and fatigue; pulmonary infiltrates appear on the chest roentgenogram, and the condition may be fatal. The pulmonary edema is assumed to be noncardiac, because pulmonary arterial wedge pressures are not elevated.[4] Bronchoalveolar fluid obtained from climbers at 4400 m on Mount McKinley was protein-rich and contained many cells, with some markers of chemotactic activity and inflammation.[5] Pulmonary hypertension, maldistribution of ventilation and perfusion, and severe hypoxemia — all suggest that high-altitude pulmonary edema is a disorder of the pulmonary circulation. What has gone wrong?

The accumulation of protein-rich fluid in the alveolar space implies an increase in the permeability of the pulmonary vascular endothelium that overwhelms the lung's capacity for removing fluid from the alveoli. The increase in permeability is probably caused by hypoxia, hypoxia plus inflammatory mediators, high intravascular pressures, or some combination of these factors. The rapid and complete restoration to normal that occurs with oxygen therapy or after descent indicates that the pulmonary architecture is preserved. The frequent association of pulmonary edema with edema of the brain and subcutaneous tissues suggests a global increase in vascular permeability.[6] However, increased permeability of the pulmonary vessels does not in itself explain the pulmonary hypertension that may precede the fluid leak.

The possibility of pressure-induced fluid leakage is suggested by severe pulmonary hypertension, by the accentuated pulmonary vascular responsiveness to hypoxia that occurs in some susceptible persons,[7] and by the association of high-altitude pulmonary edema with a restricted vascular bed in the lung, as occurs in patients in whom one main pulmonary artery is absent.[8] Furthermore, capillaries may rupture when their internal pressure is greatly elevated or when hyperventilation increases the mechanical stress on the alveoli.[9]

In their paper, Bärtsch et al.[3] appropriately emphasize the role of pulmonary arterial pressure in contributing to the edema, because the mean pressure (as estimated by noninvasive methods) at 4559 m was higher in the susceptible subjects who received a placebo (53 mm Hg) than in those who received nifedipine (41 mm Hg), and in both groups the pressures were higher than in healthy subjects who were not susceptible to high-altitude pulmonary edema (33 mm Hg). Nifedipine also improved oxygenation at high altitude without improving the effective ventilation (the partial pressure of oxygen and arterial-blood oxygen saturation rose, but the partial pressure of carbon dioxide did not fall). The mechanisms of the improved oxygenation are not clear, but if the high pressure had overridden vascular control, a lowering of pressure with nifedipine might have improved the matching of ventilation to perfusion at some sites within the lung. In any event, reducing the pressure probably reduced the fluid extravasation, the after-