for using it optimally. Additional issues, such as a means of sharing these data with researchers and others, must also be addressed.

Medicare data will offer a great opportunity to improve our ability to understand the balance of benefits and risks of drug treatment. If we take advantage of this opportunity, we will know much more about whether drugs are used as intended, whether they have their intended effects, and how risky they are.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Institute of Medicine.

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An interview with Dr. Arnold Epstein about the Medicare prescription-drug benefit may be heard at www.nejm.org. Dr. Epstein is a professor of health care policy at the Harvard School of Public Health, a professor of medicine at Harvard Medical School, and an associate editor of the *Journal*.

FOCUS ON RESEARCH

Preventing Stroke in Sickle Cell Anemia

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Related article, page 2769

In the late 1930s, William Bosworth Castle and his colleague Thomas Hale Ham were studying blood samples obtained from patients with sickle cell anemia and found that the viscosity of the blood increased dramatically as its oxygen content decreased. As Castle later reflected, "It immediately occurred to us that this was because the elongated, sickled red cells had become tangled up 'like haywire.'"[1] Castle and Ham went on to hypothesize about the pathophysiology of organ damage in sickle cell anemia in a way that still drives much of our thinking today: "a vicious cycle of erythrostasis may be set up because the critical oxygen tension for a marked increase of sickling is relatively close to that of the normal venous blood."[2] This hypothesis predicts that as red cells become deoxygenated in the capillaries, the sickle hemoglobin inside them polymerizes, decreasing the cells' ability to squeeze through the capillaries in single file. Blood flow stops, and the surrounding tissues become ischemic.

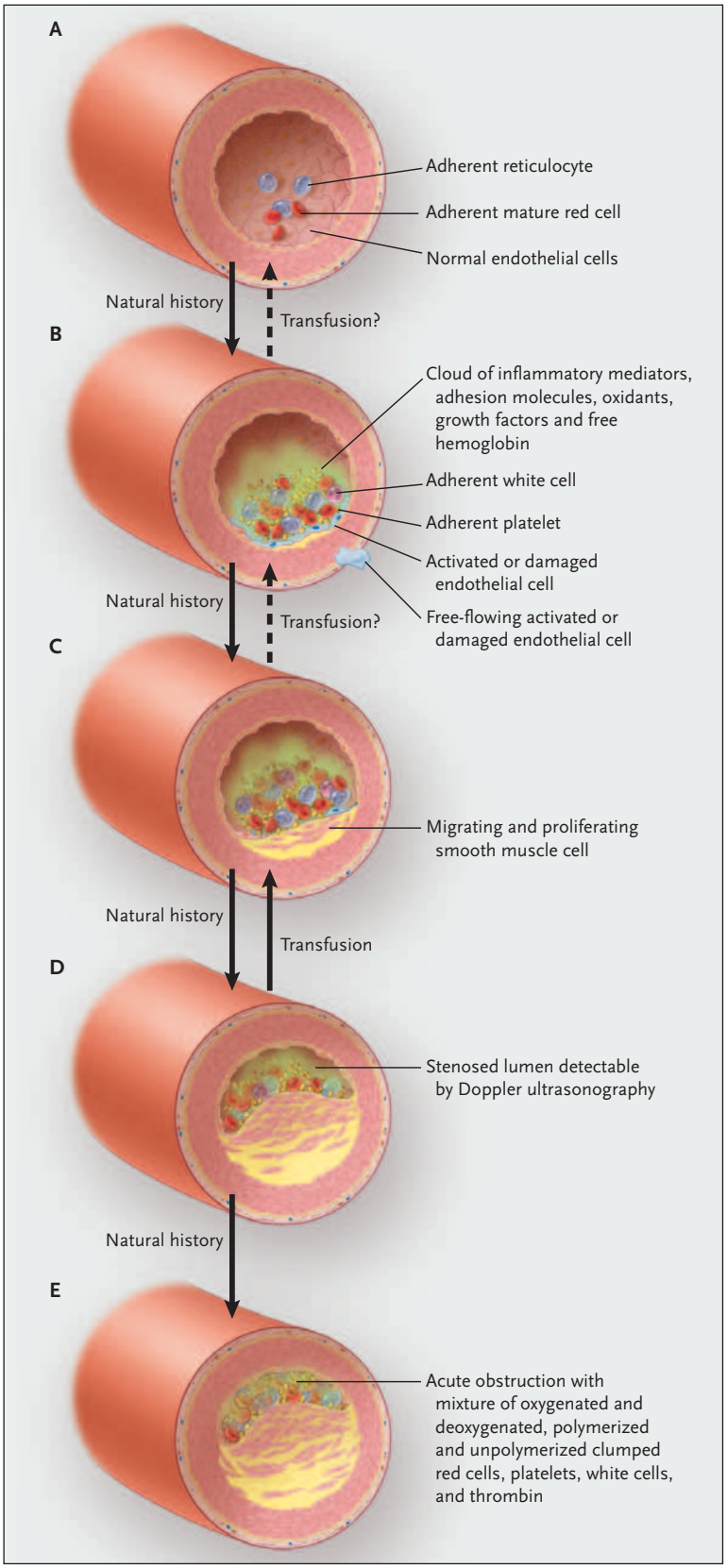
The hypothesis makes sense for tissues such as the spleen and marrow, where the blood flow is sluggish, oxygen tension is low, and the vessels are small. It does not, however, explain acute cerebral infarction — one of the most devastating complications of sickle cell anemia. Stroke in sickle cell anemia occurs in about 11 percent of patients under 20 years of age. The major symptom is sudden hemiparesis with or without aphasia, and the most common finding is obstruction of a distal intracranial internal carotid artery or a proximal middle cerebral artery. These vessels are relatively large, with diameters that are normally measured in millimeters. Oxygenated blood pulses through them with velocities of hundreds of centimeters per second. The question is, How can micron-scale red cells acutely occlude a millimeter-scale artery, especially at the low hematocrit that is typical of patients with sickle cell anemia? The answer is that the arteries themselves are not normal.

Adams and colleagues have pioneered the use of transcranial Doppler ultrasonography to study the blood supply of the brain in children with sickle cell anemia. They discovered that 10 percent of children without neurologic signs or symptoms had abnormal blood-flow velocities, indicative of clinically significant arterial stenosis.[3] If left untreated, these patients have a relative risk of stroke of approximately 40. Postmortem examination of cerebral artery stenoses in such patients reveals proliferative intimal hyperplasia reminiscent of the inflammatory vascular lesions seen in other diseases. The genesis of these lesions is probably related to the well-described tendency of sickle cells to adhere to, activate, and damage endothelial cells.

An important early event (depicted in the diagram) is the at-

Cerebral Artery Damage and Healing in Sickle Cell Anemia.

In sickle cell anemia, cerebral artery damage results as sickle reticulocytes and more mature red cells bind to endothelial cells through specific ligands and are exposed to oxidants, causing these cells to be activated (Panel A). Activated endothelial cells become increasingly adhesive for red cells, white cells, and platelets, and some are dislodged from the underlying matrix (Panel B). As more cells adhere and are activated, a "cloud" of inflammatory mediators, chemoattractants, adhesion molecules, growth factors, procoagulants, and free hemoglobin is produced. Smooth-muscle cells migrate and proliferate, causing a hyperplastic lesion that encroaches on the artery lumen (Panel C). Ultimately this lesion, although asymptomatic, becomes detectable on transcranial Doppler ultrasonography (Panel D). A transfusion regimen, by keeping the production of sickle cells to a minimum, prevents acute sickling and stroke (Panel E) and promotes the reversal of injury to the vessel. When transfusion is discontinued, the lesion (and the risk of stroke) recurs.



tachment of a particularly sticky, oxidant-generating sickle reticulocyte to an endothelial cell in the turbulent environment of the carotid artery circulation. The encounter activates and damages the endothelial cell, stimulating endothelial cells and white cells to produce inflammatory cytokines, chemoattractants, adhesion molecules, procoagulants, and growth factors. White cells and platelets also adhere, amplifying endothelial-cell activation and aggravating the inflammatory process. Some activated endothelial cells detach from the vessel wall and circulate freely. With time and sufficient stimulation, smooth-muscle cells in the blood vessel migrate into the wall, proliferate, and narrow the arterial lumen.

Transcranial Doppler ultrasonography can detect an expanding lesion, one that is large enough to put the patient at high risk for

acute arterial obstruction. The coup de grace — stroke — occurs when the tipping point is reached in the delicate relation between oxygenation and perfusion on the one hand and inflammation and coagulation on the other — when deoxygenated red cells containing polymerized sickle hemoglobin get caught up in the damaged vessel and obstruct the blood flow. This process is further complicated by the release of free hemoglobin from fragile sickle cells, which effectively quenches locally produced nitric oxide that could have stimulated a beneficial vasodilatation.

Adams and colleagues have shown that if children with stenotic cranial-artery lesions, as demonstrated on transcranial Doppler ultrasonography, are maintained on a regular program of transfusion that is designed to suppress erythropoiesis so that no more than 30 percent of their circulating red cells were their own, about 90 percent of strokes in such children could be prevented.[4] In their follow-up study, reported in this issue of the *Journal* (pages 2769–2778), they find that a high risk of stroke returns after transfusion is discontinued. It appears that transfusion does not simply prevent stroke but actually reverses the stenotic lesion — on Doppler studies, blood-flow velocities return to normal. Apparently, during the period of the transfusion regimen the reduction in the lesion-forming mechanism was sufficient to allow at least some repair to occur.

We know from studies of siblings that there is a genetic component to the risk of stroke in sickle cell anemia. There is also a genetic component to the risk of stroke in the general population. Given the overlap in the possible mechanisms underlying vascular injury in stroke related to sickle cell disease and stroke in general, it is not surprising that the same candidate genetic contributors to stroke in both populations have become of interest. I anticipate that the search for predictive genetic profiles will yield new ways to identify children with sickle cell anemia who are at high risk of stroke and to help tailor more specific treatment for them. In the meantime, it will be critically important that all children with sickle cell anemia have easy access to transfusion and to routine transcranial Doppler screening and follow-up so that in these children most strokes can be avoided.

Dr. Platt reports having received royalties on a patent for a Gardos channel blocker.

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