Sickle cell disease (SCD) is understood on a genetic and a molecular level better than most diseases. Young children with SCD are at a very high risk of stroke. The molecular pathologic abnormalities of SCD lead to microvascular occlusion and intravascular hemolytic anemia. Microvascular occlusion is related to painful episodes and probably causes microcirculatory problems in the brain. The most commonly recognized stroke syndrome in children with SCD is large-artery infarction. These “big strokes” are the result of a vascular process involving the large arteries of the circle of Willis leading to territorial infarctions from perfusion failure or possibly artery-to-artery embolism. We can detect children who are developing cerebral vasculopathy using transcranial Doppler ultrasonography (TCD) and can provide effective intervention. Transcranial Doppler ultrasonography measures blood flow velocity in the large arteries of the circle of Willis. Velocity is generally increased by the severe anemia in these patients, and it becomes elevated in a focal manner when stenosis reduces the arterial diameter. Children with SCD who are developing high stroke risk can be detected months to years before the stroke using TCD.

Healthy adults have a middle cerebral artery velocity of approximately 60 cm/s, whereas children without anemia have velocities of approximately 90 cm/s. In SCD, the mean is approximately 130 cm/s. Two independent studies have demonstrated that the risk of stroke in children with SCD increases with TCD velocity. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) (1995-2000) was halted prematurely when it became evident that regular blood transfusions produced a marked (90%) reduction in first stroke. Children were selected for STOP if they had 2 TCD studies with velocities of 200 cm/s or greater. Children not undergoing transfusion had a stroke risk of 10% per year, which was reduced to less than 1% per year by regular blood transfusions. Stroke risk in all children with SCD is approximately 0.5% to 1.0% per year. On the basis of STOP, if the patient meets the high-risk TCD criteria, regular blood transfusions are recommended. A second study was performed (2000-2005) to attempt withdrawal of transfusion in selected children in a randomized controlled study. Children with initially abnormal TCD velocities (≥200 cm/s) treated with regular blood transfusion for 30 months or more, which resulted in reduction of the TCD to less than 170 cm/s, were eligible for randomization into STOP II. Half continued transfusion and half had cessation of transfusion. This trial was halted early for safety reasons. There was an unacceptably high rate of TCD reversion back to high risk (≥200 cm/s), as well as 2 strokes in children who discontinued transfusion. There are no evidence-based guidelines for the discontinuation of transfusion in children once they have been identified as having high risk based on TCD. The current situation is undesirable because of the long-term effects of transfusion, including iron overload. Iron overload has recently become easier to manage with the introduction of an oral iron chelator. The inflammatory environment known to exist in SCD and the known effect of plasma free hemoglobin, released by hemolysis, of reducing available nitric oxide may contribute to the development of cerebrovascular disease. Further research may lead to more targeted therapies. We can reduce many of the big strokes that occur in these small persons by aggressively screening patients at a young age (and periodically throughout the childhood risk period) and interrupting the process with regular blood transfusions.

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In 1910, American physician James Herrick, MD, published the first case in the Western medical literature on sickle cell disease (SCD) in a Grenadian dental student living in Chicago, Illinois. A blood smear from this student showed “peculiar elongated cells.”1 Pauling et al drew attention to SCD as a “molecular disease.”2 Much about SCD is understood. There are approximately 80,000

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patients with the most severe form of the disease in the United States, and more than 15 000 articles have been cited in PubMed on the topic since 1949. Well before the major biological features of this genetic disorder were elucidated, stroke had been noted as an associated complication of SCD. Early brain pathologic studies described many abnormalities of the brain and its vasculature, and in a few cases, large cerebral infarctions were reported. Why would a blood disorder, characterized by severe hemolytic anemia and known to engender pathophysiologic features on a microscopic scale, lead to stroke at all, much less large brain infarctions?

Most of the neurologic reviews published before 1976 emphasized the presumed basis for circulatory problems, including stroke arising from occlusion of small vessels by the sickled erythrocytes that give the disease its name. These were known to be formed, at first reversibly, then finally into a state of permanent distortion, when cells containing sickle hemoglobin and insufficient other hemoglobins (such as fetal hemoglobin, which retards sickling) become deoxygenated. The cellular distortion is caused by sickle cell hemoglobin forming intracellular polymers. Although sickle cell hemoglobin carries oxygen in a similar manner as hemoglobin A in solution (although the oxygen dissociation curve is shifted to the right compared with normal), its presence in cells in the deoxygenated state leads to ischemia by reducing the ability of the erythrocyte to traverse the microcirculation. These cells are also subject to premature destruction, which leads to severe anemia and also releases toxic elements (eg, plasma free hemoglobin) into the circulation.

The fundamental paradigm for the most common clinical feature, the painful “crisis,” is now understood as a sequence of events that begins with attachment of large immature red blood cells (RBCs) (reticulocytes) to the postcapillary venule and propagation backward until there is delayed transit time of RBCs, causing further deoxygenation and sickling. These events take place in vessels the size of RBCs that measure 5 to 10 µm. Recent data have also implicated RBC-leukocyte and leukocyte-endothelial interactions, which may precede the RBC-endothelial attachment and do not take place in mice deficient in E selectin and P selectin.

Although the microcirculatory events have been studied ex vivo, as yet there is no comparable large-vessel animal model that would allow a better understanding of the events leading to occlusion of arteries such as the middle cerebral or internal carotid. How the genetic disorder of sickle cell anemia creates large arterial vasculopathy and leads to stroke remains somewhat of a mystery, but the schema proposed by Platt is a good approximation of what is believed to happen in large brain arteries before stroke (Figure 1).

The publication in 1972 by Stockman et al of cerebral angiography in 7 patients with SCD and neurologic complications drew the first real attention to the fact that large intracerebral arteries were sometimes involved in a stenotic and obliterator process preferentially located just beyond the origin of the ophthalmic artery and involving part or all of the anterior circle of Willis.

The example of advanced cerebrovascular disease shown in Figure 2 is based on studies performed on an 8-year-old boy who had a stroke and was studied using angiography and transcranial Doppler ultrasonography (TCD) early in our project at the Medical College of Georgia. It
massive infarction after internal carotid artery occlusion. Russell et al\textsuperscript{11} had just published an article with extensive angiographic documentation of what Stockman et al and others had reported and also suggested that regular transfusion might, if not reverse the process, at least prevent arterial worsening. Their study, while crucial, was not a clinical trial, and in fact no trial for secondary stroke prevention in SCD has yet been published. However, regular blood transfusions soon became an accepted therapy to prevent recurrent stroke in SCD based on comparison with historically high recurrence rates in children with SCD.

In 1982, Aaslid et al\textsuperscript{12} published an article on TCD for the detection of subarachnoid hemorrhage–related vasospasm. In 1985, the Medical College of Georgia SCD Cohort Study began using TCD in patients along with magnetic resonance imaging (MRI). Although both of the new techniques have much to offer in the study of stroke and patients at risk for stroke, it was to be TCD that proved more useful for primary stroke prevention in these patients, largely because it was so much easier to use.

In children with homozygous SCD, a yearly first stroke risk of approximately 0.5\% had been established by the Cooperative Study of Sickle Cell Disease based on a large population study\textsuperscript{14} that predated TCD and MRI use (Table 1). Although some risk factors for stroke were identified (slightly lower total hemoglobin level, transient ischemic attack, and acute chest syndrome), a predictive model sufficient to plan a clinical prevention trial was not available. This stroke rate, which is very high for children, was still too low to execute a practical randomized controlled trial given the limited number of patients available. Even assuming that transfusion was completely effective in preventing the first stroke, without a way to select the children at greatest risk, one would have to transfuse approximately 200 children each year to prevent 1 stroke. Primary stroke prevention would depend on finding an acceptable way to identify individuals at highest risk to make the number needed to treat more attractive and manageable.

Table 1. Stroke Risk in Children With Sickle Cell Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yearly Stroke Rate, %</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy child, no SCD or heart disease</td>
<td>0.003</td>
<td>Broderick et al,\textsuperscript{17} 1993</td>
</tr>
<tr>
<td>Adult with atrial fibrillation (no SCD)</td>
<td>5.0</td>
<td>Goldstein et al,\textsuperscript{20} 2001</td>
</tr>
<tr>
<td>Child with SCD (genotype Hb SS) (unselected by TCD)</td>
<td>0.5-1.0</td>
<td>Ohene-Frempong et al,\textsuperscript{14} 1998</td>
</tr>
<tr>
<td>SCD with silent infarct on MRI (TCD unknown)</td>
<td>2.0-3.0</td>
<td>Miller et al,\textsuperscript{16} 2001</td>
</tr>
<tr>
<td>SCD with TCD velocity &gt;200 cm/s</td>
<td>10.0-13.0</td>
<td>Adams et al,\textsuperscript{15} 1997</td>
</tr>
<tr>
<td>Regular transfusion</td>
<td>&lt;1.0</td>
<td>Adams et al,\textsuperscript{15} 1992</td>
</tr>
<tr>
<td>SCD with previous stroke (first 3 y) No transfusion</td>
<td>-3.0</td>
<td>Pegelow et al,\textsuperscript{18} 1995</td>
</tr>
<tr>
<td>Transfusion</td>
<td>-6.0</td>
<td>Pegelow et al,\textsuperscript{18} 1995</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; SCD, sickle cell disease; TCD, transcranial Doppler ultrasonography.
It seemed reasonable to focus on the large intracranial arteries rather than the brain itself for 2 reasons. First, selecting patients on the basis of infarction that had already taken place meant that we would be “following” the process of brain injury rather than preventing it first-hand. Second, the collective angiographic information, derived from children who had already had a stroke, had shown that major arteries opposite the hemispheres that had evident brain infarction often showed early or sometimes extensive arterial narrowing that had not yet become symptomatic. This suggested that the arterial process leading to large strokes might develop at a slow enough rate to create a “window of intervention” before the brain is affected in children developing vasculopathy and on this basis the high-risk state for stroke. Using angiography to screen large numbers of children who were asymptomatic did not seem practical. El Gammal et al22 had shown that major arteries opposite the hemispheres that had evident brain infarction often showed early or sometimes extensive arterial narrowing that had not yet become symptomatic. This suggested that the arterial process leading to large strokes might develop at a slow enough rate to create a “window of intervention” before the brain is affected in children developing vasculopathy and on this basis the high-risk state for stroke. Using angiography to screen large numbers of children who were asymptomatic did not seem practical. El Gammal et al22 had shown that major arteries opposite the hemispheres that had evident brain infarction often showed early or sometimes extensive arterial narrowing that had not yet become symptomatic. This suggested that the arterial process leading to large strokes might develop at a slow enough rate to create a “window of intervention” before the brain is affected in children developing vasculopathy and on this basis the high-risk state for stroke. Using angiography to screen large numbers of children who were asymptomatic did not seem practical. El Gammal et al22 had shown that major arteries opposite the hemispheres that had evident brain infarction often showed early or sometimes extensive arterial narrowing that had not yet become symptomatic.

The TCD seemed to be a possible method, but it was not clear whether it would work in this application. Use of Doppler ultrasonography had become an important way to identify extracranial carotid stenosis based on a derivation of the Bernoulli principle, which is that in the area where the vessel is narrowed, the velocity of blood flowing in that vessel is increased. However, cervical Doppler ultrasonography would at best reflect flow changes secondary to intracranial stenosis because the internal carotid artery in SCD is rarely affected by vasculopathy; TCD seemed a more direct diagnostic approach. The TCD was also attractive because it was harmless, painless, and generally well tolerated, even by children, and did not require sedation. It was also portable and low cost compared with other methods.

However, in SCD there were specific challenges in using TCD. Would these young children with so many other medical issues tolerate the examination? What velocity standards should be used? It was known that cerebral blood flow and flow velocity as estimated by TCD are increased in the anemic condition owing to the low-ered oxygen-carrying capacity of the blood. It was soon evident from work by Brass et al24 at Columbia and Adams et al25,26 that the evolving velocity standards of TCD for stenosis in adults would not apply in SCD owing to the impact of young age and anemia. Would there be sufficient separation between children with elevated TCD velocities due to anemia with no vessel disease and average risk and those with anemia who were developing stenosis and increased risk?

To determine whether TCD would predict stroke, a series of studies were performed between 1985 and 1992. The first study was to establish the expected middle cerebral artery velocity in children of the target age, with25 and without26 SCD and without stroke. Transcranial Doppler ultrasonography was also performed on children with stroke at the time of cerebral angiography, providing an opportunity to correlate velocity to stenosis visualized using that method.15 In parallel, a large cohort of children with SCD but no stroke history and not undergoing regular transfusion were recruited, studied using TCD, and followed up prospectively for stroke outcome.16,27 The portability and ease of use of TCD was instrumental because many of these TCD studies were performed in outreach clinics across Georgia during regular clinic visits. This feature of TCD greatly enhanced enrollment and follow-up.

The early use of TCD in adults had shown that the normal velocity (time-averaged mean of maximum blood flow as opposed to systolic or diastolic) was approximately 60 cm/s (Table 2). It was determined that the expected middle cerebral artery velocity in healthy children was approximately 90 cm/s, and in children with SCD without overt stroke it was approximately 130 cm/s, elevated on the basis of young age and severe anemia. When the angiogram showed severe stenosis, the velocity was always greater than 190 cm/s and often much higher except in cases of severe stenosis, in which very low velocities were recorded (<70 cm/s).15 These data provided key cross-sectional information, but what was needed to make primary stroke prevention possible was to demonstrate that TCD predicted risk of future stroke.

That elevated TCD velocity was associated with a high risk of future stroke was demonstrated in the Medical College of Georgia SCD Cohort study. The long-term outcome of 315 children aged 3 to 18 years at the time of first screening and free of stroke when enrolled was evident from the stroke-free survival curves. Arbitrary velocity cutoff points (there are no evident “inflection points” in the risk relationship, but cutoff points were needed to define risk strata) were used to stratify risk: less than 170 cm/s represented “normal” or average risk, 170 to 199 cm/s was called “conditional” and was associated with moderate risk, and 200 cm/s or greater was called “abnormal” or high risk. A risk of stroke during the next 36 months of 13% per year was observed.16,27 Although the time from abnormal TCD velocity to stroke was variable, children with the highest velocity seemed to have more proximate risk (5 children with TCD velocity >240 cm/s had a stroke within 9 months of TCD).

Armed with this information, a proposal was made to the National Heart, Lung, and Blood Institute to fund the first randomized controlled trial of stroke prevention for

### Table 2. Transcranial Velocities in Conditions of Interest

<table>
<thead>
<tr>
<th>Condition</th>
<th>Time-Averaged Mean Velocity of Maximum Blood Flow, cm/s</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adult, mean±SD</td>
<td>62±12</td>
<td>Aaslid et al, 13 1982</td>
</tr>
<tr>
<td>Adult with subarachnoid hemorrhage-related vasospasm</td>
<td>&gt;120</td>
<td>Aaslid et al, 13 1982</td>
</tr>
<tr>
<td>Healthy child, mean±SD</td>
<td>79±13</td>
<td>Adams et al, 26 1988</td>
</tr>
<tr>
<td>Child with SCD, average risk, mean±SD</td>
<td>133±19</td>
<td>Adams et al, 25 1989</td>
</tr>
<tr>
<td>Angiographically detected stenosis</td>
<td>&gt;190 or &lt;70</td>
<td>Adams et al, 27 1992</td>
</tr>
<tr>
<td>STOP risk categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>&lt;170</td>
<td></td>
</tr>
<tr>
<td>Conditional</td>
<td>170-199</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥200</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SCD, sickle cell disease; STOP, Stroke Prevention Trial in Sickle Cell Anemia.
any indication in SCD and the first primary stroke prevention trial in children with any disease. This study, STOP, was conducted between 1995 and 2000 at 14 sites in the United States and Canada. A unique feature was the selection of participants based on TCD. Almost 2000 children aged 2 to 16 years with no history of stroke were screened using TCD, and those with 2 TCDs showing a middle cerebral artery or internal carotid artery velocity of 200 cm/s or higher were approached for randomization. Rigorous operator training and standardization of TCD protocol and equipment were used to ensure uniform testing. Screening for high-risk cases in STOP showed the same prevalence of TCD findings at all 14 sites (and was similar to that found in the Medical College of Georgia cohort): approximately 10% had 1 TCD, and 85% of those with 1 abnormal TCD were confirmed to have abnormal results on a second study. The final high-risk rate was approximately 9%; approximately 15% fell into a “conditional” range of 170 to 199 cm/s, and 70% had velocities less than 170 cm/s, falling into a lower-risk group. The others had inadequate studies that had to be repeated. The TCDs were recorded as digital files, which facilitated file transfer between the research sites and the data and reading centers, study masking, and blinded reading. Neither MRI nor MRA was performed until after randomization, and imaging for “silent stroke” was evaluated as a secondary end point.

The trial was halted 16 months early when 11 of the 67 children randomized to receive standard care (episodic transfusions only depending on symptoms such as pain) had a stroke compared with a single child undergoing long-term transfusion. The observed stroke rate without transfusion was 10% per year across 2 years, confirming the reliability and validity of TCD in a multicenter application and the dramatic (>90%) reduction in stroke with regular transfusion (Figure 3). One surprising finding was that MRAs of cerebral vessels in children with velocities greater than 200 cm/s but less than 250 cm/s did not usually show severe stenosis, suggesting that TCD indicates risk at an earlier (and probably more reversible) stage than MRA.

The STOP results were announced in 1997. Despite the clear results and recommendations based on STOP from the National Heart, Lung, and Blood Institute and the American Stroke Association (also endorsed by the American Academy of Neurology) for widespread screening and prophylactic transfusion in high-risk cases, the long-term problems with transfusion, and the fact that a stopping point for transfusion was not clear, some physicians remained hesitant to adopt this strategy.

In STOP, many patients undergoing transfusion saw their TCD velocities revert to apparent low risk (<170 cm/s; approximately 53%) or intermediate risk (170-199 cm/s; approximately 17%), especially if the velocity at treatment initiation was in the low abnormal range (200-230 cm/s) and the MRA findings were relatively normal (see Figure 4 and Figure 5 for an example of change with regular transfusion). Approximately 30% of children who were compliant with regular transfusion still had abnormal TCD velocities even after years of transfusion. A second study was then planned to determine whether continued treatment was still needed in the subset that normalized with prolonged transfusion. The STOP...
II was designed to determine whether transfusion could be safely withdrawn after a defined treatment period with acceptable stroke risk and rates of return to transfusion. This trial was planned to enroll 100 children, all with originally high-risk TCD velocities that reverted to less than 170 cm/s after at least 30 months of transfusion and who had an MRA that did not show moderate or severe stenosis or occlusion. The design called for half the children to be randomized to continued transfusion and half to have transfusion stopped. All the participants received close follow-up and TCD at least every 12 weeks.

This trial was also stopped after 74 patients were enrolled when it was clear that stopping transfusion was associated with rapid reversion of TCD velocities to high-risk levels only in children who stopped transfusion (Figure 6). Two strokes occurred in children who had reversion to abnormal TCD velocities and before the re-institution of transfusion. Even in this low-risk subset (those with severe stenosis on MRA and whose TCD velocity did not normalize after 30 months of transfusion were not included), by the end of 1 year, more than half of those who discontinued transfusion had restarted it. Although the long-term problems of transfusion, especially iron overload, can be predicted and managed, new approaches that limit the long-term use of this powerful but intensive therapy are needed.

Although there are theories (see Figure 1 proposed by Platt) as to how circle of Willis vasculopathy develops, there are no animal models. Much attention has been given to the abnormal tenacity with which RBCs (especially immature cells that contain sickle hemoglobin) adhere to the endothelium in cultured cell preparations as a cause of vascular occlusion generally in SCD. White blood cells and platelets are probably involved to some extent as well. How RBC adherence might initiate or promote vascular injury and eventual stenosis of large arteries, such as those of the circle of Willis, requires further study.

A connection between SCD and nitric oxide has become a subject of increasing interest in the past several years. It has long been known that plasma free hemoglobin inactivates nitric oxide. The hemolytic anemia of SCD releases significant amounts of free hemoglobin that comes into contact with the endothelial surface. This is believed to cause abnormalities in vascular function, which could include impairment of vasodilation, one of the functions that nitric oxide plays in systemic circulation. Although it is relatively easy to see how consumption of nitric oxide and a secondary feature of hemolysis, an increase in arginase activity in the serum, which further reduces the available nitric oxide by depleting the sub-

Figure 5. A, Transcranial Doppler ultrasonography (TCD) from the right internal carotid artery (ICA) showing elevated velocity at 208 cm/s (time-averaged mean of the maximum) (arrow). B, A magnetic resonance angiogram (MRA) after 12 months showing "resolution" of the apparent lesion in the right ICA (arrow). When the 2 studies (1995 and 1996) were read side by side, the local radiologist commented that the "lesion" on the 1995 study was probably an artifact created by turbulence. This series points out the importance of MRA in avoiding misinterpretation if dephasing artifacts in the area where true lesions are also found in sickle cell disease (SCD). See the study by Zimmerman for a discussion of technical issues regarding magnetic resonance imaging and MRA in patients with SCD. C, The corresponding right ICA TCD showing that the time-averaged mean velocity of maximum blood flow (arrow) after 12 months of treatment had fallen into the low "conditional" range. In A and C, plus signs indicate the readers’ estimate of systolic, time-averaged mean of the maximum, and diastolic velocities.

Figure 6. Kaplan-Meier estimates of the probability of remaining free of an end point (reversion to high-risk transcranial Doppler ultrasonography velocity or stroke) in children randomized to continued regular blood transfusions or to immediate cessation of transfusion from the second Stroke Prevention Trial in Sickle Cell Anemia (P < .001, by log-rank test). Reprinted with permission from the Massachusetts Medical Society.
strain, lead to pulmonary hypertension by reduction in vasodilation, it is less easy to see how aberrations in nitric oxide might lead to cerebral vasculopathy. Nitric oxide has other functions, such as reduction in inflammatory mediators, and this may contribute to cerebral vasculopathy. An animal model that mimics the development of abnormally high cerebral blood flow rates and the development of large-vessel vasculopathy in the circle of Willis is a critical need to understand how nitric oxide and other metabolic factors contribute to stroke risk in SCD.

Finally, there is an encouraging indication that the approach proved in STOP may be working to reduce stroke. Fullerton et al. evaluated administrative data in California comparing the rates of hospital admission for first stroke in children with SCD between the early 1990s (before STOP) and from 1998 to 2000 (after STOP) and found a sharp reduction in first stroke admissions, whereas overall SCD and SCD pain admissions did not decline. Such data do not establish a long-term trend or prove that the change is due to use of the STOP primary prevention strategy, but they are encouraging. While we try to learn more about why these large strokes afflict these small patients, we do have a way to make a positive impact now. Early and repeated screening should result in reduction in the prevalence of severe arterial disease and stroke in SCD, albeit at the price of extensive use of transfusion until other therapies are developed. Considering the reports from the 2 STOP trials still to be published and 2 currently ongoing clinical trials in children with SCD, one testing other approaches to screening (Silent Cerebral Infarct Multi-Center Clinical Trial) and the other testing hydroxyurea compared with transfusion for secondary stroke prevention (Stroke With Transfusions Changing to Hydroxyurea trial), we can look forward to extensive data from 4 randomized controlled trials aimed at stroke prevention in children with SCD.

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REFERENCES


