Hematologic Disorders and Ischemic Stroke
A Selective Review

Robert G. Hart, MD, and Merrill C. Kanter, MD

More than a dozen primary hematologic disorders have been associated with ischemic stroke. Inherited deficiencies of antithrombin III, protein C, and protein S have been linked with stroke in case reports; optimal screening requires functional as well as antigenic assays. Antiphospholipid antibodies and lupus anticoagulants are the most frequently identified acquired states associated with ischemic stroke. Polycythemia vera, sickle cell anemia, sickle-C disease, and essential thrombocythemia are the major disorders of formed blood elements causing stroke. Special, step-wise screening for occult prothrombotic entities in stroke patients is recommended for young persons with stroke of uncertain cause, for those with prior venous thrombosis, for those with a family history of unusual thrombosis, and for those with no other explanation for recurrent stroke. Acquired, perhaps transient, abnormalities of platelets, coagulation inhibition, and fibrinolysis may contribute importantly to brain ischemia in synergy with other mechanisms, but at present these remain ill-defined. The contribution of prothrombotic diatheses to stroke is probably underrecognized and warrants further investigation. (Stroke 1990;21:1111-1121)

In approximately 1% of all patients with ischemic stroke, and in up to 4% of young adults with stroke, the major precipitant of brain ischemia is a hematologic disorder or coagulopathy that predisposes to thrombosis. Recognition and laboratory definition of these uncommon conditions has burgeoned during the past decade (Tables 1 and 2). More complete laboratory screening of stroke patients for currently identified prothrombotic states will probably increase the percentage of strokes attributed to hematologic disorders. In coming years it is very likely that additional hematologic disorders that cause or contribute importantly to the substantial fraction of ischemic strokes that are presently of obscure cause will be identified.

Most hereditary disorders of blood coagulation cause venous thrombosis much more frequently than arterial thrombosis and cause no abnormalities in commonly performed hematologic/coagulation tests. Venous thrombosis in unusual sites, such as the mesenteric veins, hepatic veins, and sagittal sinus, are especially suggestive of a prothrombotic diathesis. While not all prothrombotic states that cause venous thrombosis result in arterial thrombosis, there is considerable overlap. Surprisingly, in persons with congenital disorders of coagulation inhibition or fibrinolysis, occlusion of limb arteries is as frequently reported as stroke, despite the higher likelihood that occlusion of cerebral arteries will be symptomatic. Hematologic causes of stroke may be more frequent in younger persons, but case reports may be skewed toward younger patients, in whom the contribution of a prothrombotic state is not confounded by coexistent atherosclerosis. It is possible that prothrombotic states are equally prevalent and even more important synergistic contributors to stroke in older patients but that coexistent atherosclerosis clouds the definition of their role. When a hematologic abnormality is identified following stroke, the hematologic disorder cannot be assumed to antedate the stroke and be its cause rather than a consequence. Support for an antecedent, causal role of the hematologic disorder includes its persistence in subsequent months or identification of the abnormality in family members.

Much of the literature about prothrombotic states linked to stroke consists of case reports and small case series, unfamiliar to many neurologists. Knowledge in this area is incomplete and evolving rapidly, yet clinicians must confront the issues of whom to screen and how to optimally detect these conditions. Several recent, comprehensive reviews of hypercoagulability have discussed in detail the concepts, mechanisms, and coagulation/fibrinolytic pathways. We briefly review the hematologic disorders associated with ischemic stroke, emphasizing selected aspects of interest to neurologists.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Probable Etiologic Association</th>
<th>Uncertain Etiologic Association</th>
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<td>Hereditary deficiency of coagulation inhibitors</td>
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<tr>
<td>Antithrombin III (especially type III)</td>
<td>Protein S*</td>
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<td>Protein C</td>
<td>Heparin cofactor II</td>
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<td>Hereditary abnormalities of fibrinolysis</td>
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<td>Dysfibrinogenemia</td>
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<td>Plasminogen activator deficiency</td>
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<td>Factor XII deficiency</td>
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<td>Prekallikrein deficiency</td>
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<td>Elevated concentrations of coagulation factors</td>
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<td>Factor VIII</td>
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<td>Factor V</td>
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<td>Autoantibody syndromes</td>
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<td>Lupus anticoagulants</td>
<td>Secondary polyeythemias</td>
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<td>Antiphospholipid antibodies</td>
<td>Sickle cell trait</td>
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<td>Paroxysmal nocturnal hemoglobinuria*</td>
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<td>β-Thalasemia</td>
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<td>Erythrocyte disorders</td>
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<td>Polycythemia vera</td>
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<td>Sickle cell disease</td>
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<td>Sickle-C disease</td>
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<td>Platelet disorders</td>
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<td>Essential thrombocytosis</td>
<td>Secondary thrombocytosis</td>
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<tr>
<td>Thrombocytinaemia with other myeloproliferative disease</td>
<td>Acquired hyperaggregable (“sticky”) platelets</td>
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*Associated with cerebral venous thrombosis.

### Hereditary Deficiency of Coagulation Inhibitors

Congenital deficiencies of four inhibitors of blood coagulation (antithrombin III [AT-III], protein C, protein S, and heparin cofactor II) have been clinically linked to thrombosis. AT-III is the primary physiologic inhibitor of thrombin and other activated serine protease clotting factors. Heparin increases the activity of AT-III by 100-fold; AT-III is an important mediator of heparin’s anticoagulant effect, and heparin resistance is a clue suggesting low AT-III activity. During treatment with heparin, AT-III levels decline, recovering 48–72 hours after cessation of heparin. AT-III deficiency can be congenital or acquired. Congenital AT-III deficiency is an autosomal dominant trait with variable penetrance, estimated to occur in one in every 2,000–5,000 people. The defect may be quantitative (type I) with heterozygotes having 20–60% of normal immunologic levels or, less often, qualitative (types II and homozygous type III) with persons having normal antigenic levels of dysfunctional AT-III. Acquired AT-III deficiency can result from severe hepatic disease (impairment of synthesis), renal loss (the nephrotic syndrome), or consumption (intravascular thrombosis), as well as from oral contraceptive use or L-asparaginase therapy.

While venous thrombosis is more common with congenital AT-III deficiency, arterial thrombosis can also complicate this disorder. More than 400
patients with congenital AT-III deficiency have been reported, but stroke has occurred in fewer than 20 of them, in most due to sinus/cortical vein thrombosis. Documented cerebral arterial thrombosis has been reported in only a handful of cases, with a preponderance of homozygous type III AT-III deficiency.\textsuperscript{19–24} Most patients with congenital AT-III deficiency and stroke have had previous venous thrombosis, with rare possible exceptions.\textsuperscript{21} Low AT-III levels in patients receiving heparin or those with acute thrombosis does not indicate a congenital deficiency; demonstrating low AT-III activities in family members (including those who are asymptomatic) may be required to expediously establish the diagnosis.\textsuperscript{25,26}

Protein C is a vitamin K–dependent plasma protein that inactivates clotting factors and enhances fibrinolysis.\textsuperscript{8,27} Congenitally deficient heterozygotes with 25–50% normal antigenic levels were found in one of 200–300 unselected blood donors.\textsuperscript{28} Venous thrombosis has been associated with hereditary protein C deficiency, an autosomal dominant trait.\textsuperscript{8,18,28–31} The likelihood of a clinical prothrombotic state accompanying congenital protein C deficiency in individual families is uncertain as some afflicted families appear not to be at risk for thrombosis.\textsuperscript{28,32} Most hereditary protein C–deficient patients have low antigenic levels, but functional abnormalities with normal antigenic levels have been increasingly reported as qualitative assays become more widely available.\textsuperscript{24,33,34} Acquired protein C deficiency occurs in patients receiving warfarin therapy and in those with severe hepatic disease, disseminated intravascular coagulation syndrome, and acute thrombosis.\textsuperscript{8} Diagnosis of hereditary protein C deficiency in patients receiving warfarin requires calculation of the protein C antigen/prothrombin antigen ratio.\textsuperscript{8} Arterial thrombosis has only rarely complicated hereditary protein C deficiency.\textsuperscript{20,35} Strokes have usually been due to cerebral venous thrombosis\textsuperscript{36–38} or of unclear cause.\textsuperscript{18,29,39–45}

Protein S is a vitamin K–dependent protein that potentiates the anticoagulant effect of activated protein C.\textsuperscript{8} Similar to that of protein C, congenital deficiency of protein S has autosomal dominant inheritance, with heterozygotes having approximately 50% of normal antigenic levels, and is associated with a predisposition to venous thrombosis in reported families.\textsuperscript{8,18,24,46} The prevalence of hereditary protein S deficiency in the general population is unknown. Laboratory detection of protein S deficiency is complicated by the protein’s occurring in both free and bound (functionally inactive) forms; no standardized functional assay of protein S is commercially available.\textsuperscript{8,24,46,47} Acquired protein S deficiency occurs in patients receiving warfarin therapy and in those with the nephrotic syndrome and severe hepatic disease.\textsuperscript{47} In more than 200 reported patients with hereditary protein S deficiency, arterial thrombosis has been very rare.\textsuperscript{8,46} Reports of stroke associated with protein S deficiency have been incomplete and anecdotal and have not convincingly established an etiologic role.\textsuperscript{38,46–52}

Heparin cofactor II is a plasma protein, the physiologic role of which is incompletely defined; heparin cofactor II is catalyzed by heparin to inactivate thrombin.\textsuperscript{53–55} An autosomal dominant hereditary deficiency has been described, but whether it is associated with an increased risk of thrombosis is controversial.\textsuperscript{53–55} No convincing evidence relates heparin cofactor II deficiency to stroke.\textsuperscript{53}

**Hereditary Abnormalities of Fibrinolysis**

Four types of inherited abnormalities of fibrinolysis (plasminogen deficiency, plasminogen activator deficiency, dysfibrinogenemia, and factor XII/prekallikrein deficiencies) have been linked to thrombosis. Hereditary plasminogen deficiency, quantitative or qualitative, is transmitted as an autosomal dominant trait, with heterozygotes predisposed to venous thrombosis, including cortical vein thrombosis.\textsuperscript{56,57} Hereditary plasminogen deficiency is rare in American whites and in Germans, but it has been reported in 2% of Japanese.\textsuperscript{56,57} A single young patient has been reported in whom cerebellar infarction was associated with familial plasminogen deficiency.\textsuperscript{58} Plasminogen is activated to plasmin by tissue plasminogen activator.\textsuperscript{59} Possible hereditary deficiencies of this enzyme have been linked to venous thrombosis but not to stroke, although definitive release has been reported in stroke patients.\textsuperscript{5}

Approximately 10% of the more than 100 reported families with dysfibrinogenemias have undue thrombosis, primarily venous, but also arterial.\textsuperscript{60} The abnormal fibrin clot resists fibrinolysis. Heterozygotes with this autosomal dominant trait usually have a normal or an only mildly decreased plasma fibrinogen concentration and a prolonged prothrombin time, but the thrombin time is a more sensitive screening test.\textsuperscript{54} Rarely, thrombosis has occurred with a normal thrombin time, requiring reptilase or anecrod clotting times for detection (these latter tests are also required to detect dysfibrinogenemia in patients receiving heparin).\textsuperscript{24,61} Arterial thrombosis, but not ischemic stroke, has been reported in patients with hereditary dysfibrinogenemia, often without venous thrombosis in the propositus or family members.\textsuperscript{62,63} Hypofibrinogenemia (a quantitative abnormality) is a less common hereditary disorder that is also detected by the thrombin time, but this disorder has only rarely been associated with arterial thrombosis in the absence of therapeutic infusion of fibrinogen concentrates.\textsuperscript{64}

It is controversial whether hereditary deficiencies in factor XII or prekallikrein cause prothrombotic states.\textsuperscript{65} Deficient patients have prolonged activated partial thromboplastin times (APTTs). Of 121 reported patients with hereditary factor XII deficiency, stroke occurred in two\textsuperscript{65,66} and a third possible case had stroke and moyamoya syndrome.\textsuperscript{67} Two brothers with stroke, familial factor XII deficiency, and lupus anticoagulants have been reported.\textsuperscript{68} Of 37 reported patients with hereditary prekallikrein deficiency, two have experienced stroke; one had multi-
ple ischemic subcortical strokes and no history of venous thrombosis.65,69

Increased Concentrations of Coagulation Factors

It is uncertain whether elevated levels of coagulation factors predispose to thrombosis.7,11 Coagulation factors circulate as zymogens (inactive forms) in relatively high concentrations, and it does not necessarily follow that increased levels cause hypercoagulable states. Reports of thrombosis associated with familial factor V elevation and familial and sporadic factor VIII elevations have not been widely confirmed and antedated testing for protein C and protein S deficiencies.7,65,70-72 Factor VIII and, to a lesser extent, factor V are acute-phase reactants to thrombosis.5 At present, in our view, there is no convincing etiologic evidence linking elevations of these coagulation factors to ischemic stroke.

Autoantibody Syndromes

Lupus anticoagulants (LAs) are acquired immunoglobulins that are associated with thrombosis, not bleeding, in vivo.73 The laboratory hallmark of LA is a prolonged APTT that fails to correct when affected plasma is mixed with normal plasma, implying inhibition of the clotting system rather than deficiency of a component. LAs are more sensitively detected by the kaolin clotting time, the dilute thromboplastin assay, and the Russell’s viper venom time.74-76 LAs are a subset of a larger, heterogeneous group of antibodies against phospholipid, not all of which prolong the APTT. Antiphospholipid antibodies (APAs) that do not prolong the APTT have also been associated with thrombosis and stroke.77-81 The mechanism(s) by which APAs (and the subset of LAs) predispose to venous and arterial thrombosis has not been firmly established; preliminary evidence indicates inhibition of prostacyclin, inhibition of protein C activation, and inhibition of AT-III activity, among others.82-87 Although antibodies can be directed against many phospholipids, cardioplin is the most widely used antigen. An enzyme-linked immunosorbent assay is available and inexpensive.88,89 Approximately 70% of patients with LAs have anticardiolipin APAs, and vice versa, the percentages varying somewhat with specific techniques and criteria.76,81,90

LAs were detected by routine APTT (a relatively insensitive screening test) in 4% of 145 young adults with stroke.91 In one series of 46 consecutive young patients with stroke, 46% had APAs,92 in contrast to 0% of 38 young patients with stroke of unknown cause screened a mean of 3 years after ictus.93 At least 50 patients with ischemic stroke or transient ischemic attack (TIA) associated with LAs and APAs have been reported since 1980, the majority without prior venous thrombosis.66,81,85,91-102 Most cases have had other possible contributors to stroke (e.g., systemic lupus erythematosus, oral contraceptive use, hereditary factor XII deficiency) confounding determination of the direct role of LAs or APAs.68,85,91 In several stroke patients with LAs and APAs, nonbacterial thrombotic endocarditis has been reported.91,101,103-105 Despite the many pathogenetic uncertainties, the existence of a primary APA syndrome causing an immune-mediated prothrombotic state is likely.79-81

Erythrocyte Disorders

Polycythemia vera is a primary myeloproliferative stem cell disorder causing panhyperplasia of erythrocyte, leukocyte, and megakaryocyte cell lines in the bone marrow. The most common neurologic symptoms (headache, lethargy, dizziness) probably result from hyperviscosity-related diminished cerebral blood flow. However, thrombotic occlusion of larger cerebral arteries complicates polycythemia vera in 10-20% of patients.106-112 The incidence of stroke/TIA in phlebotomy-treated patients with polycythemia vera (mean age 60-65 years) is 4-5% per year.106,108 Thrombotic risk correlates with hematocrit elevation, age, and phlebotomy frequency but has been less convincingly linked to associated thrombocytosis.107-109,113-115 Thrombosis often complicates treatment in patients with polycythemia vera and modest hematocrit elevations (50-60%).108 Chronic prophylactic treatment of phlebotomy-treated polycythemia vera patients with 900 mg/day aspirin and dipyridamole has resulted in a substantial risk of hemorrhage and little apparent benefit and thus is not routinely recommended unless previous thrombosis has occurred.106 Arterial catheterization and surgery may precipitate thrombosis.116,117

Ischemic stroke is less frequently associated with secondary polycythemias than with polycythemia vera, but the direct influence of hematocrit elevation is obscured by the lower mean age of, the infrequency of chronic hypertension in, and the generally lower hematocrits of patients with secondary polycythemias than of those with polycythemia vera.118-121 The risk of arterial thrombosis may not be uniform in patients with all subtypes because some secondary polycythemias are compensatory responses to low arterial oxygen tension, some are caused by reduced plasma volume and a relative increase in the number of erythrocytes, and others are familial and noncompensatory.121-126 Adults with cyanotic congenital heart disease complicated by compensatory polycythemia (mean age 29 years, mean hematocrit approximately 60%) were reported to have a very low risk of clinical stroke (0% in 204 patient-years of follow-up).119,120 Pseudopolycythemia (also called spurious, stress, or Gaissbök’s polycythemia) usually occurs in hypertensive, obese, middle-aged men who smoke tobacco and who have modest increases in hematocrit (usually <60%) due to reduced plasma volume.127 The relative contribution of the elevated hematocrit to stroke in the presence of other cerebrovascular risk factors has been difficult to define.114,128-130

Several hemoglobin variants that cause sickling of erythrocytes (sickle cell anemia [HbSS], sickle cell trait [HbSA], and sickle-C disease [HbSC]) have been...
associated with cerebrovascular symptoms.131–134 Cerebral ischemia occurs in approximately 15% of patients homozygous for HbSS.131,132,134,135 The mean age for ischemic stroke in such patients is approximately 10 years; in young adults hemorrhagic strokes are more frequent.135–137 The pathophysiology of cerebral ischemia is a complex and chronic process, with intimal hyperplasia and thrombosis, occasionally resulting in moyamoya-like angiographic findings.138–140 Arteriography can precipitate a sickle cell crisis but is relatively safe if the hemoglobin S concentration is lowered to <20% by exchange transfusion.141

HbSA occurs in approximately 10% of North American blacks (Table 3). Several case reports of otherwise unexplained stroke in young patients with HbSA suggest a causal relation.142,143 However, the frequency of stroke in people with HbSA is the same as that in the general black population, making the etiologic importance of HbSA uncertain.131,142–144 Multiple subcortical infarcts have been reported without recognized precipitants for sickling.143 The clinical manifestations of HbSC are similar to, but less severe than, those of HbSS. Stroke may occur in young adults without other systemic manifestations.144,145 While sickle cell diseases are largely confined to blacks in North America, crises have been reported in many other ethnic groups.146 In patients with β-thalassemia, cerebrovascular syndromes are usually reported in association with blood transfusions, although a recent case report of cerebral thrombosis in two patients with β-thalassemia implicates extracranial carotid artery occlusion.147

Paroxysmal nocturnal hemoglobinuria is a rare, acquired stem cell disorder in which abnormal erythrocyte cell membranes are sensitive to lysis by complement. This disorder primarily affects young adults, presenting with chronic hemolytic anemia often coupled with mild granulocytopenia and thrombocytopenia. Episodes of nocturnal hemolysis with morning hemoglobinuria occur in only a minority of patients. Venous thrombosis, particularly of the hepatic and cortical veins, is common. Stroke due to arterial occlusion has not been clearly documented.148 Diagnosis is based on erythrocyte lysis during complement activation by acidification (Ham’s test) or by lowering ionic strength (sucrose hemolysis test).

### Thrombocytosis and Qualitative Platelet Abnormalities

Thrombosis (and bleeding) may be complications of thrombocytosis associated with primary myeloproliferative disorders.113,149–153 Essential thrombocythemia combines an elevated platelet count with qualitative platelet dysfunction; microvascular thromboses causing digital ischemia and neurologic symptoms including stroke are frequent.113,149–154 In essential thrombocythemia, no clear correlation exists between the degree of thrombocytosis and the risk of thrombosis, implicating qualitative platelet abnormalities.113,151 Aspirin therapy unduly prolongs the bleeding time and may precipitate bleeding in patients with myeloproliferative disorders.106,155 Cerebral venous thrombosis can complicate essential thrombocythemia.136–139

Postsplenectomy thrombocytosis and secondary (reactive) causes of thrombocytosis, even when profound, are not usually associated with thrombosis unless other risk factors are present. Anecdotal case reports of stroke associated with secondary thrombocytosis due to iron deficiency suggest otherwise, but they are not convincing.106,161

Despite more than a decade of extensive clinical and basic research, laboratory markers of an intrinsic state of platelet hyperactivity that is usefully predictive of stroke have not been defined. Based on thrombosis associated with myeloproliferative disorders, the existence of “sticky” platelets precipitating thrombosis in predisposed people seems possible.162,163 Multiple types of platelet abnormalities have been described following stroke, but the issue of cause versus epiphenomena and the influence of other variables (e.g., smoking, medications) have confounded the etiologic importance of such abnormalities.162,164–166

### Other Prothrombotic States Associated With Stroke

In one large autopsy series, 2% of consecutive patients with cancer had clinical ischemic stroke attributed to a coagulopathy, usually mediated by nonbacterial thrombotic (marantic) endocarditis, intravascular mucinosis, or low-grade disseminated intravascular coagulation.167–169 Laboratory abnormalities of coagulation or fibrinolysis commonly occur in cancer patients, especially those with metastases.170–172 Thrombosis can be precipitated by chemotherapy, which may contribute to the prothrombotic state via several mechanisms.173–175 Reliable predictors of ischemic stroke in cancer patients have not been defined to permit primary prophylaxis.

Nonbacterial thrombotic (marantic) endocarditis is a nonspecific marker of hypercoagulable states. Aseptic cardiac valvular thrombi complicate a spec-

### Table 3. Sickle Cell Disorders: Prevalence and Stroke

<table>
<thead>
<tr>
<th>Hemoglobin variant</th>
<th>Disorder</th>
<th>Prevalence in US blacks (range)</th>
<th>Prevalence of stroke (range)</th>
<th>Mean age of stroke patients</th>
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</thead>
<tbody>
<tr>
<td>HbSS</td>
<td>Sickle cell anemia</td>
<td>0.03–0.16%</td>
<td>15%</td>
<td>9 yr</td>
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<tr>
<td>HbSC</td>
<td>Sickle-C disease</td>
<td>0.02–0.21%</td>
<td>2–5%</td>
<td>30 yr</td>
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<tr>
<td>HbSA</td>
<td>Sickle cell trait</td>
<td>8.5%</td>
<td>1.5–2.0%</td>
<td>26 yr</td>
</tr>
</tbody>
</table>

Approximately 75% of strokes in patients with sickle cell anemia are ischemic, with hemorrhagic strokes more common in older patients (mean age 25 yr). Figures are derived from References 131, 132, 134, 135, and 144.
trum of illnesses having in common a prothrombotic state. Nonbacterial thrombotic endocarditis often appears in the continuum with Trousseau's syndrome and low-grade disseminated intravascular coagulation, supporting a prothrombotic pathogenesis, but underlying recent or remote valve damage is often contributory. Clinical stroke occurs in at least 30% of these patients; it is uncertain whether central nervous system vascular occlusions are primarily embolic or due to in situ thrombosis from the systemic hypercoagulable state.

**Acquired Abnormalities of Coagulation Inhibition and Fibrinolysis**

Acquired abnormalities of coagulation inhibition and fibrinolysis may cause or contribute to stroke, but these have been difficult to define. For example, the prothrombotic states associated with the nephrotic syndrome and L-asparaginase therapy may be mediated by an acquired AT-III deficiency. It is conceivable that abnormalities of coagulation inhibition and fibrinolysis occur, perhaps only transiently, which can precipitate thrombosis in synergy with underlying atherosclerosis or cardiac disease. Support for this hypothesis is found in hematologic surveys of patients following stroke, identifying abnormalities that variably persist for weeks to months. However, most studies have not screened for the full spectrum of coagulation/fibrinolytic disorders, have employed suboptimal control groups, and have given only minimal descriptions of individual patients. Results are often conflicting, and differences in mean values between patient groups and control groups usually were minimal. The issue of cause versus epiphenomena, even with persistent abnormalities, has never been convincingly settled. At present, the many intriguing observations of abnormalities of coagulation inhibition and fibrinolysis measured after stroke have limited implications for prevention and management. The circadian variation in stroke onset may be due in part to normal fluctuations in the coagulation balance combined with underlying arterial disease. Elevations of hematocrit and fibrinogen concentration have limited range may influence the risk of thrombosis in the presence of coexistent structural disease or in stasis-prone situations.

An ever-increasing number of prothrombotic states have been associated with stroke. Specific tests to exclude many of these uncommon disorders are expensive, not widely available, and usually yield little information. Clinicians are faced with the dilemma of which stroke patients to screen and to what extent to pursue the diagnosis of these disorders. In recent stroke registries, 0–7% of brain infarcts have been attributed to a hematologic cause (Table 4). Screening of the substantial fraction of patients with strokes of uncertain cause was incomplete in these studies, particularly for the more recently identified markers of prothrombotic states, and these are likely to be minimum estimates of the frequency of stroke due to hematologic disorders. Clinical studies screening consecutive stroke patients for occult hematologic abnormalities are few and are largely restricted to younger patients. Among 153 patients from two studies tested 6–16 weeks after stroke, none had quantitative antigenic AT-III deficiency or abnormal platelet aggregability. Fibrinolytic abnormalities were frequent in these two Scandinavian studies, but this has not been confirmed subsequently. In a more recent report, functional deficiencies of protein C and AT-III and low protein S antigen concentration were not found in 42 consecutive young patients with stroke of

### Table 4. Prevalence of Stroke Attributed to Hematologic Disorders

<table>
<thead>
<tr>
<th>Registry</th>
<th>Year</th>
<th>N</th>
<th>Hematologic</th>
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</thead>
<tbody>
<tr>
<td><strong>All ages</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lausanne Stroke Registry</td>
<td>1988</td>
<td>891</td>
<td>1%</td>
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<tr>
<td>Oxfordshire Community</td>
<td>1989</td>
<td>244</td>
<td>0%</td>
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<td>Stroke Project</td>
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<tr>
<td>Lone Star Stroke Registry</td>
<td>1984</td>
<td>278</td>
<td>1%</td>
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<td>(unpublished)</td>
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<tr>
<td><strong>Young (&lt;40–50 yrs) patients</strong></td>
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<tr>
<td>Hart et al</td>
<td>1983</td>
<td>143</td>
<td>4%</td>
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<tr>
<td>Klein and Seland</td>
<td>1984</td>
<td>76</td>
<td>7%</td>
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<tr>
<td>Hilton-Jones and</td>
<td>1985</td>
<td>60</td>
<td>3%</td>
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<td>Warton</td>
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<tr>
<td>Adams et al</td>
<td>1986</td>
<td>144</td>
<td>4%</td>
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<tr>
<td>Lechat et al</td>
<td>1988</td>
<td>70</td>
<td>6%</td>
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<tr>
<td>Chancellor et al</td>
<td>1989</td>
<td>63</td>
<td>2%</td>
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<td>Aggregate (n=16)</td>
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<tr>
<td>Lupus anticoagulants/antiphospholipid antibodies</td>
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<tr>
<td>Essential thrombocytopenia</td>
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<tr>
<td>Polycythemia vera</td>
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<tr>
<td>Marantic endocarditis</td>
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<tr>
<td>Sickle cell disease</td>
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<tr>
<td>Antithrombin III deficiency</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
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</table>

In all studies except that of Chancellor et al, patients were not screened in any standardized manner for most prothrombotic states. Thus, prevalences probably represent minimum values.

### Conclusions

Classification of prothrombotic states is conceptually and practically difficult and must include consideration of factors promoting stasis and endothelial abnormalities acting in synergy with primary hematologic disorders. While certain disturbances of the hemostatic balance themselves cause intravascular thrombosis, other primary prothrombotic hematologic conditions may require associated structural vascular disorders (e.g., valvular abnormalities plus a prothrombotic state producing nonbacterial thrombotic endocarditis) to cause stroke. Subtle disturbances of the hemostatic balance within the normal
uncertain cause screened 3 years after stroke.93 These data suggest that congenital deficiencies of AT-III, protein C, and protein S and fibrinolytic abnormalities are uncommon in young stroke patients. Screening of young stroke patients for APAs has yielded widely varying results in available studies (2–46%), perhaps reflecting timing of the screening and laboratory techniques/criteria.92,93

Based on available data, special laboratory screening for prothrombotic states contributing to stroke is recommended only for selected patients (Table 5). Because the laboratory definition of prothrombotic diathesis is evolving rapidly and additional clinical studies continue to identify high-risk subgroups, we emphasize the tentative nature of current screening algorithms (Table 6). The cause and imminent precipitant of ischemic strokes remain unexplained in many patients. The potential contributory role of prothrombotic states warrants further investigation.

### Table 5. Selective Screening for Prothrombotic States in Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Situation</th>
<th>Abnormalities on routine screening laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history of stroke</td>
<td>Hemoglobin and hematocrit</td>
</tr>
<tr>
<td>Prior venous thrombosis</td>
<td>Platelet count</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>Prothrombin time and partial thromboplastin time</td>
</tr>
</tbody>
</table>

### Table 6. Special Laboratory Screening for Prothrombotic States in Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Initial screening</th>
<th>Anticardiolipin antibody assay by enzyme-linked immunosorbent assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Activated partial thromboplastin time with 1:1 mix or kaolin clotting time (serial dilutions) for lupus anticoagulants</td>
</tr>
<tr>
<td>Hemoglobin electrophoresis</td>
<td>Sedimentation rate</td>
</tr>
<tr>
<td>Associated with evidence of systemic disease</td>
<td>Fibrin degradation products</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Prior personal or family history of thrombosis</td>
</tr>
<tr>
<td>Functional assay for antithrombin III (including heparin cofactor activity for homozygous type III deficiency)</td>
<td>Functional assay for protein C activity</td>
</tr>
<tr>
<td>Thrombin time for dysfibrinogenemia</td>
<td>Electroimmunoassay of free protein S antigen*</td>
</tr>
</tbody>
</table>

*General recommendations, to be individualized to patient circumstances. Screening for heritable disorders is modified from recommendations by Mannucci and Tripodi94 and Rodgers and Shuman.9

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References


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