ANTHONY B. WEKSLER, M.D., AND MARGARET LEWIN, M.D.

SUMMARY Anticoagulation clearly benefits patients at risk of stroke from cerebral embolism. Conversely, patients with completed ischemic stroke are not benefited, and may show a higher mortality and morbidity because of hemorrhagic complications. Technical advances in the early, accurate diagnosis of cerebral hemorhage, the constant infusion of heparin, and closer monitoring of anticoagulation have continued to reduce the risk of hemorrhage in treated patients. In patients with TIA, alternative therapy with anti-platelet agents, which appears to prevent stroke at less bleeding risk, is under study. Current results show no differences between the two therapies, but only historical controls are available for evaluation of benefit. Whether or not anticoagulation prevents progression of neurologic deficit in patients with strokes-in-evolution remains an unanswered question, which can be resolved only by prospective, randomized, controlled trials.

Although anticoagulation therapy is now frequently advised in the management of cerebrovascular disease, studies are needed in which the efficacy of this therapy is accurately evaluated by long-term, well-controlled investigations of large numbers of patients. This challenge, issued in 1961 by R.N. Baker reporting for the Neurology Section of the Veterans Administration Cooperative Study of Atherosclerosis, is still unmet.

When this subject was last reviewed in this journal in 1977 by the Joint Committee for Stroke Resources, analysis of the available literature led to the conclusion that data from randomized prospective trials of anticoagulant use in cerebral ischemia were few, that patient numbers were small, and that efficacy of anticoagulants was either not proven or not deductible, particularly because of inadequate control populations. The current review will demonstrate that although new methods of diagnosis and treatment, and new means of monitoring treatment have been developed, definitive clinical studies have yet to be performed. Therefore, improved methods for differentiating ischemic infarction from intracranial hemorrhage, for the administration of heparin by infusion rather than bolus injection, for the control of hypertension, and for the monitoring of anticoagulant effect which have become available in the routine care of patients with cerebral ischemia, postdate most of the published major studies of anticoagulation for cerebral ischemia, and need to be incorporated into new trials.

While it is generally agreed that thrombosis is an important cause of cerebral ischemia, the thrombotic factors contributing to ischemic manifestations may differ in transient ischemic attacks (TIA), stroke-in-evolution, completed stroke and cerebral embolus of cardiac origin. Separate studies of hemostasis in these conditions are therefore warranted.

Hemostatic Function in Patients with Cerebral Ischemia

It is difficult to document hypercoagulability in patients with cerebrovascular disease; that is, to find signs predictive of a high risk for thrombosis, particularly imminent thrombosis. Plasma coagulation factors are normally present far in excess of the amounts required for normal blood clotting; elevation of these factors is, therefore, a non-specific finding. On the other hand, activated coagulation factors — evidence of intravascular coagulation — are cleared so rapidly from plasma that their elevation cannot be detected. Moreover, several coagulation factors such as fibrinogen and Factor VIII (anti-hemophilic factor) which may be elevated in patients with atherosclerosis, are acute phase reactants whose levels rise with any inflammatory condition such as vasculitis, infection or tissue damage induced by stroke.

Platelet hyperactivity is measured by augmented aggregation or by increased plasma levels of platelet release products such as beta thromboglobulin. This hyperreactivity is often present after acute cerebral ischemia but frequently returns to normal within weeks, suggesting a result, rather than a cause of the ischemic insult. In special risk groups such as patients with diabetes or hyperlipidemia, platelets may be chronically hyperactive, as has been reported in young patients with stroke.

Elderly normal subjects, as well as elderly stroke patients, have increased levels of Factor VIII and increased platelet activity. Mettinger recently reported an extensive study of hemostasis in 119 patients under the age of 55 who had suffered a TIA or RIND within the preceding three months, and whose acute hemostatic changes (elevat-
ed fibrinogen and ESR levels) had returned to normal. There was a trend toward persistent elevation of Factor VIII if the carotid angiogram showed atherosclerotic disease; the antithrombin III (AT III) antigen level also remained elevated, although its biologic activity was normal. AT III is the major plasma inhibitor of thrombin; persistent elevation thus suggests an increased rate of turnover or inactivation, possibly in response to increased thrombin generation.

The same patient group had lower levels of plasminogen activator, a major stimulus of fibrinolysis. Female patients had higher antiplasmin than did controls, but overall the fibrinolytic system showed normal synthetic capacity.

Platelet function was mildly abnormal: patients with a positive angiogram had greater release of ADP upon collagen stimulation and a modestly (20%) shortened platelet survival.

Fibrinogen and ESR were (by study design) normal in all patients. This suggests that the above-described changes in hemostasis reflect ongoing vascular disease rather than an acute phase reaction. Vascular endothelium produces Factor VIII antigen (von Willebrand factor), and thrombin can cause its release; the elevated levels observed in these patients may reflect chronic vascular damage.

In acute progressive stroke, deBoer et al found that serum Fragment E (a fibrin cleavage product) is elevated, whereas plasma beta thromboglobulin (evidence of platelet release) remains normal. While this suggests a more important role for thrombin generation than for platelet activation in progressive stroke, it should be remembered that trace amounts of thrombin activate platelets and increase platelet procoagulant activity. Thus, activation of the hemostatic mechanism follows cerebral ischemia and in some cases continues into the chronic phase, probably because of abnormal vascular surfaces.

Binding of coagulation factors to the vascular endothelium, and localized activation at the endothelial surface, has recently been demonstrated. This suggests that coagulation can be initiated locally on the undamaged vascular surface in a manner similar to clotting factor activation on the platelet surface. This process might mediate thrombotic events in cerebrovascular disease, even in the absence of specific endothelial disruption by plaque, possibly in regions of reduced blood flow.

**Heparin Therapy**

The heparin used in clinical practice is an immediately-acting anticoagulant which is a mixture of sulfated mucopolysaccharides. The anticoagulant effect of heparin results from its capacity to bind to and activate a plasma inhibitor of serine protease coagulation factors: the heparin cofactor AT III. Heparin markedly accelerates the rate at which AT III complexes with and irreversibly inactivates coagulation factors $X_e$ and thrombin. Since factor $X_e$ has a catalytic effect upon thrombin generation, even low concentrations of heparin (mini-heparin) can prevent venous thromboembolism. Once acute thrombosis has begun, however, full dose heparin is necessary to inactivate pre-formed thrombin. Heparin is generally begun as soon as intracerebral hemorrhage has been ruled out and is continued for 5–7 days, or until anticoagulation with oral medications has reached a steady state.

During administration of full dose heparin, some patients have a progressive reduction in AT III levels, paradoxically increasing their thrombotic tendency. In addition, high molecular weight fractions of commercially-available heparin, can activate platelets, inducing spontaneous aggregation, potentiating aggregation by other stimuli, and enhancing platelet thromboxane release. Thus, heparin in clinical use may promote coagulation by inducing a decrease in AT III or by inducing platelet hyperreactivity.

Conversely, heparin administration frequently causes thrombocytopenia (25% of patients) by at least two mechanisms: commonly by augmenting platelet aggregation, and rarely by inducing a heparin-dependent antiplatelet antibody. While a fall in platelet count below 100,000/mm$^3$ is unusual, it may occur, and in the setting of anticoagulation, bleeding complications ensue. The occurrence of thrombocytopenia is not dose related; it frequently occurs after about one week of treatment and is seen more often with the use of beef lung heparin than with that prepared from porcine intestine. Thrombocytopenia resolves rapidly when the heparin is discontinued.

Two technical developments in the control of heparin therapy postdated the major studies of anticoagulation in stroke: the use of constant infusions (rather than intermittent intravenous or deep subcutaneous injection) and the measurement of activated partial thromboplastin time (instead of whole blood clotting time). Salzman et al showed that more effective heparinization could be achieved at a lower total daily dose of drug if it were administered by pump-controlled intravenous infusion than by intermittent bolus.

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**Oral Anticoagulants**

The coumarin anticoagulants act by decreasing hepatic synthesis of four normal Vitamin K-dependent coagulation factors: II, VII, IX and X. Thus, the onset of anticoagulation by coumarins is slow, requiring 6–8 hours before factor VII (the most short-lived factor) falls, and several days before a steady-state is achieved.

Oral anticoagulation is monitored by the prothrombin time, which measures three of the four Vitamin K dependent factors (II, VII, X). Heparin only slightly prolongs the prothrombin time. In recent years it has been recognized that hemorrhagic complications,
which may occur even when the prothrombin time is in therapeutic range — about 1½ to 2 times control — rise sharply if the prothrombin time exceeds 2½ times baseline. Factors which affect Vitamin K availability (nutrition, antibiotics, bowel disease) as well as those affecting plasma binding or clearance of coumarins (drugs, fever) and hepatic function (drugs, disease) all influence the control of anticoagulation.

The studies of anticoagulation for TIAs of stroke performed in the 1950’s and 1960’s used more intensive anticoagulant therapy than is used in current practice. This may have contributed to the high reported incidence of bleeding. In a recent Dutch study of long term oral anticoagulation of elderly patients after myocardial infarction, it was shown that 75% of hemorrhagic events occurred when the prothrombin time was prolonged 2.7–4.5 times.16 In this study, the incidence of bleeding was not related to sex, age or duration of therapy (in a 2 year study) — the last contradicting findings in older studies. The country-wide organization of thrombosis monitoring in the Netherlands may have contributed to better long term control and patient compliance, and to fewer bleeding complications.

Anticoagulation in Transient Ischemic Attacks

The use of anticoagulants to prevent further TIA or stroke in patients presenting with one or more TIAs has been popular since the 1950’s. Clear evidence for efficacy of such therapy has been limited, however. Brust, reviewing 27 published studies of TIA carried out before 1977, noted great variation in definition of TIA, duration of observation, rate of recurrence or spontaneous clearing of attacks, the frequency of subsequent stroke or death, and the effects of age or other disease.17 Thus, the frequently cited figure of 5% stroke per year following an index TIA represents an average derived from highly variable data on natural history.

In a more recent series of 969 patients with TIAs prospectively followed over 14 months, more patients with vertebrobasilar TIA continue to have TIA (47%) than did patients with carotid TIA (32%); a single TIA, however, was a greater risk factor for subsequent infarction (10% overall), suggesting heterogeneity of prognosis.18 Other important risk factors for infarction were older age (over 63), male sex, and unreliability in taking medication. The rate of recurrent TIA or cerebral infarction was no different for those without specific treatment than it was for those treated with surgical, anticoagulant or antiplatelet therapy. There was, however, a significantly higher mortality rate among patients receiving anticoagulants, and a significantly lower mortality rate among those receiving antiplatelet agents.

Four prospective randomized studies of anticoagulation in TIA were carried out in the 1960’s and have been extensively reviewed.1, 2, 19-21 The total number of treated patients in these four studies combined was only 93, with 85 untreated controls; they were followed for an average of 19 and 21 months, respectively. No significant evidence of stroke prevention was found in any of these studies; eight ischemic strokes were observed in treated patients and ten in controls. Of the 15 deaths in the treated group, six were due to hemorrhage, compared to ten deaths (one from hemorrhage) among the controls. Reduction of recurrent TIAs was only clearly observed in one of the studies.

Of eight nonrandomized studies of anticoagulation in TIA published by 1977, six claimed benefit from anticoagulation (but study designs failed to indicate whether treatment and control groups were comparable), one showed no benefit, and one suggested benefit only in the first six months for vertebrobasilar TIAs alone.2, 19

Four prospective studies comparing anticoagulation with antiplatelet therapy in TIA patients have been published since 1979.20-25 None of these studies included an untreated control group. Salient features are summarized in Table 1.

Link22 treated 31 selected patients with carotid TIA and 86 with cerebral infarction with anticoagulation for an average of 11 months. During this period, there were no TIA’s and only one cerebral infarction; ten patients had bleeding complications. Anticoagulation was then discontinued, and in the ensuing observation period averaging 4.4 months, 1/20 TIA patients and 9/56 stroke patients had a cerebral infarct. There was one death from stroke and one from myocardial infarction. Among 45 untreated patients (anticoagulation “not indicated”), there were 6 strokes and 7 deaths, including 3 myocardial infarcts and a stroke during a similar period of observation.

Three studies compared anticoagulation with antiplatelet therapy (aspirin or aspirin/dipyridamole) in patients with TIA or RIND, with follow-up periods of 12–24 months. In Olsson’s23 study, all patients were treated for the first two months with anticoagulants and were then randomized between two treatment regimens. In the other two studies, patients were entered into treatment arms within 14 days of the ischemic event.24, 25 No difference in efficacy between the two arms was observed in any of these studies. Treated patients were, however, protected from cerebral infarction as compared to historic controls.

Anticoagulation in Stroke in Evolution

Two randomized studies of anticoagulation in progressive stroke, carried out in the early 1960’s, were reviewed by Genton et al.2, 19, 26 These totalled 150 treated and 154 untreated patients, followed for 6–15 months. In the treated groups, there were 34 cerebral infarctions and 25 deaths; while in the control groups 60 infarctions and 34 deaths occurred. Thus, there was a trend toward reduction of stroke progression in each of the controlled studies, but there was no significant change in the number of deaths. Information about early responses to treatment is not available. Similar trends toward benefit appeared in the non-randomized studies, but methodologic problems in patient assignment prevent clear interpretation. No recent studies have been undertaken.

The difficulties in achieving clinical improving with other available therapies have been summarized in a
recent review in this journal. Moreover, early heparinization may have detrimental results, as noted in a recent case report concerning progressive lacunar stroke; and the danger of hemorrhage complications increases with duration of therapy.

**Anticoagulation in Completed Stroke**

Seven randomized studies, all carried out before 1965 and comprising a total of 383 treated and 381 control patients studied for 1.5 to 42 months, showed no benefit from anticoagulant therapy. 100 subsequent strokes and 116 deaths occurred in the treated patients; and 83 strokes and 96 deaths in the control groups. Severe bleeding occurred in 40 treated but only 5 control patients. Risk of hemorrhage increased with duration of treatment.

There is a high rate of mortality from pulmonary embolism in patients with completed stroke. Recent evidence indicates that the use of low dose heparin (5000 units subcutaneously every 8–12 hours) in immobilized post-stroke patients decreases the incidence of deep venous thrombosis and subsequent pulmonary embolism without increasing hemorrhagic risk, even in neurosurgical patients. This use of anticoagulation deserves further study.

**Anticoagulation in Cerebral Embolism**

Cerebral emboli lead to an immediate mortality of 25–35%; there is an equal incidence of significant, long-term morbidity among survivors. The heart is the major source of such emboli, with transmural myocardial infarction, rheumatic heart disease (RHD), non-valvular atrial fibrillation (NVAF), and cardiomyopathy being the most common conditions predisposing to intracardiac thrombi.

In 1977, the Joint Committee for Stroke Resources reviewed 11 trials of anticoagulation for the prevention of cerebral embolism from cardiac sources. None of the trials was optimally designed; nevertheless, the combined results in over 500 patients suggest that anticoagulation decreases the incidence of initial and recurrent emboli in patients with rheumatic or ischemic heart disease.

Based on a study of 100 patients with chronic sinoatrial disorder, Fairfax and colleagues suggest that impaired atrial function appears to be a key factor in predisposing to intracardiac thrombosis. Paroxysmal supraventricular tachycardias and changing rhythms increase the risk of subsequent embolization.

Reviewing RHD, Easton and Sherman note that at autopsy, up to 50% of patients with RHD and mitral stenosis show evidence of systemic emboli, 60–75% of these being cerebral. Approximately 20% of patients with RHD will sustain a clinically-evident, major embolus; 50–60% of these will be cerebral, and 30–75% will have at least one recurrence — up to 40% within the first month. Trials evaluating small numbers of patients suggest that with adequate long-term anticoagulation, this incidence can be decreased by 30–40%.

Non-valvular atrial fibrillation (NVAF) is found in 9–25% of patients with cerebral emboli. At autopsy, Hinton et al found that 35% have emboli and 20% demonstrate left atrial thrombi. Darling and colleagues report that in 59 patients with systemic emboli and NVAF, nearly half re-embolized: 48% of these within the first two weeks. This approaches the 40% rate of re-embolization in patients with RHD and AF.

In this issue of Stroke, Sage and Van Uitert report a retrospective study of 140 patients with NVAF with cerebral emboli — both diagnosed by clinical criteria alone. The 62% who survived the initial embolus were followed without anticoagulation and showed a 20% recurrence rate during each year of the entire nine-year follow-up period. The first recurrence was seen at day 12. The study suggests that long-term prophylactic therapy is necessary, but that it need not be initiated immediately. In the same issue, however, Hart et al report a 32% recurrence rate in the first two weeks. Easton and Sherman summarized reviews of patients following transmural myocardial infarction. While only 2–12% of such patients show clinical evi-
idence of systemic emboli (up to 90% being cerebral), at autopsy, 45–60% of such patients had peripheral emboli. Up to 85% of these emboli occurred within one month of myocardial infarction; anticoagulation halved the natural occurrence rate.

Cardiomyopathy, especially idiopathic and alcoholic, also predisposes to intracardiac thrombi and subsequent cerebral emboli. In the review by Easton and Sherman, 35–100% have autopsy evidence of mural thrombi; approximately 20% have arterial emboli, half of these involving the brain. In approximately 13%, the emboli are clinically evident prior to death; enlargement of the heart and atrial fibrillation are additional risk factors for thromboembolic disease.

The true incidence of asymptomatic mitral valve prolapse (MVP) is unknown; thus, whether TIA’s and stroke in this population is coincidental or the result of the valvular abnormality is unclear. The rate of recurrent stroke is also unknown. Watson 39 followed for a maximum of 11 months a group of 11 patients with TIA’s or non-progressive stroke (without arteriographic evidence of great vessel or arch disease) and MVP documented by echocardiogram. Of 8 patients treated with antiplatelet agents, there was one recurrence; there were no recurrences in the three patients treated with warfarin.

**Diagnostic Advances in Cerebral Ischemia Evaluation**

Accurate distinction between ischemic and hemorrhagic lesions must precede anticoagulant therapy of TIA, evolving stroke or cerebral embolus if risk is to be minimized. Whereas lumbar puncture was once the mainstay of such diagnosis, computed tomography (CT) has become recognized as a more accurate diagnostic procedure, particularly for intracerebral lesions. Ruff and Dougherty 39 reviewed 217 cases clinically diagnosed as stroke and evaluated by CT, finding 23% of the lesions non-ischemic. All 37 cases of intracerebral hemorrhage were diagnosed by CT, whereas only 9 were detected by lumbar puncture. Conversely, CT detected only 9 of 17 cases of subarachnoid hemorrhage whereas all were detected by lumbar puncture — only one of these cases, however, did not have headache or stiff neck.

In the same paper, the authors retrospectively compared 167 of these anticoagulated patients and 175 anticoagulated historic controls treated before CT scanning was available. They found a significant decline in mortality and in the incidence of fatal cerebral hemorrhage in the more recent group (7.2% deaths and 2.4% cerebral hemorrhage in patients treated between 1975 and 1979, compared to 12% deaths and 7.4% cerebral hemorrhage in patients treated between 1970–74). Risk factors for fatal cerebral hemorrhage included hypertension, excessive anticoagulation and age. Waiting at least one hour after lumbar puncture before starting heparinization significantly decreased the rate of spinal hematoma and other complications. In this study, 42% of clinically diagnosed strokes-in-evolution were found to have nonischemic lesions; in contrast, only 16% of clinical TIA’s were nonischemic. Seventy percent of cerebral hemorrhages occurred in the first 4 days of anticoagulant therapy.

Several recent retrospective studies address the risk of cerebral hemorrhage during anticoagulation for nonseptic embolic cerebral infarction. Furlan et al 40 found one hemorrhage in 54 consecutive patients; that patient had been anticoagulated at the time of embolization. Seven patients had recurrent emboli, all at a time when adequate anticoagulation had not been achieved. In contrast, there were no cases of hemorrhage or further emboli in those who had received adequate anticoagulation following the initial insult.

Lodder and van der Lugt 41 studied 39 similar patients initially screened by CT scan; they administered anticoagulation within 24 hours to 21 patients, despite the presence of hypodense areas on CT scan in eight cases. There were three deaths, including two from cerebral emboli and one from pulmonary embolism during the three week observation period. An additional ten patients were anticoagulated within five days of presentation; they showed no evidence of emboli or hemorrhage. Koller 42 found that 25% of 44 patients with embolic cerebral infarction suffered early recurrences of emboli. Fifteen patients promptly treated with anticoagulants had neither further emboli nor hemorrhage.

The risk of hemorrhage during long term anticoagulation has been estimated as 20%, with a subsequent mortality of up to 1%. The risk of intracranial hemorrhage has been estimated at 5%. In Whisnant’s retrospective analysis of intracranial hemorrhage in TIA patients, 43 the risk was eight times greater in those who were anticoagulated. There were 1.14 hemorrhages per 100 patient years in the treated group; the incidence was higher in patients 55–74 years old but was not greater in the presence of hypertension. Most intracranial hemorrhages occurred following one year of treatment and in patients over 65. Data from the Cooperative Study of TIA 44 indicated significantly higher mortality in patients receiving anticoagulants (18%/year) than other therapies (3–6%/year), but patient comparability was not established between treatment groups. Overall, four intracranial hemorrhages in 112 treated patients were reported.

The Dutch reinfarction study of elderly patients anticoagulated to therapeutic levels after myocardial infarction 45 reported that 6% sustained a major extra-cranial hemorrhage (41% of these were due to local disease and many of these patients had been over-anticoagulated); 6% suffered strokes, most of which were hemorrhagic. In contrast, 0.6% of patients treated with placebo suffered hemorrhage outside the central nervous system, and 5% suffered strokes, most of which were non-hemorrhagic.

While these studies all have limitations, it appears that the long term hemorrhagic risk in the older patients outweighs the possible benefit of anticoagulant for stroke prevention, with the exception of the patient at high risk for recurrent cerebral embolism of cardiac origin.
Should anticoagulant prove to decrease substantially the risk of cerebral embolus from cardiac sources, the decreased morbidity and mortality must justify the risk of treatment. In general, therapeutic anticoagulation with warfarin leads to a hemorrhagic risk of 5% per patient-year; serious or fatal bleeding approaches 1% per patient-year.

References

Anticoagulation in cerebral ischemia.
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