XIV. Cerebral Ischemia: The Role of Thrombosis and of Antithrombotic Therapy

Study Group on Antithrombotic Therapy

Edward Genton, M.D., Chairman;1 H. J. M. Barnett, M.D.,2 William S. Fields, M.D.,3 Michael Gent,4 and John C. Hoak, M.D.5

SUMMARY A revival of interest in antithrombotic agents for the treatment of ischemic cerebrovascular disease has resulted in the widespread use of oral anticoagulants for the prophylaxis and therapy of the ischemic variety of stroke, and has generated enthusiasm for the use of platelet-suppressant agents such as aspirin, dipyridamole, and sulfipyrazone. In delineating the several clinical types of focal ischemic disease and outlining the causes of cerebral ischemia and infarction, the study group considers the problems of data interpretation in the face of inconsistent terminology. The basic mechanisms of hemostasis and thrombogenesis are concisely detailed. Finally, the study group critically reviews extensive earlier reports of clinical trials of anticoagulants, platelet function suppressants, and thrombolytic agents, and reassesses according to present-day statistical standards the significance of the results. The information contained in this report should familiarize the reader with sufficient data to permit him to utilize antithrombotic agents under a variety of circumstances and to appreciate the contraindications and potential dangers in their use.

The socioeconomic importance of stroke is well documented.1,3 The economic impact in the United States can be assessed from the figures provided by Cooper and Rice2 who placed the total cost of stroke to the nation in 1972 at $6.2 billion dollars. Their calculation had three components: (1) direct costs for hospital care, physicians' services, nursing home care; (2) morbidity costs representing lost earnings and dollar value of unperformed housekeeping services; and (3) mortality costs referring to lifetime earnings (at present value) lost by premature death. Thromboembolism, in a comprehensive epidemiological review,4 accounts for the majority of vascular stroke. Recently, the results of a prospective population study carried out in Framingham, Massachusetts, analyzed with respect to cerebrovascular disease,6 substantiate that review. Over a period of 18 years during which 5,184 men and women from the community were followed, 196 became symptomatic as a result of cerebrovascular disease. Of these strokes, 78% were considered to be due to thromboembolic phenomena (cerebral infarction due to thrombosis 57%, "transient ischemic attacks"6, 6%, and cerebral embolism 15%); 12% were caused by subarachnoid hemorrhage, 5% by intracerebral hemorrhage and the remaining 5% were ascribed to miscellaneous causes.

It has been estimated1 that 40% of the approximately 395,000 persons in the USA who have a thromboembolic stroke each year will die within the first 30 days after the stroke, and of those who survive more than a month (numbering about 237,000), one-half will require either long-term special care because of physical difficulties or will be bedridden and/or need institutional care.

Etiology

Cerebral emboli follow a path from heart-to-artery or artery-to-artery. Classically, the heart has always been considered the source of a "cerebral embolus." Ten percent to 15% of cerebral infarcts are caused by embolism from the heart.4,6 Rarely a thrombus will originate in the pulmonary veins or a systemic venous clot will be carried through an atrial septal defect. Cardiac emboli vary in size but commonly are large.

Mitral stenosis gives rise to one variety of large cardiac emboli, and when accompanied by atrial fibrillation, the incidence of thromboembolism is said to be increased.7 Fibrillation is not a prerequisite to embolization; regular rhythm was present in 17 of 72 cases of mitral stenosis and cerebral embolism in one series.4 Forty-seven patients with rheumatic heart disease were studied by McDevitt.8 The hearts of 37 of these were in auricular fibrillation, and the rest were in sinus rhythm at the time of the stroke. One study9 indicates the incidence of systemic embolism (60% cerebral) in surgically treated patients to approximate 9.6%. In another series,10 cerebral embolism occurred in 34 of 172 (20%) rheumatic heart disease cases. Below the age of 35 years, the incidence of embolism is stated to be under 5%, but above this age it rises beyond 30%.12

A patient with a major cerebral embolus from the heart has a poor prognosis, with one in three experiencing an immediate mortality.13 The first year or two after the initial embolus carries a greater risk of recurrence than is present thereafter. Various reports give details concerning this outlook.10,14-16

One of the best contemporary studies on survival, and therefore prognosis, after the first cerebral embolism secondary to heart disease, is from a group of 42 cases followed without treatment for 20 years.9 At the end of this period, one patient survived; 13 died of recurrent embolism, 22 of congestive heart failure, and six of pneumonia and other causes.

In a study14 of 194 patients with systemic arterial em-
bolism in rheumatic heart disease, 30% of the 79 who had single embolic episodes at the time of the first examination died immediately. Of the total number of patients, 130 had one or more episodes of cerebral emboli, and 64 of the 130 (49%) died as a result of this complication. In an attempt to trace the fate of patients who survived the first episode, a follow-up study was made of those in whom the initial attack had occurred prior to the year 1940. This provided a follow-up of ten years or to death as a minimum, with 19 years as the maximal period. Of the 52 known deaths during this period, 14 occurred in the first year. In a further series of 125 patients with systemic emboli from mitral stenosis, 66% of the emboli were cerebral, and during the nine and one-half year follow-up, recurrences developed in 30% of the patients (35% of these within the first month of the initial event; a total of 58% within the first year). In another study of 754 patients afflicted with established rheumatic cardio-vascular disease, 36 instances of cerebral embolism occurred in those with atrial fibrillation, and 27 in those with sinus rhythm. Among those patients who had recurrent embolism, 40% of the attacks appeared within one month and a total of 66% within 12 months of the initial embolus. The incidence of emboli in this large series was calculated to be 1.5% per patient-year. In another series of 17 patients (a control group), 22 further embolic episodes occurred after the first one during an average follow-up of five years, and 13 took place in the first two years.

Mural thrombi associated with myocardial infarction are a significant cause of stroke-producing cardiac embolism. The risk of cerebral embolism during six weeks of acute myocardial infarction may be as high as 5%. During the immediate postsynaptic period about one-third of the patients die. Unless there is recurrent myocardial infarction, the risk of further embolization decreases rapidly after four to six weeks.

More than 100 years ago, pathologists noted that embolic strokes in patients with extracranial disease with embolization into the more distal intracranial portions of the carotid arteries. From the view-point of the examiner, it is mandatory to determine whether individual episodes of embolism were cerebral or extracranial in origin. The term, cerebral embolism, has been expanded to include artery-to-artery emboli (intraarterial source). Such emboli are of two main varieties which may exist in combination: platelet-fibrin emboli and atheromatous material.

1. Platelet-Fibrin Emboli

White bodies were observed coursing through or lodging in the retinal arterioles during an attack of amaurosis fugax. Later, this material was studied and shown to contain platelets and fibrin. To identify platelet-fibrin emboli in the vertebral-basilar territory is a more difficult task, since the terminus of the vertebral-basilar circulation is not accessible to direct visual examination as is the retina. One can

reasonably postulate that similar mechanisms operate in both major arterial circulations to the brain, in the vertebral-basilar branches, this theory remains to be established.

2. Atheromatous Material

"Bright plaques," as the atheromatous fragments in the retinal arterioles have been called, may be seen when there is ulceration of a plaque in the carotid arteries. Commonly there is no special cause of the ulceration but it may be seen after trauma to the carotid arteries. Following vigorous palpation of diseased carotid arteries, and occasionally after angiography or operation, a careful scrutiny of the fundus is mandatory since cholesterol emboli may be present in the retinal arterioles either with or without a history of amaurosis fugax. Irregular atheromatous and ulcer formation may be visualized in angiograms of the neck vessels of patients with transient ischemic attacks (TIA).

Ulcered lesions are located most commonly on the posterior aspect of the lumen of the distal portions of the common carotid and proximal segments of the internal carotid arteries, but they can be identified laterally as well, particularly in oblique views. Ulcers are observed much less commonly at a distance from the cervical bifurcation, in the carotid siphon, or in the vertebral arteries.

Statements have been made that the development of occlusion in a carotid artery on the side appropriate to the clinical signs and symptoms will lead to cessation of TIA. Although this is generally the case, exceptions are well documented that, subsequent to carotid occlusion, patients have experienced ischemic episodes in the territory distal to the obstructed artery. Several explanations are possible. Hemodynamic factors may cause the blood pressure to drop sufficiently to deny blood to the area of the brain now being served by collateral circulation. Alternatively, the soft, friable tail of the occluding thrombus may break off and obliterate a distal vessel that previously had been functioning well through collateral supply. The possibility also exists that in the presence of internal carotid artery occlusion, emboli from a roughened or ulcerated lesion in the ipsilateral common or external carotid artery, or in the contralateral common or internal carotid artery may be carried distally through various anastomotic communications. Finally, the patent intracranial portion of a proximally occluded artery may be the site of atheromatous disease, producing stenosis and/or thromboembolism into the distal artery.

Incidence of Extracranial Versus Intracranial Lesions

Angiographic evaluation of the patients who were entered into the Joint Study of Extracranial Arterial Occlusion demonstrated multiple atherosclerotic lesions and emphasized the importance of the extracranial compared to the intracranial vascular lesions (table 1).

On clinical grounds, even with the support provided by angiographic and other examinations, one frequently encounters difficulty in determining whether individual patients have extracranial disease with embolization into the intracranial arteries, intracranial disease with or without embolization from the aorta and/or heart, or primary obliterative disease occurring simultaneously in the extracranial and intracranial cerebral arteries. From the view-
point of selecting appropriate therapy, these diagnostic possibilities need to be examined as carefully as possible. Despite painstaking study, however, frequently one is led to the conclusion that, although reduced flow or obstruction is present within a certain vascular territory, the exact etiology of such ischemia is not identifiable with certainty.

Atherosclerosis is the most common cause of disease of the aortoarterial arteries and indicates the presence of numerous small ruptures in the arterial wall. Other vascular lesions are rare, but include fibromuscular dysplasia, systemic lupus erythematosus, periarteritis nodosa, giant-cell (“temporal”) arteritis, allergic granulomatous vascular lesions are rare, but include fibromuscular dysplasia, systemic lupus erythematosus, periarteritis nodosa, giant-cell (“temporal”) arteritis, allergic granulomatous arteritis, Wegener's granulomatosis, and the vasculitis accompanying rheumatic fever, rheumatoid arthritis, or scleroderma, as well as infections such as syphilis and brucellosis.26 Other conditions, related more to abnormalities of clotting than to disease of the arterial wall, are rather uncommon. Nevertheless they should be considered when other evidence points to their presence. These include: (1) hematologic diseases: primary thromboembolism, leukemia, sickle cell anemia, thrombotic thrombocytopenic purpura; (2) disseminated intravascular clotting (DIC); heat stroke, eclampsia, falciparum malaria, surgical shock, malignancy; (3) hyperviscosity syndromes: polycythemia rubra vera, Waldenström's and secondary forms of macroglobulinemia, cryoglobulinemia, multiple myeloma; and (4) hereditary metabolic diseases: hereditary hyperlipidemia, homocystinuria.

Venous Disease

Primary cerebral venous thrombosis is uncommon. For the purpose of this review one should note that intracranial venous occlusion occurs under the circumstances in which spontaneous venous thrombosis is known to arise,27 for example, in the veins of the pelvis and lower extremities. In the presence of multiple etiologies accounting for systemic venous thrombosis, the possibility of intracranial venous thrombosis should always be kept in mind. Recent reports indicate that the use of oral contraceptive medication is a precipitating factor, thereby adding to the varieties of thrombosis already known to be associated with hormonal influences operating during pregnancy and the puerperium.

Clinical Varieties of Cerebral Ischemia

In the new Classification of Cerebrovascular Diseases,28 the Clinical Stage (temporal profile) of ischemic stroke contains a number of categories including transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND), progressing stroke (stroke-in-evolution), and completed stroke. Partial nonprogressing stroke is an added term for a stroke that results in a minimal residual deficit.

### Table 1: Sites of Arterial Stenosis and Occlusion in Cerebrovascular Ischemia

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence of lesions*</th>
<th>Symptom</th>
<th>% Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid arteries</td>
<td></td>
<td>Stenosis</td>
<td>33.8</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>34.1</td>
<td>Occlusion</td>
<td>8.5</td>
</tr>
<tr>
<td>Internal carotid (distal to bifurcation)</td>
<td>8.0</td>
<td>9.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Vertebral</td>
<td>18.4</td>
<td>Left</td>
<td>23.3</td>
</tr>
<tr>
<td>Intracranial arteries</td>
<td></td>
<td>Right</td>
<td>4.0</td>
</tr>
<tr>
<td>Carotid siphon</td>
<td>6.7</td>
<td>9.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Basilar</td>
<td>7.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>3.5</td>
<td>4.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Percent of lesions at designated sites in 9,748 patients subjected to angiography.

### Table 2: Carotid Artery TIA: Presenting Symptoms in 133 Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresis (mono, hemi)</td>
<td>61</td>
</tr>
<tr>
<td>Paresthesia (mono, hemi)</td>
<td>57</td>
</tr>
<tr>
<td>Monocular visual</td>
<td>52</td>
</tr>
<tr>
<td>Paresthesia (facial)</td>
<td>40</td>
</tr>
<tr>
<td>Paresis (facial)</td>
<td>22</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>17</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>16</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Light-headedness</td>
<td></td>
</tr>
<tr>
<td>&quot;Dizziness&quot;</td>
<td>&lt;3% each</td>
</tr>
<tr>
<td>Convulsion (focal)</td>
<td></td>
</tr>
<tr>
<td>Convulsion (grand mal)</td>
<td></td>
</tr>
<tr>
<td>Binocular visual (hemianopia)</td>
<td></td>
</tr>
<tr>
<td>Visual hallucination</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Mental change</td>
<td></td>
</tr>
</tbody>
</table>

These are episodes of transient and focal cerebrovascular ischemia of vascular origin, rapid in onset (no symptoms to maximal symptoms in less than five minutes and usually less than a minute), which are variable in duration, commonly lasting from 2 to 15 minutes but occasionally persisting as long as a day (24 hours). The resolution or disappearance of each episode is swift, ordinarily a few minutes at most. A prolonged attack may take longer to clear. Usually, no neurologic deficit remains after an attack. Transient ischemic events occur in the territory of the carotid and of the vertebral-basilar arteries. Attempts to provide a clear understanding of the ischemic phenomena in each of these territories and of their usual expression are important. Otherwise, therapy may be misdirected and the critical appraisal of the efficacy of alternative treatment programs may be erroneous. However, this distinction cannot invariably be made with certainty and some patients may, over the course of a few weeks or months, manifest attacks indicative of ischemia in both the carotid and vertebral-basilar territories. Table 2 is a tabulation of symptoms presented by patients judged to be suffering from carotid territory TIA, as recorded in one unpublished study.29 Table 3 enumerates the symptoms exhibited by a group of patients from the same unpublished study30 who were judged to have vertebral-basilar TIA. The main distinguishing feature, of course, is the presence of unilateral symptoms in the carotid syndrome (e.g., monocular blindness, hemiparesis) compared with the bilateral symptoms in patients with vertebral-basilar syndrome. Furthermore, a number of isolated symptoms occurring without associated, more definitive manifestations cannot, of themselves, be attributed to TIA. These include recurrent vertigo, diplopia, drop attacks, transient amnesia, and episodes of unconsciousness. However, impaired con-
The etiology is presently considered to be a most important one for TIA because of the possibilities for instituting corrective medical or surgical therapy.

**Pathogenesis**

The pathogenesis of TIA falls into two major categories, thromboembolic and hemodynamic.

**Thromboembolic.** Thrombi can form at the site of an ulcerated plaque or in an artery either at or beyond a stenotic area. Many of these will not become sufficiently large to constitute major emboli, but some will result in symptoms of TIA or even a completed stroke, either by their transport to intracranial branches or, in combination with an intruding thrombus, to be produced in the diseased arterial wall.

**Hemodynamic.** In every instance of TIA, an analysis of the blood pressure, specifically the diastolic readings generally at or above 130 mm Hg, may be emphasized. In the human, a carotid artery must be very severely narrowed before there is any change of pressure gradient or of flow. Thus, diminished cerebral perfusion results from these factors in focal cerebral symptoms appears to be uncommon. Furthermore, the frequent observation of multiple major arterial occlusions is associated with sufficiently well-developed collateral circulatory channels to prevent major infarction. Alternative vessels appear to compensate satisfactorily for the potentially low perfusion until such time as either the collateral arteries themselves become diseased, or cardiac function becomes inadequate. TIA are not major features of stroke symptomatology in patients known to have multiple major arterial occlusions.

**Hypertension** and **cardiac dysrhythmia** are highly significant risk factors in the prediction of TIA. Furthermore, these conditions serve as markers for potential stroke. It is well documented that a number of patients with TIA do not have a history of hypertension, but rather have hypertension discovered at the time of evaluation. Cardiac dysrhythmia, too, can precipitate transient ischemia. Therefore, although the primary treatment of the hemodynamic group of conditions is medical, the potential for institution of corrective therapy must be considered.

**TABLE 3 Vertebral-basilar TIA: Presenting Symptoms in 54 Patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binocular visual</td>
<td>57</td>
</tr>
<tr>
<td>Vertigo</td>
<td>50</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>40</td>
</tr>
<tr>
<td>Diplopia</td>
<td>38</td>
</tr>
<tr>
<td>Ataxia</td>
<td>33</td>
</tr>
<tr>
<td>Pareseis</td>
<td>33</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>14</td>
</tr>
<tr>
<td>Visual hallucination</td>
<td>7</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>5</td>
</tr>
<tr>
<td>Mental change</td>
<td>5</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>3</td>
</tr>
<tr>
<td>&quot;Drop attacks&quot;</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td></td>
</tr>
<tr>
<td>Hyperacusis</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 4 Hemodynamic Causes of Diffuse Cerebral Ischemia**

1. Orthostatic hypotension
   a. Spontaneous
   b. Iatrogenic
2. Carotid sinus hyperesthesia
3. Bradyarrhythmia — tachyarrhythmia
4. Valvular aortic stenosis
5. Angina with cardiac decompensation
6. Increased blood viscosity
7. "Steal" mechanism
8. Low perfusion states
9. Vasospasm
10. Vascular compression by musculoskeletal structures

had evidenced TIA prior to therapy, in contrast to the 81% with generalized neurologic symptoms, the most common of which was syncope.

Increased viscosity of the circulating blood, as in macroglobulinemia and polycythemia, is accompanied occasionally by secondary transient ischemic episodes. In the steal mechanism, the radiologic identification of deviation of flow from the brain toward an upper limb, the scalp, or the face, as the result of subclavian, external carotid, or brachio-cephalic artery occlusion is probably an uncommon event.

Most clinicians are agreed that for symptoms to result from this altered flow alone is unusual, and that almost invariably occlusive disease in the other extracranial arteries is widespread.

The role of low perfusion has probably been over-emphasized. The human, a carotid artery must be very severely narrowed before there is any change of pressure gradient or of flow. Thus, diminished cerebral perfusion resulting in focal cerebral symptoms appears to be uncommon. Furthermore, when multiple major arterial occlusions are encountered and identified, they are frequently associated with sufficiently well-developed collateral circulatory channels to prevent major infarction. Alternative vessels appear to compensate satisfactorily for the potentially low perfusion until such time as either the collateral arteries themselves become diseased, or cardiac function becomes inadequate. TIA are not major features of stroke symptomatology in patients known to have multiple major arterial occlusions.

The possibility that vasospasm produces transient attacks has not proved to be important in the etiology of TIA and threatened stroke. Nevertheless, on rare occasions, the sudden development of excessively high blood pressure, with diastolic readings generally at or above 130 mm Hg, may be associated with transient ocular and/or cerebral ischemic episodes. In ophthalmoscopic examination during such a vascular crisis, intensive retinal arteriolar narrowing is apparent. Management of the hypertension alone has been observed to bring about cessation of symptoms and disappearance of the ocular changes.

The literature is replete with reports of TIA produced by extravascular compression of the vertebral arteries by structures such as laterally placed osteophytes on the cervical vertebrae. Tortuous, coiled, and kinked internal carotid arteries have also been implicated. Despite a large number of reports on the subject, extravascular compression has proved to be a very uncommon cause of TIA.

The primary treatment of the hemodynamic group of con-
dions will, and indeed must, be directed at the responsible circulatory mechanisms rather than at the thrombotic process. Therefore, it is imperative to make this clinical distinction. Nevertheless, the impaired circulation occasioned by disturbed hemodynamic phenomena may result secondarily in the initiation of thrombotic processes, especially in the presence of diseased arteries. Indeed severe forms of hemodynamic alteration can lead to massive cerebral infarction. White thrombi (largely platelets) appear in the watershed pial arteries in patients dying from cardiac failure, cardiac dysrhythmias, blood loss, and hypotension.

Incidence, Natural History, and Prognosis

Four outcomes are possible in patients with recurrent TIA: (1) the attacks may cease spontaneously, (2) the attacks may continue, (3) cerebral infarction may occur, or (4) the attacks may be associated with other major vascular catastrophes (e.g., myocardial infarction), since the affected population is at high risk of vascular disease.

Data are incomplete to delineate clearly the natural history of TIA and the prognosis for patients with this disorder. A number of studies have been reported, but both the clinical definitions employed and methods of compiling the information lack standardization. Nevertheless, from retrospective and a few prospective studies some useful information can be derived.

In retrospective studies of patients who have had a completed cerebral infarction, from 10% to as high as 79% were reported to have been afflicted with previous TIA. The variability and range of the figures probably reflect the individual observers’ interpretations of what has constituted a preceding “attack,” as well as the tenacity with which they pursue the questioning with each patient.

Prospective studies may prove to be more accurate, but again, the answers will be affected remarkably by the definition of TIA employed by the investigators. In a compilation from several reported series with follow-ups ranging from slightly less than one year to five years, the incidence of cerebral infarcts following TIA varied, including 10% within 11 months, and 32% within 60 months. In a population study, the clinical courses of 44 persons who had a transient ischemic episode were followed for periods averaging 27.4 months. Half of the number were given anticoagulants and half were not. Of the 22 untreated patients, cerebral thrombosis developed in seven (32%).

Studies are available to indicate that the first month following the onset of TIA is the period of most serious risk. A 15-year population study indicated that among the 72 patients with untreated TIA who had subsequent stroke, in 51% the stroke occurred in the first year, including 21% during the first month. A combined retrospective and prospective study indicated that if TIA were followed by a major stroke, in 50% of the patients it occurred within one month of the initial TIA.

A figure commonly cited suggests that 4% of the patients will die each year after the first TIA, and most of those surviving the immediate episode will die ultimately from vascular causes, one-third of which will be from stroke and two-thirds from other vascular disorders, particularly myocardial infarction.

In attempting to assess the overall significance of TIA, the prognosis has been examined under three special sets of circumstances. Firstly, in a five-year follow-up of 64 patients with a history of TIA but with normal carotid angiograms, 20% had further transient attacks, 13% had a completed stroke, and 22% had fatal cardiovascular or cerebrovascular events, with heart disease occurring more frequently than stroke. Secondly, TIA confined to the retina (amaurosis fugax) have been surveyed in a study involving 80 persons followed for periods of three months to ten years or more. Five had a stroke and nine sustained permanent visual loss during the period of follow-up, all in the territory of the appropriate carotid artery. Thirdly, minimal information is available correlating the development of stroke with frequency of TIA episodes. As reported in one series, 76% of those patients having transient focal ischemia in the carotid territory, in contrast to 52% of those in whom the vertebral-basilar system was involved, had stroke after only one or two antecedent TIA. Further data are needed on this important subject to obtain a reliable estimate of prognosis.

Reversible Ischemic Neurologic Deficit (RIND)

The distinction between RIND and TIA, as defined previously, is one of degree. To discuss its nature, pathogenesis, and treatment in a separate way is probably redundant, because this condition may be only a temporal extension of TIA beyond the limits arbitrarily established for the cessation of transient symptomatology.

Partial Nonprogressing Stroke

Partial nonprogressing stroke can be described as an episode of localized cerebral ischemia, with a minor or moderate residual neurologic deficit. Events such as these may or may not be preceded by single or multiple TIA without residual deficit. Many authors prefer to include this condition in the “completed stroke” category.

Pathogenesis

The pathogenesis is presumed to be identical to that of TIA and RIND. The difference depends upon the size of the thrombus or embolus, the location and extent of the cerebral territory involved, and the condition of available anastomotic channels at the time of interference with flow through the primary vessels.

One particular kind of partial stroke which should be set apart from the rest is the so-called “lacunar stroke.” This type of cerebrovascular disease is associated with longstanding severe hypertension, and over a period of weeks or months the patient has repeated minor ischemic episodes, frequently with accumulating residual disability. The etiology is still the subject of controversy because some authors favor the concept of repeated small hemorrhages. The severity is variable; some patients with episodes of lacunar infarction have no symptoms whatsoever, while others have many “small strokes.”

Diagnosis and Prognosis

The criteria for diagnosis and prognosis for the patient with a partial nonprogressing stroke and the principles of therapy to be applied are the same as those for the patient with TIA. In both instances appropriate management requires as exact and definitive a diagnosis as can be reached with certainty.
Progressing Stroke (Stroke-in-Evolution)

In the past this clinical state has been imprecisely described. A definition has been attempted and its acceptance urged so that there can be uniformity in reporting the condition. According to this definition, a progressing stroke is one in which the neurologic deficit is still increasing in severity or distribution after the patient's admission to observation, with evidence that this progression has been going on during the few minutes immediately preceding and up to two or three hours previously. It is stated that only under these circumstances is the pathophysiologic process a progressing one, for which this diagnosis should be considered.

Some would restrict the time interval of progression to a number of hours while others would consider it reasonable to include those who worsen over a period of days or even several weeks. The stuttering or stepwise stroke progression would be included, to which the term "stroke-in-evolution" has previously been ascribed. Jones and Milikian indicated that a progression-free period of 18 to 24 hours for the carotid system and up to 72 hours for the vertebral-basilar system should ordinarily be sufficient to remove the patient from this category and to label him as an example of "completed stroke." Each author has utilized his own definition of progressing stroke, thus precluding meaningful comparisons between reports of frequency, prognosis, and results of therapeutic measures designed to affect this condition, and leaving profound gaps in our knowledge.

Since some clinicians regard progressing stroke as an indication for the emergency use of heparin, a resolution of the dilemma of terminology is an urgent matter.

Incidence

The incidence of progressing stroke has been variously reported. In the Cooperative Study on Anticoagulant Therapy, 128 of 443 cases included in the overall study were considered to be "progressive" or "thrombosis-in-evolution." In this particular study, the definition of the clinical entity was that of a progressive, stepwise lesion. In one early report on carotid artery occlusion, it was stated that of 35 cases, ten had a slowly progressive onset, and 22 an episodic (stuttering) course. In another report, 122 of 277 patients admitted over a four-year period with a diagnosis of cerebral thrombosis were classified as progressing stroke.

Pathogenesis

It is important to note that stroke-in-evolution does not necessarily indicate thrombus-in-evolution. The variety of pathogenetic mechanisms that can lead to either the slowly progressive or the stepwise development of a stroke are summarized as follows:

1. A progressive thrombus extends from its site of origin in a primary artery and obliterates collateral branches, thereby interfering with anastomotic circulation and extending the area of insult.
2. At the site of maximal atherosclerotic involvement with or without ulceration and/or stenosis, initially there is insufficient thrombus to produce occlusion. Continuing accretions to this thrombotic nidus slowly obliterate the lumen of the vessel and either gradually or intermittently add to the area of brain ischemia.
3. Brain edema spreads in concentric fashion and progressively reduces clinical function without extension of the original area of infarction.
4. The general condition of the patient, including his cardiorespiratory function, altered water and electrolyte regulation, and/or acid-base balance, or the acquisition of systemic infection, interferes with cerebral metabolism sufficiently to increase the extent of the neurological dysfunction. In the event that cardiorespiratory function is altered, the area of infarction actually may be extending.

The problems of pathogenesis are seen to be complex, and thus decisions respecting therapy in this condition become very difficult. Serial follow-up of these patients by means of computed tomography is an encouraging area for research in order to clarify our understanding of the pathological alterations in stroke, in stroke progression, and in the regression of brain lesions.

Course and Prognosis

Progressing stroke has a poor prognosis. Of 41 patients entered into the National Cooperative Study and reported in 1961 as having "thrombosis-in-evolution," 30% worsened in the two weeks after recognition of their condition, and between two weeks and six months thereafter another 17% deteriorated. In a British study where the symptoms of ischemic deficit had been progressing over a period of two hours or more, a control series of 38 of the 76 cases was followed for six months. At the time of follow-up, 11 had recovered, 8 had improved, 12 were unimproved, and 7 had died. In an analysis of five series, followed for periods ranging from six months to 15 months, the percent of patients not treated by anticoagulants who had progressed to deterioration or death ranged from 40% to 64%. The conclusion can be drawn that the recognition of a progressing stroke, whatever its cause, carries an uncertain prognosis.

Completed Stroke

The term "completed stroke" is usually employed to signify a focal neurologic disability that came on abruptly and has become stabilized. Some authors indicate that 18 to 24 hours without progression if the lesion is in the carotid system, and up to 72 hours if the territory of involvement is the vertebral-basilar system, would suffice to place the patient in the stabilized category. It is also noteworthy that only a gradation in severity differentiates a partial non-progressing stroke from a completed stroke.

The variability in symptoms and in the degree of initial deficit, as well as the variability in recovery of lost function, are dependent on a number of factors, many of which are similar to those which determine the "progression" of a stroke. These include the adequacy of collateral circulation, the state of cardiorespiratory function, and the presence or absence of major systemic dysfunction that might critically alter cerebral metabolism. Unilateral carotid occlusion and even, on occasion, bilateral carotid occlusion can sometimes be silent events. Angiographic studies performed on these patients subsequently often show remarkable collateral circulation in many of the deficit-free individuals. In those with a fixed and serious neurologic deficit, the channels of the potential collateral circulation, although demonstrable, apparently did not function with sufficient rapidity to protect the territory supplied by the occluded vessel.
Pathogenesis

The Framingham study indicated that 78% of vascular strokes in that population were thromboembolic and that thrombosis of the aorto-craniocerebral arteries occurred between three and four times as frequently as did strokes from cardiac embolism. Embolus from the pulmonary veins is an extreme rarity, as is paradoxical embolism. The thrombotic process may be: (1) initiated and completed in the heart, with fragments subsequently lodging in the great vessels or their intracranial branches; (2) initiated, completed, and fixed in the great vessels of the neck; (3) initiated in the neck and carried to the intracranial branches; or (4) initiated and completed in the intracranial branches.

Regardless of the source of the thrombus, the final result is an area of brain infarction whose extent will depend on the size of the embolus, on the immediate availability and utilization of collateral circulation, and on the state of systemic oxygenation and circulation.

It is important to reemphasize that the majority of patients with completed stroke will have a history of one or more previous TIA. Furthermore, for practical purposes, one should recognize that a stroke may be regarded as "completed" because of a stabilized neurologic deficit and yet another stroke of abrupt or stepwise progression, or a subsequent TIA may occur. An apparently simple extracranial carotid lesion may thus be responsible for major or minor embolization repeated over a long or a short period of time.

The preceding résumé underscores the importance of thrombosis as a prime factor in the pathogenesis of a variety of cerebrovascular disorders. Clearly the intelligent management of threatened and developed cerebral ischemia requires an understanding of thrombosis and of antithrombotic therapy.

Hemostasis and Thrombogenesis

Since the time of Virchow, it has been appreciated that alterations in the vessel wall, increased coagulability of the blood, and vascular stasis operate to provoke a thrombotic episode. In experimental thrombosis, usually two of the above components of the triad are sufficient to provide a suitable model for study of the process of thrombogenesis.

Hemostatic and Thrombotic Mechanisms

The hemostatic-thrombotic mechanism acts to prevent loss of blood from the circulation by rapid repair of breaks in vessel walls with a minimal compromise of blood flow. Hemostasis and thrombosis involve interaction between: (1) the blood vessel, (2) platelets, and (3) coagulation factors, to form a fibrin-platelet patch of the defect, which is then subjected to modification by the fibrinolytic system prior to and during tissue repair (fig. 1).

Blood Vessels

Vascular damage elicits responses of all components of the hemostatic system. Vasconstriction follows direct injury to the vessel and is associated with constriction of adjacent vessels. Although vasocostriction is not required for hemostasis, it is a critical reaction to prevent rapid ex-
Coagulation Factors

Blood clotting involves a series of enzymatic reactions which converts circulating inactive coagulation proteins to active forms culminating in the transformation of blood from a liquid to an insoluble gel through the conversion of fibrinogen into fibrin (fig. 3). Fibrin formation extends and stabilizes the hemostatic plug in its evolution to a thrombus.

Fibrin formation can be effected by either of two major overlapping mechanisms termed intrinsic and extrinsic. All the coagulation factors required for the intrinsic system to function are present in circulating blood; the extrinsic system, by means of a lipoprotein released from damaged cells ("tissue factor"), provides a bypass of the usual intrinsic activation pathway. Factor X plays a central role in coagulation since it can be activated by either the intrinsic or extrinsic pathway.

Fibrinolytic System

The fibrinolytic system plays a major role in the maintenance of blood fluidity, particularly in the small vessels. Vascular endothelium contains a potent tissue activator which converts an inert plasma protein, plasminogen, into the potent enzyme plasmin (fig. 4). Activation of the fibrinolytic mechanism is linked inevitably to activation of the hemostatic process, and fibrinolysis should be considered an integral component of hemostasis. An inverse relationship has been demonstrated between vessel size and fibrinolytic activity. Thus the small vessels appear to be more resistant to occlusive thrombus formation than the large ones.

Protective Mechanisms Against Activated Coagulation

Several physiologic mechanisms are known to protect against thrombogenesis: (1) An increased rate of blood flow reduces the chance of focal fibrin formation by removing procoagulant material before activation can be completed and by diluting substances that may have undergone activation. (2) Activated clotting components are removed from the blood rapidly by hepatic cells. Particulate material, including fibrin, is taken up by reticuloendothelial cells, and activated coagulation factors, especially Xa, are removed by hepatocytes. (3) Thrombin and Xa are inactivated slowly in vivo by the formation of complexes with a physiologic plasma inhibitor. This inhibitor, referred to as antithrombin III or factor Xa inhibitor, also functions as a heparin cofactor in a reaction involving ionic binding of heparin. Of interest are reports of a high incidence of recurrent venous thrombosis in families among whose members are a large number having decreased antithrombin III activity.
Thrombosis and Blood Coagulation

A thrombus is defined as a solid mass or plug formed during life within the heart or vessels from constituents of the blood (fig. 5). A blood clot is a blood mass solidified under static conditions outside the body. Consideration of the different types of thrombi is important from the standpoint of their histologic structure and the sites and nature of the flow conditions under which they develop. In a clot, all the formed elements of the blood are distributed at random in the fibrin meshwork. Platelets are found in the meshwork, but do not form significant aggregates. In contrast, a thrombus consists of two types of material, usually referred to as white thrombus and red thrombus. White thrombus consists of closely aggregated platelets (figs. 6 and 7). Red thrombus fills the interstices between the platelet aggregates and is made up chiefly of red cells and fibrin. The type of thrombus formed is related to the velocity of blood flow. White thrombi form at sites of more rapid flow (arteries, arterioles) while red thrombi or mixed thrombi develop in sites where stasis is likely to occur (veins, venules). The composition of the thrombus also has implications for therapeutic approaches. Fibrin formation is inhibited best by anticoagulants which interfere with the formation and action of thrombin (e.g., heparin, warfarin), and therefore these agents may be appropriate for the management of venous thrombosis. On the other hand, antiplatelet agents (e.g., aspirin, diprydamole, sulfipyrazone) should be more effective against arterial thrombi. The situation is highly unlikely to be as simple as this, since thrombin takes part in the formation of arterial platelet thrombi, and it has been shown that platelet adherence and aggregation participate in deep vein thrombosis.

Thrombosis and Atherosclerosis

Thrombosis can be related to atherosclerosis in at least two possible ways. First, the "encrustation" or "thrombogenic" theory suggests that thrombosis is involved in the pathogenesis of the atherosclerotic lesion. Second, whatever the origin of atherosclerosis may be, thrombosis is clearly a most important complication of the established lesion and is responsible for a majority of the lethal and disabling features of the disease.

Von Rokitansky was the first to suggest that the lesions of atherosclerosis were caused by the deposition of material from the blood onto the inner walls of affected arteries. Interest in this hypothesis declined until, in 1946, Duguid put forward the theory in a revised form which has since come to be known as the thrombogenic theory of atherosclerosis. Duguid, studying serial sections through stenosed coronary arteries, found gradations between tissue that had all the characteristics of an organizing thrombus and that which had the appearance of a typical atherosclerotic plaque. Despite the careful and comprehensive morbid anatomical studies, acceptance of this theory has had to await experimental proof that the end result of the organization of a mural thrombus is a lesion which has the detailed features of an atherosclerotic plaque.

Several key points essential to the thrombogenic theory have been proved by experiment. These include the demon-
Stratification that endothelium can grow over the surface of an organizing mural thrombus so that the lesion appears to lie within the intima rather than to be attached to its inner surface. The endothelium of large blood vessels is capable of substantial regeneration and of behaving as the thrombogenic theory requires. Another serious question has been answered concerning the presence of smooth muscle cells that lie beneath the endothelium in atherosclerotic plaques. Electron microscopic evidence has established that smooth muscle cells are found in organized thrombi and, therefore, could represent a source for those observed in evolving atherosclerotic lesions. However, additional data to explain the quantity and type of lipid found in advanced atherosclerotic lesions are required for support of the thrombogenic theory. The phagocytosis of platelets by monocytes may contribute lipids to organized thrombi.

It seems likely that the organization of mural thrombi contributes to the enlargement of already existing severe lesions. Whether the organization of mural thrombi can account for the total development of the atherosclerotic lesion from beginning to end is debatable. Before significant progress can be made in understanding this process, it is essential to learn more about the conditions under which thrombi form spontaneously.

The atherosclerotic lesion is prone to complications arising from loss of the endothelial cover and the subsequent development of thrombi. Atheromatous "gruel" causes platelet aggregation and has a procoagulant effect, including that modulated by tissue thromboplastic activity. In addition, platelets are capable of adhering to the subendothelial structures including collagen, microfibrils, and endothelial basement membrane. Although undoubtedly thrombosis complicates atherosclerosis, additional investigations are necessary to elucidate: (1) the magnitude of and the mechanisms involved in platelet adherence to intact endothelium, (2) the thrombogenic complications of vascular injury, and (3) the efficacy of agents used to prevent these complications.

Diagnostic Tests

Despite the urgent need for tests to detect the individual in whom thrombosis is impending or incipient, progress has been slow in the development of procedures which are both accurate and practical for large numbers of patients. Procedures that prove useful for the diagnosis of peripheral venous thrombosis may have little value for the patient with an impending stroke or TIA.

While importance has been attached to the association in various clinical and pathophysiologic states between excess coagulant activity and a tendency to develop thrombosis, the term "hypercoagulable state" is probably best reserved for the circumstance in which activated coagulation factors are present in the blood. These activated factors may not, of themselves, precipitate massive thrombosis or even disseminated intravascular coagulation (DIC), but may become thrombogenic under certain conditions, such as vascular stasis or impairment of physiologic inhibitory mechanisms. In addition, certain activated clotting factors (thrombin or Xa) have the potential to cause aggregation or adherence of platelets.

Of the blood tests available which may be useful in selecting stroke-prone patients, most are directed at measurements of platelet function, the presence of fibrinogen derivatives as a result of in vivo thrombin activity, or changes in fibrinolytic activity. The use of routine coagulation tests, such as the bleeding time, prothrombin time, clotting time, tests of platelet adhesiveness or platelet aggregation with aggregating agents, is rarely of help in predicting thrombosis. Other approaches include the measurement of 51Cr-labeled platelet survival, detection of "circulating" platelet aggregates, testing for "spontaneous" platelet aggregation using platelet aggregometry, and the use of a...
screen filtration method for platelet aggregation. The latter three tests have demonstrated abnormalities in patients with cerebral ischemia and may be useful to identify patients who are likely to respond to antiplatelet agents. However, prospective studies remain to be performed with these techniques to establish a cause-and-effect relationship between either the findings of platelet aggregates associated with TIA symptoms and signs or the disappearance of clinical signs and symptoms with subsidence of platelet aggregates as a result of drug therapy.

**Therapeutic Inhibitors of Thrombosis**

The oral anticoagulants, of which warfarin is an example, exert their effects by inhibiting the synthesis of coagulation factors II, VII, IX and X in the liver. Warfarin inhibition of the action of vitamin K causes defective factor synthesis resulting in the production of dysfunctional zymogens that are antigenically identical with their corresponding clotting factors but lack coagulant activity. There is a time lag between the beginning of therapy with warfarin and attainment of the desired depression of clotting factor activity. Likewise, restoration of coagulation activity to normal is delayed when vitamin K is administered to overcome the anticoagulant effect of warfarin.

Heparin, unlike warfarin, causes no deficiencies of coagulation factors, but instead interferes with the coagulation process at several points as follows: it inhibits the activation of factor IX by XIa; it inhibits IXa, thrombin, and Xa; and in the absence of thrombin, activation of factor XIII is prevented. Heparin also strikingly enhances the ability of antithrombin III to inhibit the action of activated factor X (Xa).

Considerable interest has developed in drugs which interfere with platelet function and thus might serve as effective antithrombotic agents, but the role of these preparations in the management of cerebrovascular disease is still being evaluated. Platelet aggregation is blocked by various pharmacologic agents, the most potent of which is prostaglandin E1. This effect is associated with an increase in cAMP (cyclic adenosine monophosphate) concentration in the platelet. Other drugs include aspirin, diprydiamole, sulfipyrazone, and phenylbutazone.

Aspirin interferes with the production of certain intermediate metabolites in platelets, and this intracellular change may be associated with changes in platelet function. The effect of aspirin on platelets occurs as a consequence of acetylation of the platelet membrane. Therefore, the analgesics, sodium salicylate and acetaminophen (Tylenol), do not interfere with platelet function. Other platelet inhibitors include adenosine and its analogues, sulfhydryl-binding agents, and numerous other drugs that block glycolysis and oxidative phosphorylation. Antiplatelet agents vary in the duration of their effects. In the case of aspirin, this lasts for the remainder of the life of the exposed platelet, whose total life span is eight to ten days. As a consequence of the theoretical implications, the use of antiplatelet agents in antithrombotic therapy has excited intense interest. Whether currently available preparations will fulfill the expectations of their proponents remains to be determined.

**Evaluation of Antithrombotic Therapy**

An appreciation that thrombosis or thromboembolism is etiologic in many cerebral ischemic events has encouraged the employment of therapeutic approaches intended to influence the thrombotic process. These have included the use of anticoagulants, platelet-suppressant, or thrombolytic drugs, depending upon clinical circumstances and therapeutic objectives. In the following pages, reported studies for each of these categories are reviewed and an attempt is made to determine from the data presently available the potential of the respective treatments for preventing or modifying the results of an ischemic stroke.

**Design of Clinical Trials**

A number of basic principles should be considered in the design and execution of clinical trials. In general, there should be a clear statement of the objectives of the study, together with a detailed description of the type of patient under study, the actual maneuver to be evaluated, the outcome variables of interest, and the methods of analysis. Specificity should be sufficient to allow replication. Within this general framework, the types of studies which have been carried out include individual case reports, retrospective studies, and prospective studies, both randomized and nonrandomized. Genton et al. in a critique of studies of platelet-suppressant therapy in clinical thrombotic disease, have identified and discussed certain basic principles for clinical trial design. Among these, randomization and sample size are of particular relevance to this evaluation of antithrombotic therapy. Unless the patients are allocated rigorously to their respective treatment according to some prescribed randomized arrangement, there is the danger that bias, either unconscious or deliberate, might influence which treatment a particular patient receives. In the nonrandomized trials to assess anticoagulants, for example, it is possible that patients too sick to receive anticoagulants are left untreated and then are included as controls; or a patient who experiences another cerebrovascular episode or dies while under evaluation as one to receive anticoagulant therapy might be listed as an untreated subject, and hence introduce an obvious bias to the disadvantage of the control group record. This also implies that studies should be prospective, with controls which are concurrent in time and place.

Reports of individual case histories or of accumulated experience with a series of patients in which the observed therapeutic benefits are compared either with those noted during the author’s previous experience, or with those of a concurrent group of patients who were ineligible to receive that therapy, have the strong possibility of bias, and the findings from these studies can be regarded as only suggestive.

One encounters a particularly difficult problem in the evaluation of antithrombotic therapy in cerebrovascular ischemia because of the large number of patients required to achieve statistical significance. Since the immediate death rate from cerebral thrombosis is lower than in other types of stroke, long-term follow-up and large-scale multicenter trials are necessary. For example, the overall frequency of stroke in patients with transient ischemic episodes is ap-
proximately 7% each year. Thus, even if a drug brought about 50% reduction in the incidence of stroke, more than 1,000 patient-years would be required for a study to be statistically meaningful! Even trials of secondary stroke prevention require a study of comparable size, since the frequency of recurrent stroke is similar.

Evaluation of Reports

The following review deals in order with the studies relating to anticoagulant, platelet-suppressant, and thrombolytic therapy, respectively. Within the first and largest category, that relating to anticoagulants, attention is given separately to TIA, progressing stroke, completed stroke, and cerebral embolism. Studies are considered individually and include a description and critique of the design, methodology, and results. The accumulated evidence is summarized as to evidence of possible therapeutic benefit derived by patients within each of the four functional categories of stroke. The studies are few from which to evaluate antplatelet and thrombolytic therapy and therefore a single summary is provided for each of these two types of agents.

One should bear in mind that most of the studies of anticoagulants were carried out 15 years ago, and are here being judged against standards and methodologies which have been improved and refined in recent years. What is being presented, therefore, is not a denigration of work done in the past, but rather a reassessment, by present-day standards, of the data which bear upon the efficacy of antithrombotic therapy in cerebrovascular ischemia. The discussions to follow are not intended to reflect upon the interest, capabilities, or competence of the investigators, but to provide information which will be of value in future clinical research.

Anticoagulant Therapy

Rationale

In patients with cerebral ischemia, the objective of therapy acutely is to preserve the integrity of the ischemic tissue as far as possible, and to prevent progression or recurrence of the insult. When the genesis of an ischemic event is thrombotic or thromboembolic, theoretically the objective is to prevent further development and propagation of the thrombus so as to minimize tissue damage and, in the long term, to prevent recurrence of local thrombosis of cerebral vessels and/or reembolization from a distant site.

The clinician has drugs available which have been demonstrated experimentally to arrest active thrombosis and to decrease the incidence of recurrence. Heparin, by combining with a plasma globulin, forms a complex which rapidly and reliably inhibits several activated clotting factors, including the thrombin presumably present at the site of active thrombosis. By inhibiting thrombin activity, further fibrin formation is prevented and the propagation of thrombosis interrupted. Consideration of such treatment is rational for patients suspected of having an active thrombotic state.

In other circumstances, such as after recovery from an ischemic stroke, the therapeutic objective is prevention of recurrent thrombosis or embolization of a cerebral vessel. Experimentally, it has been established that by interfering with the hepatic synthesis of vitamin K-dependent clotting factors, oral anticoagulants (e.g., coumarin) can retard the response to a moderate thrombotic stimulus and in that way act as prophylactic agents.

Randomized Trials of Anticoagulants in Patients With TIA

The Veterans Administration Cooperative Study was a multicenter randomized trial to evaluate the benefit of oral anticoagulants in patients with TIA or with cerebral infarction. Most of the cases were entered into the study within one month of onset of their last cerebral episode. Uniform laboratory and clinical criteria were established for the inclusion and exclusion of patients — among the latter, those with severe hypertension and blood in the spinal fluid. Angiograms were not performed to determine the location of arterial disease. Anticoagulation was monitored using the one-stage prothrombin time method and in 80% of patients good control was maintained. The study was not blind and the treated patients were seen more frequently than the untreated, so that the interpretation of recurrent symptoms was not free from bias, although this should be regarded as less important, inasmuch as mortality and cerebral infarction were the principal end points. Over a two-year period, 1,409 patients in all were screened, of whom 155 were accepted for entry into the study; their assignments were randomized into treatment and nontreatment groups. The two groups were comparable in general and all the patients were male. No patient was observed for less than one month, the average follow-up period being 12.8 months in the control and 9.3 months in the treated group.

The outcomes for the 37 patients with TIA are summarized in table 5. One can see that only one patient in the treated group had a new ischemic attack, compared with eight patients in the control group. The figures on stroke and death are too few for sound inferences to be drawn. Figures on bleeding were not given separately for the patients with TIA and those with completed stroke. There were ten major bleeding complications in the treated group, including four fatal massive hemorrhages, compared with only three in the control group, one of which resulted in death. Members of the treated group experienced many more minor hemorrhages than did the controls.

Baker, Broward, Fang et al. reported a multicenter trial carried out between 1958 and 1961 in seven clinics. Patients were categorized as having: (1) TIA, (2) thrombosis-in-evolution, (3) thrombosis — completed stroke, (4) "thrombom" (thrombosis or embolism), and (5) cerebral embolism. Inclusion and exclusion criteria were specifically defined, lumbar punctures were carried out, but angiograms were not utilized. Hypertensive patients were not excluded. Only persons whose last cerebrovascular episode had occurred within the eight weeks before randomization were admitted to the study. Those qualifying for inclusion were randomized into either the anticoagulant or the control group, the latter receiving placebo capsules. The comparability of the two treatment groups was based on sex, race, age, blood pressure, territory of brain damage, a neurologic disability scale, time since the qualifying neurologic episode, previous stroke, and smoking. In the follow-up, both control and anticoagulant patients returned at the same intervals for evaluation of clinical status.
A total of 443 patients was studied. Of the 44 who had TIA, 24 received anticoagulants and 20 were in the control group. Recurrence of TIA was much more frequent in the control group — 547 episodes compared with only 25 in the treated group during average follow-up periods of 18 and 21 months, respectively. In the first month, ten control patients and two on treatment continued to have attacks. Two of the 20 patients in the control group died, compared with five of the 24 receiving treatment; two of the latter deaths were due to intracerebral hemorrhage. Progression or recurrence of infarction occurred four times in the control group. Three of these infarctions were moderate and one mild compared with the single severe case in the treated group. There were 11 patients in the treated group who had bleeding problems, three of them severe, as compared with one minor bleeding complication in the control group.

Pearce et al.49 carried out a randomized double-blind trial with 37 patients aged less than 70 years who had had one or more attacks of transient cerebral dysfunction with no neurologic deficit lasting more than 24 hours. Patients with malignant hypertension or peptic ulceration were excluded. The clinical examination included assessment of cerebrospinal fluid; carotid angiography was carried out in 29 of the patients. None had significant narrowing of the extracranial portions of the internal carotid arteries. Patients were randomly allocated to a high-dosage (50-mg tablets of phenindione) or an ineffective low-dosage (1-mg phenindione tablets of identical appearance). Seventeen patients received phenindione in effective dosage over an average period of 11.1 months; 20 control patients were followed for an average of 10.6 months.

The two groups were comparable with respect to age and sex, but a few more patients with vertebral-basilar artery insufficiency were included in the control group than in the high-dosage group. Ten patients in the treated group (59%) had further TIA, compared with nine in the controls (45%). One patient in each group sustained a nonfatal completed stroke; one control patient died from a stroke and two others died from cardiac causes. None of the patients had major hemorrhagic complications, and no instance of minor bleeding was definitely attributable to anticoagulant therapy. The average period of follow-up was less than a year, so that the study was a limited one, and therefore the benefits of treatment would have to be fairly spectacular in order to be established as statistically significant.

Baker, Schwartz and Rose62 reported an eight-year randomized study designed to evaluate long-term anticoagulant therapy for patients with TIA. Sixty of 204 individuals were selected after excluding those who were poor risks for anticoagulation; these were the severely hypertensive persons, those critically ill, near death, and those of advanced age (more than 80). The patients were all male veterans, their ages averaging 62 years. During the study, the desired therapeutic range of prothrombin time (determined by the one-stage method) was achieved an average 79% of the time, and for most patients, for 90% of the time or better. Each patient was examined neurologically once a month during the first few months of follow-up, and then every two months. Only ten of the 60 patients had arteriography. There was no report that a placebo was given to the control patients and no evidence that the assessments were made blindly.

The 60 patients were randomized into groups of equal size. The average period of follow-up was 38 months for the treated and 41 months for the control group; 10 and 14 patients respectively in the two groups had further TIA. There were nine new cerebral infarctions. Of the four in the control group, two recovered without neurologic disability and two had severe residual deficits. One should note that in the last three cases the infarctions occurred after anticoagulants had been stopped (for reasons unspecified). It is not clear in the report how long after dis-
continuance of therapy the infarctions happened, or why the anticoagulants were discontinued. If the time between therapy withdrawal and infarction was short, or if the reason for withdrawal of anticoagulants related in some way to the clinical condition of the patient, then these therapeutic failures should be charged against the treatment. In the long run, this may constitute a bias against showing a favorable treatment effect — it is judged, however, that this is probably the preferable direction in which to err. The alternatives are to omit these cases entirely from the analysis or to charge them against the controls, since the patients were no longer being treated. This is likely to result in a bias toward an apparent benefit of treatment.

Of the 14 deaths, nine were in the treated group and only five in the control group. It is interesting that nine of the 14 deaths were the result of cardiac disease. A few minor hemorrhagic complications arose, but only one patient (in the control group) had a fatal cerebral hemorrhage. The authors noted that the limitations of their study included the small number of cases and the large number of variables in patients with TIA which might influence prognosis.

Nonrandomized Trials of Anticoagulants in Patients With TIA

Fisher reported on 29 patients with TIA who were treated with dicumarol for periods varying from two months to four years (average 14 months). TIA ceased in 28 of the 29 patients after effective anticoagulant therapy had been established; only one patient had a stroke, and that nearly three years after beginning treatment. Following cessation of treatment, 12 of 20 patients had recurrent episodes. When anticoagulation was resumed, the attacks ceased. The criteria for stopping and starting treatment were not stated.

In contrast, a group of 23 patients was studied for whom anticoagulants were not prescribed for various reasons. Of these, 12 had further TIA over an unspecified period of follow-up and eight patients had a stroke (six of a major type).

This study raises a number of questions. Patients were not randomized to treatment and control groups, nor was a rationale given for deciding whether or not a patient would receive anticoagulants. Considerable bias is possible in that one-third (mostly those admitted late in the study period) were followed for some time before a decision was made to place them on anticoagulants. The description of the patients was generally rather imprecise and none was excluded on the basis of age, blood pressure, or location of the lesions. As the author himself said, "The present data do not provide incontrovertible evidence of the therapeutic efficacy of anticoagulants because satisfactory control patients have not been studied."

Siekert, Whisnant, and Millikan from 1954 to 1958 observed 335 patients with TIA for whom anticoagulant therapy was prescribed except when specifically contraindicated. Anticoagulants were administered to 175 patients on a continuous basis; the remaining 160 patients did not receive anticoagulant therapy or received it only for several months. The diagnosis of ischemic disease was based on clinical examination. Contrast arteriographic studies, generally of four major cerebral vessels, were performed on selected patients to identify the site and completeness of the obstructive process.

The follow-up period ranged from three to eight years for both groups. Information is not available in this particular report about recurrences of TIA, but a preponderance of the cerebral infarcts appeared in the control group — 33 as compared with four in the treated group. The total number of deaths was similar in the two groups. Information is incomplete about bleeding problems; the authors stated that the incidence of fatal cerebral hemorrhage was higher in the group treated (7.4% versus 4.4% in the untreated patients) but they indicated that this increase was minimal compared with the incidence of fatal thrombotic infarcts.

The major deficiencies of the study are the lack of randomization and the failure to define the criteria for treatment, non-treatment, and curtailment of treatment. For example, it could have been that the anticoagulant treatment was withdrawn from any patient who became very ill. Should patients such as these be counted in the control group, then clearly the evaluation of efficacy would be biased in favor of anticoagulant therapy.

Whisnant, Matsumoto and Elveback carried out a chart review of patients in the Rochester community during a 15-year period. Of 198 patients identified as having experienced TIA, 80 had received long-term anticoagulant therapy and 118 had not. There was no known selection process for those who were treated with anticoagulants; the levels of blood pressure were generally similar in the two groups. The actuarial method of analysis was used to compare the survival times of patients treated and those not treated with anticoagulants. These, in turn, were compared with survivorship of a group of the same age and sex, using the Minnesota death rates for 1960. The conclusion was reached that no difference in age-corrected survival between treated and untreated patients was apparent, but that there were significantly fewer strokes in treated patients. It is interesting that this difference was established within a month after starting therapy and that no significant difference between treated and untreated groups was seen during the remainder of the five-year follow-up period.

The criticism of the study is, once again, that patients were not randomized. The authors were interested in the probability of stroke following the first TIA and did not document the incidence of further TIA in their paper. One could raise the question (common to all the nonrandomized studies) as to whether some of those patients who were untreated and had prognostic factors which made anticoagulation inappropriate or who died while under evaluation for possible anticoagulant therapy would be listed as untreated subjects, and hence introduce an obvious bias in favor of the treated group.

Friedman et al. reported an epidemiologic survey of a retirement community in which 60 cases of TIA were observed over a period of five years. Most of these patients were neither hospitalized nor referred beyond their primary physicians and the neurologic examinations therefore were less uniformly thorough than in most reported studies. Of these 60 individuals, the subsequent clinical course was examined in 44, half of whom had received anticoagulants. It was observed that only one subsequent cerebral thrombosis was seen among the 22 patients receiving anticoagulants, whereas seven patients in the untreated group had cerebral thrombosis.

Once more, these observations were not obtained from a
controlled experiment. Information is not given as to why some were treated with anticoagulants and some were not. Also, the treated and untreated groups may have been quite different as regards important clinical characteristics and the manner in which they were managed; for example, the patients receiving anticoagulants were noted to be generally somewhat younger (68 years) than those for whom therapy was not elected (72 years).

Some of these studies, including that of Fisher,* raise a question about the effect on TIA when anticoagulants are withdrawn from a patient who has been receiving them for some time. Marshall and Reynolds* addressed themselves to this problem. Of 26 male patients who had been receiving anticoagulants for at least three months because of having previously experienced TIA, one-half had therapy gradually replaced by identical placebos. The allocation of patients to continued therapy or withdrawal was made according to a random process after matching patients in pairs for site of the ischemia (carotid or vertebral-basilar) and previous duration of the anticoagulant therapy. These investigators found that only two of the 13 patients who continued anticoagulants had further TIA over a follow-up period of four months, compared with eight of the 13 in the group for whom anticoagulant therapy was withdrawn. This difference is statistically significant (p < 0.05).

Summary of Clinical Studies of Anticoagulant Therapy in TIA

Of the eight studies in which the effect of anticoagulants on TIA has been evaluated, four were randomized and four were not. Most of them included only a small number of patients and for three studies, the average duration of follow-up was only about 12 months. The consistent finding in all eight was that no benefit derived from anticoagulants in terms of lower mortality. However, the report by Whisnant, Matsumoto and Elveback** did show significantly fewer strokes in the 80 treated patients as compared with the 160 patients who did not receive anticoagulant therapy. Significantly, none of the four randomized trials showed a reduced incidence of stroke attributable to anticoagulant therapy, whereas all four nonrandomized studies indicated that there was such a benefit.

Three of the eight studies did not report on recurrences of TIA. In three other studies, including two which were randomized, the investigators concluded that treatment with anticoagulants resulted in a reduction of TIA. Of these, Fisher's study** was neither randomized nor blind and the apparent benefit of anticoagulants may simply be a reflection of other factors. The Veterans Administration Cooperative Study* was not blind, and the authors admit that this factor could have influenced their interpretation of recurrent symptoms. Baker, Broward, Fang et al.* showed an appreciable difference between the two treatment groups in the number of patients having attacks in the first month as well as a remarkable difference in the total number of attacks (although most of this was chargeable to only two patients). The study was not blind, thus weakening the inference of actual benefit.

Baker, with Schwartz and Rose, subsequently carried out a study with larger numbers and a longer period of follow-up. Although they concluded that the data suggested a reduction in TIA with anticoagulants, they did not focus attention on recurrences which took place after patients stopped therapy. These recurrences cannot necessarily be disregarded. If included in the overall evaluation, the results for the two treatment groups are remarkably similar. Finally, although the numbers of patients were small, the best study methodologically is that of Pearce and his colleagues who were unable to demonstrate any benefit of anticoagulants in reducing TIA.

The report of Marshall and Reynolds* is interesting in that it showed an increased incidence of TIA after withdrawal of anticoagulant therapy. The question arises as to whether this represents a protective effect of anticoagulants or simply a rebound phenomenon after withdrawal of therapy.

In summary, therefore, the evidence is unconvincing that anticoagulants are of benefit to patients with TIA in terms of increased survival and reduced incidence of stroke. Further, the evidence that anticoagulants are of benefit in reducing the number of TIA recurrences remains equivocal. Even if there were some reduction in the frequency of TIA, one must ask if this is really a benefit when the four randomized trials showed that 16 persons in the treated group died, compared with only ten in the control group, and correspondingly there were 13 major bleeding problems in the treatment group compared with only four in the control group.

Randomized Trials of Anticoagulants in Patients With Progressing Stroke (Stroke-in-Evolution)

Carter processed 122 patients with progressing ischemic stroke out of 277 consecutive admissions of patients with cerebral thrombosis. Of these, 76 were ultimately selected as eligible for study after excluding those with severe hypertension, xanthochromic or blood-stained CSF, evidence of hepatic disease or past peptic ulceration, age more than 70 years, and other conditions. These 76 patients were allocated at random to treatment or control. In another account of this study, Carter indicated that, "Alternate patients were treated by anticoagulants ..." and so a question arises as to whether or not patients were truly randomized. The treatment was begun with heparin and followed for four weeks with oral anticoagulants (phenindione) before treatment was slowly phased out. The control group did not receive a placebo and the study, therefore, was not blind. Patients were followed up for six months. Assessment was made by clinical examination and the condition of the patient was classified as recovered, improved, not improved, or died. The outcomes for the patients were reasonably similar in the two groups; 11 of the 38 in the control group recovered completely compared with 13 of 38 on anticoagulants. Three deaths and seven deaths in the untreated group were analyzed with 13 of 38 on anticoagulants. There were seven deaths in the untreated group compared with three in the treated group. No information is given as to when the deaths occurred but autopsies were obtained in five of the untreated and three of the treated patients. Pulmonary infarction accounted for three of those in the untreated group. Whether any died as a direct result of their cerebral infarction is not clear.

When the data were reanalyzed by classifying the patients as to whether or not the stroke was complete at the time treatment was begun, those in whom the stroke was still
progressing did somewhat better when treated with anticoagulants than did the controls. The appropriateness and validity of this assessment can be questioned since treatment would have begun at varying times after randomization in those given anticoagulants, and no dummy treatment was given to controls. The nonblindness in the clinical assessments is also a cause of concern; the author indicates that, “Selected material is always suspect.”

Baker, Broward, Fang et al. included in their series 128 patients with stroke-in-evolution. In the control group, 17 of 67 patients died, compared to 13 of 61 patients in the treated group. These rates are reasonably similar when allowance is made for the corresponding periods of follow-up of 15 and 12 months, respectively. Progression of infarction was recorded in 21 patients in the control and in only eight patients in the treated group. There were 26 separate episodes of progression in the controls (14 severe, seven moderate, five mild), and nine in the treated group (three severe, three moderate, three mild). Little detail was given regarding recurrences of TIA except that the number of monthly periods in which they occurred totaled 20 in the control group compared with only three in the treated group. Minor hemorrhagic complications were much more frequent in the treated group, but the incidence of major complications was low and similar in both groups.

Nonrandomized Trials of Anticoagulants in Patients With Progressing Stroke

Fisher reported 14 cases of progressing stroke. These patients were treated with heparin followed by oral anticoagulants, apparently for an indefinite period. The results were evaluated in comparison with a similar group of 14 patients who were not given anticoagulants — the basis on which these patients were selected from the total group being unclear. The author was impressed with the improvement seen when anticoagulants were begun and also with the deterioration that occurred in three of five persons following termination of the anticoagulant therapy. He indicated, however, that conclusions regarding the value of anticoagulants in this group were difficult to draw without control studies.

Millikan and colleagues, as part of their assessment of anticoagulant therapy, followed 241 patients with progressing stroke for 12 months. Of the 181 who received anticoagulants only 12 died, compared with 25 out of 60 patients who were in the control group. This difference is striking, but the results are difficult to evaluate. That this finding has potential importance is reflected in the three separate reports of the study. However, it was neither randomized nor blind. Questions can be raised regarding the criteria for allocation to treatment and nontreatment, and how the patients in the two groups compared with respect to important prognostic factors.

Summary of Clinical Studies of Anticoagulant Therapy in Progressing Stroke

The evidence that anticoagulants are of significant benefit to patients with this condition is quite suggestive but not conclusive. All four studies were interpreted by their authors as having demonstrated benefit of treatment, but methodologic weakness in the design raises questions about the weight to be given the conclusions. The previously stated limitations of Fisher’s nonrandomized and nonblind study weaken the inferences made regarding efficacy. Lack of information about certain selection factors does not permit firm conclusions to be drawn from the Mayo Clinic study. Carter did not consider stroke as an end point but instead developed a classification of patient function which would appear to be subjective and therefore open to the possibility of bias, since the study was nonblind. He also considered a number of possible reclassifications of his data, some of which showed a benefit of treatment to be marginally significant.

The evidence from the study by Baker et al. is probably the most persuasive. There was little difference in the number of deaths in the two groups but a marked benefit of anticoagulant therapy with regard to progression of infarction, particularly after the first month of treatment. However, confirmation of these findings would be very desirable.

Randomized Trials of Anticoagulants in Patients With Completed Stroke

Marshall and Shaw carried out a study to assess the influence of anticoagulant therapy on immediate mortality (within six weeks of the cerebrovascular accident) in patients under 70 years of age who, during the 72 hours before admission to hospital, had sustained a completed stroke for which neither a hemorrhagic lesion nor cerebral embolism was considered to be the causative factor. All patients qualifying for the trial had lumbar puncture and cerebral angiography performed, and they were randomized in pairs to either anticoagulant therapy or control. Treatment was continued for 21 days and then gradually withdrawn, and satisfactory anticoagulation was monitored daily using the Quick one-stage test. The control group did not receive placebo therapy but otherwise was given the same general care and physiotherapy as the anticoagulant therapy group. The lack of placebo therapy and the nonblindness were less important here, since the patients were hospitalized and death was the principal end point assessed.

The study comprised 51 patients randomized in pairs to anticoagulant therapy or control. Twenty-six patients were treated and 25 served as controls. The two groups were comparable with respect to age, sex, and anatomic site of the vascular lesion; of ten patients with a mean diastolic pressure of 110 mm Hg or more, four were in the treated group and six in the control group. The data on deaths were analyzed sequentially using a "restricted procedure" to such a point that it was impossible to conclude in favor of anticoagulant efficacy. In absolute terms, six treated patients died within six weeks compared with three patients in the control group. It was decided to continue observation of the patients up to six months and during this extended period of follow-up two more patients in the treated group and four in the control group died. The authors concluded "... that anticoagulants, when used according to the criteria of selection and management of the trial, are of value."

The Veterans Administration Study included 118 patients with a completed stroke who were randomized into their respective treatment groups. The incidence of TIA and of stroke were similar in the two groups and there were
rather more deaths among the treated, 12 compared to seven, which becomes more significant when account is taken of the longer period of follow-up for the control patients. Hemorrhagic complications were far more common in the treatment group than in the control group.

Baker, Broward, Fang et al included in their study 132 patients who had a completed thrombotic stroke. Fifteen of the 60 patients in the control group and 18 of the 72 in the treated group died. When allowance is made for the difference in exposure in the two groups, the mortality per 1,000 patient-months was 15.4 in the control group and 23.0 in the treated group. Progression of infarction occurred in five cases in the control group compared to 12 in the treated group. Little information is given about recurrences of TIA other than that the number of monthly periods in which such attacks occurred was four for the control group and two for the treated group. Once again, there were considerably more hemorrhagic complications in the treated group than in the controls, amounting to a total of 31 in the treated as contrasted to two in the control group. Overall, the treated group fared less well than the control group with respect to the important clinical end points.

Hill, Marshall and Shaw carried out a trial of long-term anticoagulant therapy in patients under 70 years of age who had one or more disturbances of neural function lasting more than 24 hours and attributable to nonhemorrhagic arterial disease. Admission to the trial was permitted any time after 14 days had elapsed since the last acute episode. Patients were excluded for the usual contraindications to anticoagulants and were included only if it seemed likely they would give adequate cooperation.

Cerebral angiography was carried out in about one-third of the patients entered into the study. Those admitted to the trial were differentiated by sex and allotted by pairs to a high-dosage (treatment) or low-dosage (control) group at random. The former received tablets containing 50 mg phenindione in a dosage sufficient to maintain the prothrombin time at two to two-and-one-half times the control value. The low-dosage control group received tablets apparently identical but containing only 1 mg of phenindione; their management did not differ otherwise from that of the high-dosage group. All patients were seen and blood taken for prothrombin estimation at least once every four weeks. After 20 months (end of Phase I), the authors reported their data and modified the protocol by excluding hypertensive patients before going on to complete Phase II of the study.

The results of Phase I are summarized in table 5. Not only did these data provide no evidence of benefit from anticoagulants, but there was some indication that anticoagulants were dangerous, since none of the control group died, but four deaths occurred in the treated group, all of which were thought to be attributable to the treatment. One additional patient died as the result of a possible complication of treatment. Three of the four patients who died of cerebral hemorrhage had diastolic blood pressures greater than 110 mm Hg and it seemed important, therefore, that the hypertensive patients should be excluded.

Accordingly, the trial was modified by withdrawing the patients with hypertension. The 94 patients remaining, who were not hypertensive, continued treatment without interruption according to the original protocol, and an additional 37 patients were admitted over the next year, making 131 in total. No more patients were admitted, but follow-up of those already in the study was continued for another ten months.

The results for the second phase are also summarized in table 5. Of the 131 patients in the modified trial, 66 were in the high-dosage group and 65 in the low-dosage group; these were comparable in respect to age, sex, and diagnosis of the anatomical site of the lesion; the average duration of follow-up was similar for both groups.

The recurrence rate of nonfatal cerebrovascular accidents differed little in the two groups. The high-dosage group had 17 recurrences in 12 patients, and the low-dosage group 18 recurrences in ten patients. However, the treatment group had five fatal strokes compared to only one in the controls. Three of the patients who died while on treatment were autopsied, and in every case, the cause of death was found to be cerebral hemorrhage. Another death was attributed to treatment. Deaths from other causes were six in the treated group to three in the controls. The overall number of deaths was 12 in the treatment group and only four in the control group.

Clearly all the evidence from this study indicates that anticoagulants are of no benefit to patients who have had a completed thrombotic stroke. In fact, it suggests that it is dangerous to employ anticoagulant treatment for these persons. This trial was extremely well designed and apparently was carried out with considerable attention to detail. However, by current standards, the level of anticoagulation achieved might be considered greater than recommended at the present time. A level of two to two-and-one-half times the control value was maintained.

Howard et al, as part of a larger investigation, carried out a controlled double-blind study in which 30 carefully selected patients with completed thrombotic stroke were randomized into two groups of equal size, one treated with anticoagulants and the other with matching placebo, and followed for 12 months. No information was given regarding the extent to which anticoagulant control was achieved. No assessment was made of either TIA or stroke recurrence but there were three members of each group who died. No major hemorrhagic complications were encountered and only three minor complications in each of the two groups. This study appears to have been well carried out but the numbers of patients are too few to add significant weight to the accumulated evidence.

McDowell and McDevitt carried out a long-term study, with 92 patients randomized to anticoagulant therapy and 99 to the control group; they were followed for an average of nearly three years. All participants met well-defined inclusion and exclusion criteria. The control patients received placebo therapy but were seen less frequently for follow-up and whether the follow-up clinical assessments were blind is not clearly indicated. The occurrence of important end points such as TIA, stroke, death, and hemorrhagic complications was reported within three categories of patients: those in the control group, those in the treatment group still on therapy at the time of the episode, and those who had been on anticoagulants originally but whose medication was stopped at the time of the attack. The authors chose not to incorporate the third group in making their evaluation of the efficacy of anticoagulants and concluded that such therapy had provided a real benefit.
CEREBRAL ISCHEMIA/Joint Committee for Stroke Resources

However, the matter of discarding one segment of the study raises an important question concerning the authors' conclusion. As discussed earlier, once a patient has been randomized to anticoagulant therapy, the subsequent clinical episodes should be charged against such therapy unless one can find a specific reason for not doing so. Only in this way is one given a true picture of what is likely to happen if anticoagulants are recommended as therapy in a defined population. The outcomes relating to all the patients randomized to treatment and to control are summarized in table 5. One can observe that the two groups are not appreciably different with respect to the occurrence of TIA, stroke, and particularly death. As might be expected, bleeding complications in the treated group exceed those in the controls.

Enger and Bøyesen\textsuperscript{19} carried out a well-designed and well-executed study in which specific inclusion and exclusion criteria were clearly defined. Rejected from the study were those patients who were aged more than 75 years, were unable or unwilling to cooperate, repeatedly exhibited diastolic blood pressures more than 120 mm Hg, were shown to have hemorrhagic or xanthochromic cerebrospinal fluid, or were severely ill from other causes. All patients were examined by angiography, and 111 patients with completed thrombotic stroke were assigned at random to either anticoagulant therapy or to a matching placebo. The trial was double-blind and both series were submitted to the same medical and social care. Follow-up neurologic assessments were made without the examiner's knowledge of which treatment the patient had been receiving.

Eleven patients who were followed up for less than three months were excluded for reasons unrelated to their cerebrovascular disorder. This left 51 remaining in the treated series and 49 in the controls; initially the groups were comparable with respect to important clinical characteristics. Anticoagulant control and assessment were satisfactory. After an average follow-up lasting nearly two years for both groups, little difference in outcome between the two was evident, as shown in table 5.

After treatment was withdrawn from all patients, those in both series were followed for an additional 15 months, on the average. During this time four more cerebral infarctions appeared in the treated series (one fatal) and five occurred in the control series, with no fatalities. Thus, no difference was apparent between the two series with respect to the occurrence of cerebrovascular episodes after discontinuance of both anticoagulant and placebo administration. The authors concluded that their study spoke against the long-term use of peroral anticoagulants in the treatment of patients with a completed cerebral infarction of a probable thrombotic and/or atheromatous origin.

Nonrandomized Trials of Anticoagulants in Patients With Completed Stroke

Howell, Tatlow and Feldman\textsuperscript{22} reviewed the case records of 272 unselected patients with completed stroke, 77 of which were discarded either because of death resulting from the qualifying stroke or because the subject had been followed for less than one month. Of the 195 patients remaining, 103 had received anticoagulants and 92 had not. The average period of follow-up was 16 and 36 months, respectively, for the two groups. The benefits deriving from administration of anticoagulants appear impressive, in that 28 of the control patients had another stroke compared with only seven of those who were under treatment; the corresponding numbers for the first 16 months of follow-up were 13 and five, respectively.

No explanation is given for the marked difference between the two groups in the length of follow-up period, and, consequently, one must be concerned about the initial comparability of the two groups, especially since the controls comprised those patients for whom maintenance of anticoagulant therapy would be difficult. The authors indicated that, "This experience does suggest that anticoagulant therapy has an effect in controlling the frequency and severity of cerebral infarction, even if the significance is limited by our failure to randomize our patients."

Thygesen et al.\textsuperscript{23} selected into three groups a number of patients with presumed cerebral infarction. There were 68 for whom anticoagulant therapy was instituted immediately after admission to the study and who, after six weeks, were discharged from the hospital as outpatients. Thirty-three of these continued their anticoagulant therapy; for the remaining 35, therapy had been reduced and was replaced with placebo after discharge from hospital. The 41 patients in the third group were given neither anticoagulants nor placebo. The results for these 41 untreated and the 33 continuously treated patients were similar. There were four deaths in each group, 12 patients in each group had TIA, and there were 11 strokes in the treated group compared to seven in the control group. The 35 patients for whom the anticoagulants were discontinued and who were discharged from the hospital on placebo also had similar outcomes.

Considerable care appears to have been taken in selecting and describing these patients, and all the clinical evaluations were carried out without knowledge as to which group a particular patient belonged. However, it was not made clear whether patients were allocated to their respective groups according to a prescribed randomized arrangement. Furthermore, it is not evident how the analysis of results takes account of those patients who were treated with anticoagulants in hospital but could not be followed as outpatients on discharge because they either were too ill or had died. If these are not counted as failures in the treated group, then the data reported are likely to present anticoagulants as having no benefit when, in fact, they might even be harmful.

Summary of Clinical Studies of Anticoagulant Therapy in Completed Stroke

Of the seven randomized, controlled clinical trials evaluating anticoagulant therapy in patients with completed stroke, those reported by Baker, Broward, Fang et al.,\textsuperscript{48} Hill, Marshall and Shaw,\textsuperscript{70} and Enger and Bøyesen\textsuperscript{19} are considered to be the most satisfactory in plan and execution. Each of these contained more than 100 patients who were randomized into active and placebo therapy groups and otherwise received similar medical care and attention. The studies by Hill et al.\textsuperscript{70} and by Enger and Bøyesen\textsuperscript{23} were both double-blind and the Baker et al.\textsuperscript{59} study was single-blind. The findings are consistent and clear that no therapeutic benefit from anticoagulants derives to patients with completed stroke. Indeed, the study by Hill et al.\textsuperscript{70} suggests that actual danger attaches to the treatment of patients such as
these with anticoagulants. While the design and execution of the other four randomized trials were relatively less rigorous, they are reasonably sound and provide further evidence that no real benefit results from anticoagulant therapy in patients with completed thrombotic stroke.

Of the two nonrandomized trials, the one reported by Thygesen et al.\(^\text{35}\) came to the same conclusion, whereas Howell and his colleagues\(^\text{36}\) concluded that some benefit is evident. However, this last study is methodologically weak and therefore the data are unconvincing.

**Clinical Trials Involving Patients With Cerebral Embolism**

Studies of patients with rheumatic heart disease and of those with acute myocardial infarction allow assessment of the efficacy of anticoagulants in the prevention of cerebral embolism, either initial or recurrent, or in altering the immediate course and outcome after the ischemic event has occurred.

**Rheumatic Heart Disease.** The single properly randomized trial with rheumatic heart disease patients is that of Baker, Broward, Fang et al.\(^\text{41}\) which included only 12 patients who were treated with anticoagulants and 16 controls. Therapy was begun with heparin followed by oral anticoagulants if symptoms had occurred during the week prior to randomization. Most of the patients were seriously ill and death occurred "early" in approximately 50% of both groups. Only two of the treated patients were given anticoagulants for a prolonged period. The recurrence rate and mortality, both early and total, were similar in the two groups but the sample size was too small for meaningful conclusions to be drawn. It was not suggested that progression of the neurologic deficit was associated with anticoagulant therapy.

Owen\(^\text{42}\) compared 17 patients with rheumatic valvular disease who were treated with oral anticoagulants following a first episode of embolization with a similar number who served as untreated controls. During a total of 90 patient-years' follow-up in the treated patients, only one recurrent embolic episode was observed compared to 22 major recurrent episodes in 81 patient-years' observations in the control patients. Details concerning the method of allocation are lacking in this study, as are data pertaining to any complications that resulted from therapy.

Székely\(^\text{43}\) retrospectively reviewed the medical course of 72 patients with rheumatic heart disease and clinically diagnosed systemic embolization, which involved the cerebral circulation in 48 instances. In 23 of these, anticoagulants were administered for a total of 58 treatment-years and there were two recurrent embolic episodes, one of which occurred following temporary discontinuance of the drug. The incidence of recurrent emboli was 3.4% per patient-year compared to a 9.6% incidence per patient-year in 46 patients with embolization who were not treated with anticoagulants. The author concluded that a benefit from anticoagulants was shown in those patients treated after a first embolus.

This author also reported on the outcome in 30 patients with atrial fibrillation but without embolization who were followed for 46 patient-years. Comparison was made with a more or less similar group of 98 patients not given anticoagulants and followed for 499 patient-years. In the treated group, two embolic episodes occurred, compared with 34 among the untreated patients. No mention of bleeding complications is made in the report and a major deficiency of the study is the lack of information as to the basis upon which cases were selected for treatment and details concerning the adequacy of follow-up in each group.

McDevitt\(^\text{44}\) compared the results in 47 patients with rheumatic heart disease who were followed while on and off anticoagulants. Twenty-seven embolic events (five involving cerebral vessels) occurred in 1,315 patient-months on anticoagulant therapy and 132 episodes (33 cerebral) occurred during 1,437 patient-months off anticoagulants. Considerable detailed information is given concerning the guidelines for the use of anticoagulants followed in the author's institution, i.e., criteria for administering or discontinuing anticoagulants, procedure for follow-up assessments and possible complications of therapy, particularly on a long-term basis. However, the lack of specific information on these matters as applied to the patients included in the "on-off" study limits one's ability to interpret these data.

Fleming and Bailey\(^\text{45}\) retrospectively assessed anticoagulant treatment in 217 patients with mitral valvular disease and a history of embolism during 649 patient-years of treatment. A total of five emboli occurred, an incidence of 0.8% per treatment-year. The authors concluded that this incidence of recurrence was well below that to be expected in an untreated group and mentioned that several patients in the study had systemic emboli soon after the drug was withdrawn. The incidence of bleeding was 2.3% per patient-treatment and in only one case was the hemorrhage fatal.

Adams et al.\(^\text{46}\) conducted a retrospective analysis of a 20-year experience with 84 patients having mitral valvular disease and atrial fibrillation and sustaining a stroke from a clinically diagnosed embolus. One-half of these were given oral anticoagulant treatment, initiated within two weeks after the embolic episode; the other half were untreated. The groups were not concurrent in that most untreated patients were observed in a ten-year period that began prior to the one during which the largest number of anticoagulant-treated patients was admitted.

Significant differences in survival favoring the use of anticoagulant therapy were noted. The differences became apparent early and, in fact, were maximal at six months but continued for ten years of follow-up. Recurrent embolism was considered the cause of death in 13 of the untreated and in only four of the treated patients. The lack of concurrence in the time periods covered makes comparison of these two groups difficult. The majority of deaths were due to causes other than emboli and the greatest difference between the treated and the untreated was observed during the first six months. This raises the question whether bias entered into selection of patients for anticoagulant treatment by excluding from receiving the drug those who were the most seriously ill and therefore had the poorest prognosis. Only fatal emboli are mentioned in the report and it would be valuable to know the total incidence of recurrent embolism.

In several uncontrolled studies, including those by Askey and Cherry\(^\text{47}\) and Cosgrove,\(^\text{48}\) oral anticoagulant therapy was administered to patients with cardiac disease, usually associated with atrial fibrillation and systemic embolization. Most of these authors concluded that the treatment was practical, reasonably safe, and effective in reducing the in-
incidence of recurrent embolization.

Wells evaluated the effect of anticoagulant therapy on the short-term outcome following an acute cerebral embolic event. In this retrospective study, 63 embolic events occurred in 53 patients not treated with anticoagulants as compared with 34 embolic episodes in a group of 29 patients who were given anticoagulant drugs. The patients in the two groups were reasonably comparable.

Anticoagulants were begun within 24 hours of the embolic episode in most instances and by 48 hours in all; however, an unspecified number were started with heparin and the rest were given only oral anticoagulants. The degree of anticoagulation produced was not stated. Death occurred in 25% of the untreated as compared to 6% of the treated patients, and severe permanent disability in 35% of the untreated and 40% of the treated patients. One-third of deaths in the untreated patients appear to have happened during the first 24 hours, at a time before any beneficial action of anticoagulants, if such existed, could be expected to take place in the patients receiving them. This observation suggests the possibility of bias in case selection, with avoidance of anticoagulants for the most severely ill patients. Evidence was presented to indicate that anticoagulants, when given to patients with red cells in the spinal fluid, worsened the prognosis although the data presented were inadequate to document this point. The authors concluded that anticoagulants given soon after an embolic event certainly did not worsen the outcome and that they might have slightly reduced mortality and had significantly decreased morbidity. It is difficult to draw sound conclusions from this nonrandomized, retrospective, and nonblind study in which the case-selection also may well have been biased.

Carter also has been interested in the effects of early anticoagulation. In an uncontrolled study, the data suggested benefit of anticoagulants begun early, in that two-thirds of 49 patients with cerebral embolism recovered or improved; in contrast, only one-third of a prior group treated without the use of anticoagulants made a similarly improved recovery. Based on previous experience, the author identified a history of bleeding disorder, severe hypertension (diastolic pressure of 120 mm Hg and above), age greater than 70 years and evidence of bleeding into the cerebrospinal fluid as contraindications to the use of anticoagulants. Presumably because of an unacceptable incidence of bleeding, the dose of anticoagulants was reduced; however, the revised regimen as outlined still resulted in levels of anticoagulation which would be considered excessive today. Later, Carter summarized experience gained with more than 100 patients with cerebral embolism, treated in various ways. Most of these had either rheumatic heart disease or ischemic heart disease and atrial fibrillation.

One-third of 34 patients who were untreated died early from the immediate effects of the embolism (more than one-half were dead within one year) and more than one-half of the survivors remained permanently disabled. By contrast, during the period 1954 to 1957, 43 patients were admitted, all of whom received a single four-week course of anticoagulants immediately after their embolism. At the end of six weeks, nine of these had died, eight had made little recovery, seven were improved, and 19 had recovered. Only patients with incomplete lesions were admitted to the series from 1958 to 1963 inclusive. Of 26 patients in this group who were treated with anticoagulants, one died, three were not improved, five were improved, and 17 had recovered.

The author concluded that anticoagulants are useful in the immediate treatment of patients with mild or incomplete lesions. Caution was urged in prescribing treatment for patients with completed lesions for whom anticoagulants are of little value and even appear to be hazardous. Late recurrence of embolism in treated patients was 16% during two years of observation as compared to 57% in an earlier untreated group during a similar length of time. Carter recommended that for patients with embolism, anticoagulant treatment be continued for at least a year, by which time the period of greatest risk for recurrence will have passed, particularly for patients with ischemic heart disease. In those with mitral stenosis, especially when associated with atrial fibrillation, two years of treatment were advised and even longer for those in whom embolism recurred during follow-up.

Myocardial Infarction. Numerous studies have evaluated the effectiveness of anticoagulant drugs in the management of patients with acute myocardial infarction and have resulted in much controversy. Consequently, their therapeutic role in the routine management of patients such as these is presently unclear.

Without question, mural thrombus overlying infarcted myocardium is a frequent source of the material causing cerebral embolism. Several studies have provided both clinical and postmortem documentation to suggest that oral anticoagulants are of value in reducing the incidence of mural thrombi and consequently of cerebral embolism.

In a study reported by Wright et al., in which more than 1,000 patients were included (442 in the control group and 589 in the treated group), the clinical incidence of cerebral embolism was approximately 4.9% in the controls and 0.7% in the treated patients. Similar data were obtained in two later trials which were randomized, controlled, well designed, and well executed. These two studies, one sponsored by the Medical Research Council (M.R.C.) and the other by the Veterans Administration (V.A.), reported an incidence of cerebrovascular lesions diagnosed clinically in 2.5% to 3.7% of patients in the control series, while in the treated groups the incidence fell to about 1%. In those who came to autopsy, the incidence was about 7% in controls and 4% in the treated group in the M.R.C. study and 0% in the treated group of the V.A. study. The presumed source of embolic material, i.e., mural thrombosis, was found in nearly one-half of the autopsied patients in the control group and in 22% of the patients who had received oral anticoagulants.

Evidence has been presented suggesting benefit of long-term anticoagulants on incidence of cerebral embolism in patients following recovery from myocardial infarction. For example, in the study by Harvald et al., a 1:11 difference between the anticoagulated and control patients was observed. The cerebral thromboembolic complications were listed under the heading of "cerebrovascular thrombosis."

Summary of Clinical Trials Evaluating Anticoagulants in Cerebral Embolism

Although optimally designed studies on this important subject are lacking, the data reported here represent more
than 500 cases. The results have been consistent and suggest that in patients with rheumatic or ischemic heart disease anticoagulants reduce the incidence of initial and recurrent cerebral embolic episodes. If these results are accepted as a basis, it seems reasonable to recommend that anticoagulant therapy be employed in such patients who have suffered cerebral embolism or in those thought to be at high risk of experiencing such an event. Bleeding is the only significant complication of prolonged therapy with the oral anticoagulants and the incidence is acceptably low if patients with systemic hypertension or previous bleeding tendency are excluded.

The duration of therapy must be individualized and anticoagulants should be discontinued when the risk of further embolic episodes becomes minimal. In patients with emboli following myocardial infarction, the recommendation by Carter that treatment be discontinued after one year seems reasonable since it is to be expected that organization of the mural thrombus would have occurred during that time and further progression of thrombosis would be unlikely. Obviously, if a patient has ventricular aneurysm and repeated embolism, prolonged therapy, perhaps for an indefinite period, would be indicated.

With rheumatic heart disease, especially that involving the mitral valve and with atrial fibrillation, the occurrence of a systemic embolus probably identifies the patient who will remain at continuous risk of recurrence and for whom lifelong anticoagulant therapy should be considered.

A more difficult question to answer from the available data is when anticoagulants should be instituted for a patient with cerebral embolism. Obviously, to prevent early recurrences, it is desirable to begin therapy without delay as soon as it becomes safe to do so. On the other hand, a feeling of concern is always present that beginning anticoagulant administration too soon may lead to hemorrhage into the infarcted area.

This concern has its source in studies such as those reported by Sibley et al. and by Moyes et al. who experimentally produced cerebral infarcts in dogs and demonstrated that anticoagulation significantly increased hemorrhage into the infarct. In animals anticoagulated prior to embolization, the infarct may have been smaller, but was also more hemorrhagic. When large doses of anticoagulants were begun on the day of embolization, striking evidence of intracerebral hemorrhage occurred. When the drugs were employed in doses of more conventional size, the hemorrhage that developed was less, but still significantly more than in the control animals. This tendency to hemorrhage persisted even when initiation of anticoagulation was delayed for up to three days following cerebral infarction, nor was a reduction in infarct size apparent.

Whether immediate anticoagulation with heparin is hazardous or beneficial to the patient with cerebral embolus. The studies by Wells and Carter suggest possible benefit without hazard, although selection bias may have influenced their results, as previously discussed. These authors' conclusion seems reasonable, that an embolic stroke which is completed at the time a patient is seen is unlikely to be benefited by anticoagulants, and suggests that early heparinization should be used only for patients with incomplete, progressing symptoms, and then only with caution. The use of heparin is contraindicated for hypertensive patients and for those with a tendency toward bleeding. From the standpoint of preventing recurring embolism, it is likely that anticoagulation can be delayed with safety for several days. Although Daley et al. found a high percent of recurrences occurring in the first week, most studies indicate recurrence within the first ten days to be uncommon.

Thus, present evidence suggests that patients with cerebral embolism should be given anticoagulant therapy unless a serious contraindication exists. In those with evidence of progressing stroke, the therapy should be started early with heparin. In other patients, treatment can begin with oral anticoagulants at the time the patient is seen, with therapeutic anticoagulation being achieved three or four days later. If, during that interval, evidence of progressing recurrence develops, heparin should be given.

Platelet Function-Suppressant Therapy

Of the large number of drugs that alter platelet function tests in vitro, only a few are potentially useful clinically based upon consideration of toxicity and the dosage required. These drugs, which are available and in therapeutic use for other of their actions, include acetylsalicylic acid, clofibrate, dipyridamole, and sulfinpyrazone.

Four prospective studies have been carried out to evaluate therapy in cerebrovascular disease with drugs that have been demonstrated to be platelet suppressive. One retrospective study and some well-documented individual case studies have also been reported.

Acheson, Danta and Hutchinson evaluated the effect of dipyridamole at two dose levels in a total of 169 patients, each of whom had partially or completely recovered from a clinical episode of cerebral ischemia. A dose of 400 mg daily was used for periods varying from six to 24 months, and this dosage was later doubled when it became clear that the lower dosage was of no benefit. Dosage at the higher level likewise gave no evidence of reducing the frequency of TIA, ischemic stroke, or death. However, it is unlikely that a definite answer could have been obtained from this trial in any event, since the number of patients investigated was small, the length of study relatively short, and the incidence of the two most important end points, stroke and death, was low (table 6).

Acheson and Hutchinson compared the effects of clofibrate with placebo in patients with hypercholesterolemia and cerebral ischemia manifested by either TIA or ischemic stroke. The study was designed to determine the effect of reducing elevated blood cholesterol on the incidence of further episodes of cerebral ischemia and the mortality rate. Although the study design appears adequate, specific details of randomization and assurance of blindness with respect to treatment are not provided. The study was continued for seven years, with an average follow-up of four
years per patient. Although the blood cholesterol was reduced, no differences were noted in the three end points examined, i.e., TIA, stroke, and death (table 6).

Evans carried out a double-blind crossover study in which each of 20 patients with amaurosis fugax, including six who had TIA also, received either sulfinpyrazone (200 mg four times daily) or an identical placebo, and after six weeks were then crossed over to the alternative therapy for another six weeks. Five patients showed improvement on both treatments and two did not improve on either, but the remaining 13 patients all showed a significant improvement on sulfinpyrazone and none on placebo. The difference is statistically highly significant (p < 0.001). This study was criticized by its authors because it was retrospective, and because other unrecognized variables may have accounted for the difference in number of attacks.

Harrison et al. have reported their experience with aspirin and dipyridamole in two cases of amaurosis fugax. During a brief follow-up, they found a significantly reduced number of attacks of transient blindness when the two patients were treated with aspirin. Dipyridamole was concluded to be ineffective — although the evidence for this statement is extremely weak. Mundall et al. reported a single case of amaurosis fugax associated with thrombocytosis and spontaneous platelet aggregation in which the patient’s episodes of transient blindness disappeared when aspirin was given and recurred only when the aspirin was stopped temporarily. She remained symptom-free over a follow-up period of five months while on aspirin.

Several studies have been carried out to evaluate the effect of platelet-suppressive therapy on the incidence of systemic embolization in patients with prosthetic heart valves. While such studies do not deal specifically with cerebral embolization, they are important to include in a discussion of trials of platelet suppressants. The best-designed trial was that reported by Sullivan et al. who compared the effect of dipyridamole plus coumadin to coumadin therapy alone in a prospective randomized double-blind trial in 163 patients with older-type prosthetic heart valves. During a one-year period of observation they reported a 14% incidence of embolization in those patients receiving coumadin alone, compared to 1.3% in the dipyridamole-coumadin group. These

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of report</th>
<th>Drug (daily dose)</th>
<th>Condition</th>
<th>No. pts.</th>
<th>Average follow-up period (mo.)</th>
<th>Results</th>
<th>Treatment</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acheson et al.</td>
<td>1969</td>
<td>Dipyridamole (400 mg)</td>
<td>TIA/CVA</td>
<td>77 76 14</td>
<td>38 43 6 9 10 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acheson, Hutchinson</td>
<td>1972</td>
<td>Clofibrate (1-2 gm)</td>
<td>TIA/CVA</td>
<td>47 48 60</td>
<td>17 15 49 46 49 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans</td>
<td>1973</td>
<td>Sulfinpyrazone (800 mg)</td>
<td>Amaurosis fugax</td>
<td>20 20</td>
<td>6-wk crossover</td>
<td>0.55c 2.7f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blakely, Gent</td>
<td>1975</td>
<td>Sulfinpyrazone (600 mg)</td>
<td>CVA</td>
<td>43 56</td>
<td>Up to 4 yr</td>
<td>— — 30f 36f</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Strokes.
†Mean number of eye symptoms per week.
‡Based on estimated four-year death rates from vascular causes.
data are suggestive that platelet-suppressant therapy may reduce the emboli from prosthetic heart valves, an increasingly important source.

Studies in Progress

In progress at the present time are two large cooperative studies evaluating the effects of platelet function-suppressing drugs in patients with cerebrovascular disease. A Canadian study,88 which has been going on for more than four years, is a multicenter trial comparing the effects of aspirin, sulfinpyrazone, aspirin plus sulfinpyrazone, and placebo in patients with TIA. The study is designed to determine the effects of these treatments on the incidence of recurrent transient ischemia and stroke and on survival. A complementary study also has been started by the same group of investigators in which sulfinpyrazone is being compared with placebo in patients with TIA who have had reconstructive cerebrovascular surgery.

A study in the United States, sponsored by the National Institutes of Health, is comparing the effects of aspirin with those of placebo in both surgical and nonsurgical patients with TIA. This study, which has been in progress for approximately two years, is assessing the effect of aspirin on recurrent TIA, stroke, and survival.

Summary of Trials Evaluating Platelet-Suppressant Therapy in Cerebrovascular Disease

Genti95 has reviewed the reported clinical evaluations of platelet inhibitor therapy in cerebrovascular disease. The conclusion expressed there remains unchanged after a re-evaluation: none of the studies reported so far has established efficacy with regard to the important end points of stroke and death, although some evidence suggests that both aspirin and sulfinpyrazone may reduce recurrence of TIA.

The patients in the two Acheson86-87 studies were not well defined clinically and appeared to be a heterogeneous group. Both studies were limited in terms of total patient-years of study and neither was likely to produce an answer relating to the prevention of stroke or to increased survival. Evans88 study was well controlled but the outcome related only to short-term relief of symptoms and the nature of these symptoms was uncertain. Blakely and Gent89 studied elderly people who are at high risk of death from both myocardial infarction and stroke and thus are not representative of the general population. This is, however, an interesting clinical model and has provided valuable data confirming that initiation of a long-term multicenter trial with sulfinpyrazone would be a worthwhile endeavor.

The study by Dyken et al.93 was thoughtfully carried out and analyzed but, as the authors recognized, in a retrospective study of this kind it is possible that unknown factors other than aspirin might account for the differences in frequency of attacks. They stressed the importance of their findings in strongly supporting the urgent need for prospective controlled studies before platelet-suppressive drugs become widely adopted and indiscriminately used.

The members of the study group hope that the data from the ongoing Canadian and U.S. multicenter studies will provide definitive information as to the role of these platelet function-suppressive drugs in the treatment of ischemic cerebrovascular disease.

Thrombolytic Therapy

Because brain tissue is so extremely sensitive to hypoxia, the disastrous consequences of thrombotic occlusion of cerebral vessels result almost entirely from reduction in blood flow. Irreversible damage occurs within ten minutes of total cessation of blood flow and within 60 minutes if blood supply is decreased below 20% of normal. Therefore, the concept of employing therapy in thromboembolic cerebrovascular ischemia to dissolve the obstructing thrombotic material, and thereby to restore blood flow rapidly while salvage is still possible, is theoretically a very attractive one. Such treatment would permit removal of single or multiple thrombi from extracranial vessels as well as from surgically inaccessible intracranial vessels. Nevertheless, some potential hazards are associated with this approach. These include the danger of converting a so-called white infarct to a red or hemorrhagic infarct when blood flow to ischemic or infarcted tissue is reestablished. In addition, emboli may be produced from the dissolving thrombi; these could enter previously uninvolved vessels and cause worsening of ischemia.

Several approaches are available to produce and sustain a marked increase in the fibrinolytic activity of blood and thereby create a "thrombolytic" state. These include the intravenous administration of plasmin which has been activated from the precursor plasminogen by one of several activators, e.g., streptokinase or urokinase. Alternatively, the plasminogen activators may be infused and produce a thrombolytic state by activating in vivo plasminogen in the plasma or, perhaps even more desirably, the plasminogen which is incorporated on the surface and within the lattice-work of a thrombus or embolus.90

Experience with thrombolytic agents in the management of patients with cerebrovascular ischemia is limited. Early studies with small numbers of patients involved the use of plasmin-plasminogen activator mixtures and the results suggest that lysis of angiographically documented cerebral thromboli is achievable.91,92 Later the use of streptokinase was shown to be effective in individual cases.93 Meyer et al.94 conducted a nonrandomized and uncontrolled trial including 70 patients with clinically diagnosed stroke-in-evolution. Treatment consisted of intravenous infusion of urokinase-activated or streptokinase-activated plasminogen in combination with full-dose heparin for four to six hours daily on two to four consecutive days. Improvement was observed in 54% of these patients and stabilization without further deterioration of their condition occurred in another 20%. In half of the ten cases in which angiography was performed before and following treatment, resolution of the occlusion was demonstrated and in two others improvement was observed. The outcome was impressively better if treatment was begun within 72 hours after onset of symptoms.

These results were considered sufficiently encouraging to justify further study and led the same authors to perform a randomized controlled trial evaluating the effects of streptokinase-activated human plasminogen.95 Forty normotensive patients with stroke-in-evolution were studied. In 85%, the status of the cerebral circulation was confirmed by angiography — in most cases carotid or middle cerebral artery occlusion from thrombus or embolus was demonstrated. Patients were randomized and treated in a double-blind manner with either streptokinase-plasmin mix-
CEREBRAL ISCHEMIA/Joint Committee for Stroke Resources

ture or placebo for four-hour periods on three successive days, in combination with full-dose subcutaneous heparin, followed by oral anticoagulants. Treatment was begun within 72 hours after onset of symptoms of cerebral ischemia. The effect of treatment on components of the fibrinolytic system was documented by serial determinations of fibrinogen and plasminogen levels. Clinical assessment of results was made by neurologic examinations, performed by the same neurologist, prior to and ten days following initiation of treatment. In addition, 20% of patients underwent posttreatment angiography.

The patients appeared to be well matched generally, although those given lytic therapy were somewhat older than those in the placebo group. The trial was apparently well conducted. No significant differences in outcome were noted between the two groups. Fourteen patients died, seven in each group, and nine patients in each group improved. Eight patients underwent follow-up angiography and in one from each group there was evidence of improved blood flow. Biochemical evidence that lytic activity had been produced was observed in 80% of those given thrombolytic therapy, although the intensity of the changes was not detailed in the report. Complications were minimal. The authors concluded that no significant differences between the groups had been demonstrated but considered it likely that the period of treatment had been too short and that posttreatment angiography of all patients would be required to determine precisely the effects of fibrinolytic therapy.

Another randomized and double-blind trial was conducted which had design features similar to the earlier one except that all but one of the patients underwent angiography prior to randomization and arteriography was repeated after ten days in those who survived. Streptokinase was employed as the thrombolytic agent and the drug was administered by sustained infusion for a single six-hour period beginning within 72 hours after onset of ischemic symptoms. Heparin followed by coumadin was given to both control and treated cases after the streptokinase infusion. The dose of streptokinase was individualized and determined in a conventional manner. Clinical assessment of results was made by a neurologist presumably blind to treatment, based upon evaluation prior to and ten days following admission to the trial.

Seventy-three patients were studied. In the 37 given thrombolytic therapy, there were 13 deaths (35%) and improvement in 43% compared to an 11% mortality and improvement in 58% of the control patients. Even when the dose of streptokinase was progressively lowered in an attempt to avoid hemorrhagic complications, the deleterious effect continued. Cerebral hemorrhage was demonstrated in three of the ten patients treated with streptokinase, and another had a hemorrhagic infarct at autopsy. Furthermore, there were six examples of anemic infarction. In contrast, no cerebral hemorrhage was evident in the three control patients autopsied and each had white infarction. Evidence of dissolution of thromboembolic material was observed in all patients who received streptokinase. The data relating to follow-up angiography are not stated clearly enough to permit determination as to the frequency of thrombolysis in the two groups, but this occurred frequently, though not invariably.

The authors concluded that treatment of stroke-in-evolution with thrombolytic agents was of no apparent value and, in fact, in the case of streptokinase was harmful to the patient. They believed that dissolution of thrombus and the reperfusion of ischemic or infarcted tissue probably explained the frequent cerebral hemorrhage or hemorrhagic infarction observed.

Thus, from the admittedly limited amount of reported experience, it must be concluded that, although theoretically attractive, the employment of thrombolytic therapy in acute cerebral ischemia appears to lack benefit and, as has been indicated by several authors, may, in fact, be hazardous.

Conclusions

1. Stroke ranks third in frequency as a cause of death in the USA, accounting for approximately 200,000 death yearly. Of the numerous types of stroke, the thrombosis-related ischemic variety leads the list by a wide margin. The economic impact of stroke is estimated to have totaled 6.2 billion dollars in 1972, and is undoubtedly much higher today.

2. As the first essential step in diagnosis, cerebral hemorrhage should be identified, if it is the cause of the stroke. The physician should then attempt to distinguish between cerebral embolism and cerebral thrombosis, although exact clinical differentiation of the several varieties of ischemic stroke is not always possible. He should also attempt to categorize the stroke according to the clinical condition encountered, i.e., transient ischemic attack (TIA), progressing stroke (stroke-in-evolution), and completed stroke.

3. The physician should remain familiar with basic information relative to the mechanisms of blood clotting and with factors operative when consideration is given to the use of the various types of antithrombotic therapy in the patient with, or at risk of, stroke.

4. The study group has outlined in detail a number of trials conducted in the past, with a critique of each.

5. The information presently available indicates that anticoagulant therapy should be considered for the patient with ischemic cerebrovascular disease on an individually selective basis, depending on the pathogenesis of the cerebral lesion, the type of disorder encountered, and concurrent systemic disorders. The physician must familiarize himself with the contraindications to the use of anticoagulant drugs, in particular. If he elects to use anticoagulants, a calculated risk is introduced for his patient, namely, the possibility of hemorrhage. Many findings from clinical trials are controversial and can be reconciled only by further definitive data.

6. Indications for the use of anticoagulants in TIA remain controversial. In reported clinical trials, anticoagulant therapy has been demonstrated neither to increase survival rate nor to reduce the incidence of subsequent stroke; the evidence that anticoagulants are of benefit in reducing the incidence of TIA recurrences is equivocal.

7. In ischemic progressing stroke (stroke-in-evolution), anticoagulant therapy may have value in retarding the progress of the infarction.

8. Present evidence appears clear that, in patients with completed stroke, anticoagulant drugs have not proved to be useful.
9. According to current information, embolism of cardiac (rheumatic or ischemic heart disease) origin can be prevented with anticoagulants. These drugs should be given unless the patient has a condition that would contraindicate, such as hypertension or bleeding tendencies. In most cases of rheumatic heart disease, long-term treatment is necessary.

10. A review of platelet function-suppressant therapy, which is a popular subject today, indicates that no clinical trial so far has established the efficacy of these preparations safe. To be awaited with great interest are the reports of agents. To be awaited with great interest are the reports of

11. The employment of thrombolytic therapy, although theoretically attractive, appears to lack benefit and is not safe.

Acknowledgment

The members of the study group wish to thank the following colleagues for reviewing the manuscript and providing valuable suggestions and advice:

Alvan R. Feinstein, M.D.
Professor of Medicine and Epidemiology
Yale University School of Medicine
New Haven, Connecticut 06510

William K. Hass, M.D.
New York University School of Medicine
New York, New York 10016

Jack P. Whisnant, M.D.
Professor and Chairman
Department of Neurology
Mayo Clinic and Mayo Foundation
Rochester, Minnesota 55901

References


42. Jones HR, Millikan CH: Temporal profile (clinical course) of acute carotid system cerebral infarction. Stroke 7: 64-71 (Jan-Feb) 1976


AMERICAN HEART ASSOCIATION
1976 SUBSCRIPTION RATES

CIRCULATION
A monthly devoted to clinical research and advances in the cardiovascular field.
Eugene A. Stead, Jr., M.D., Editor

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>Elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$25</td>
<td>$30</td>
</tr>
</tbody>
</table>

CIRCULATION RESEARCH
A monthly concerned with basic research in the cardiovascular field. Brian F. Hoffman, M.D., Editor

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>Elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$50</td>
<td>$55</td>
</tr>
</tbody>
</table>

STROKE
A journal of cerebral circulation, bi-monthly. Clark H. Millikan, M.D., Editor

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>Elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$25</td>
<td>$30</td>
</tr>
</tbody>
</table>

RECURRING BIBLIOGRAPHY
OF HYPERTENSION
Bi-monthly, in cooperation with the National Library of Medicine.

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>Elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$12</td>
<td>$16</td>
</tr>
</tbody>
</table>

Publishing Office
AMERICAN HEART ASSOCIATION
7320 Greenville Ave.
Dallas, Texas 75231
XIV. Cerebral ischemia: the role of thrombosis and of antithrombotic therapy. Study group on antithrombotic therapy.
E Genton, H J Barnett, W S Fields, M Gent and J C Hoak

Stroke. 1977;8:150-175
doi: 10.1161/01.STR.8.1.150
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/8/1/150