SUMMARY  Transient ischemic attacks are the most important warning symptoms of impending stroke. They occur in up to one-half of all patients who develop stroke but, unfortunately, less than half of the patients who have them seek help from their physicians before stroke occurs. Physicians should regularly question patients about the possibility of such symptoms and patients with them should seek prompt help. When transient ischemic attack is diagnosed, patients should be evaluated for elevated blood pressure, hyperlipidemia, cardiac dysrhythmia, cardiac disease, anemia, polycythemia and thrombocytosis. When these conditions are found they should be treated. Patients with carotid system TIAs should be evaluated clinically and radiologically for evidence of vascular disease. The neck should be auscultated for bruit and absent pulses and the peripheral vessels palpated. Patients with carotid system TIAs should have angiography of all 4 cerebral vessels and the angiogram should be evaluated for the presence and number of arterial stenoses and the presence of ulcerated plaques. When patients with carotid system TIAs are found to have localized extracranial atherosclerotic obstruction or ulcerated plaques in a vessel appropriate to the side of their symptoms of cerebral ischemia, they should be considered for prompt surgical correction of the lesion. For patients with carotid system TIAs, who have multiple sites of extracranial vascular disease, medical treatment is advisable with either anticoagulants or platelet antiaggregating agents. In view of the recently reported favorable results using aspirin in the prevention of TIA and stroke, this agent may be preferable to anticoagulants in instances where hypertension, patient compliance and laboratory facilities are a problem.

STROKE from cerebral infarction is often the most devastating of human illnesses because of its high initial mortality (up to 30%) and because of the high incidence of serious and incapacitating permanent neurologic defects. To date there is no known method of treatment which will limit infarction once it starts or reverse it once it occurs. Prevention then emerges as a logical course of action. Fortunately, not all strokes come without forewarning. The most definite of warning symptoms is the "transient ischemic attack" (TIA). When such attacks occur, proper evaluation of patients with them and proper treatment may prevent the devastation that may follow cerebral infarction. This review is designed to evaluate current suggestions for treatment and to suggest a program of management.

Transient Ischemic Attacks

TIAs are episodes of temporary and focal cerebral dysfunction of vascular origin, rapid in onset (no symptoms to maximal symptoms in less than 5 minutes and usually less than a minute), which are variable in duration, commonly lasting from 2 to 15 minutes but occasionally lasting 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. Each attack leaves no persistent neurological deficit. It is common practice to define these events as related to the carotid arterial system or the vertebrobasilar arterial system, meaning that the clinical locus of ischemia is in the customary distribution of one or the other of these arterial systems. There may be only 1 attack or there may be multiple attacks at varying intervals. There are unusual instances which fall outside of this standard definition which is constructed in an arbitrary fashion in an attempt to provide a common basis for identifying groups of patients with TIA.

The typical history for a TIA in the carotid system is swift (no symptoms to maximal symptoms in less than 5 minutes, usually less than 2 minutes) onset of:

1. Motor defect (weakness, paralysis, poor use, or clumsiness of both extremities on the same side).
2. Sensory defect (numbness, including loss of sensation or paresthesias involving 1 or both extremities or the face on the same side).
3. Aphasia (speech and/or language disturbance which may be only a minor defect or may be global and may or may not include difficulty in reading, writing, or performing calculations).
4. Loss of vision in 1 eye or in part of 1 eye when vision in both eyes was intact (amaurosis fugax).
5. Homonymous hemianopia.
6. Combinations of the above.

These clinical phenomena generally represent a decrease or absence of function. When there is a sensory event, it is commonly described as coming on all at once, that is, without a march.

The typical history of a TIA in the vertebrobasilar arterial system is a swift (no symptoms to maximum symptoms in less than 5 minutes, usually less than 2 minutes) onset of:

1. Motor defect (weakness, clumsiness, or paralysis of any combination of the 4 extremities up to quadriplegia, sometimes changing from one side to another in different attacks).
2. Sensory defect (numbness, including loss of sen-
sation or paresthesias in any combination of extremities including all 4 or involving both sides of the face or mouth. The symptoms are frequently bilateral and the distribution may change from side to side in different attacks.

3. Loss of vision, complete or partial in both homonymous fields (bilateral homonymous hemianopia, or altitudinal field defects).

4. Homonymous hemianopia.

5. Ataxia, imbalance, unsteadiness, or disequilibrium not associated with vertigo.

6. Hearing loss either unilateral or bilateral.

7. Combinations of the above.

Vertigo (with or without nausea and vomiting), diplopia, dysphagia, or dysarthria should not be considered as a TIA when these symptoms occur alone, but in combination with one another or with any of the above (numbers 1, 2, 3, and 4) the attack should be considered a TIA.

The clinical phenomena generally represent a decrease or absence of function. At times, the motor, sensory or visual defect constituting the content of a vertebrobasilar attack may be unilateral. In such instances it becomes difficult to make a distinction between whether the locus of ischemia is in the carotid arterial system or in the vertebrobasilar system. In the list above, "drop attacks" are omitted. Fainting (syncope) is frequently confused with a "drop attack" so the latter should be included in the vertebrobasilar profile only when the patient’s description of the "drop attack" is absolutely clear. The variety of manifestations included in the vertebrobasilar profile makes the potential pattern of symptoms considerably more variable and complex than that for the carotid system.

Principles of Therapy

The primary objective of therapy in occlusive cerebrovascular disease is to maintain a normal or adequate metabolic substrate for brain tissue by maintaining the quality and quantity of blood delivered and removed from brain tissue and to prevent infarction. This primary goal may be attained by treatment of any mechanism which interferes with 1) the cardiac capacity to maintain adequate cerebral blood flow, 2) alteration in any property of the blood which may impair the maintenance of adequate neural metabolic substrate (including thrombus formation, anemia), 3) changes in the arterial wall which may lead to occlusion (including atherosclerosis and arteritis), as well as, in some instances, 4) the relatively transient protection of certain aspects of neurone metabolism (hypothermia, steroids and so forth). The objectives of treatment include:

1. Stop or ameliorate focal transient cerebral ischemic attacks.

2. Prevent cerebral infarction (and the attendant persistent neurological deficit) in patients having transient ischemic attacks.

Because the natural history of occlusive cerebrovascular disease is extraordinarily variable from patient to patient, an attempt will be made to summarize the existing recorded (literature) evidence concerning each mode of therapy; in some instances, conflicting views have been expressed and these will be included.

Because of the importance in distinguishing the clinical stage of occlusive cerebrovascular disease in relationship to treatment and the many modes of therapy available, transient ischemic attack management will be discussed from the standpoint of:

1. Treatment related to the heart
2. Treatment related to the blood
3. Treatment related to the arterial vessel wall
4. Treatment of the brain parenchyma

Transient Ischemic Attacks

I. Treatment Related to the Heart

Arrhythmia (medical, pacemaker)

Sources of emboli

Prosthetic valves (anticoagulant, dipyridamole ?)

Myocardial infarction (medical, anticoagulant ?)

Arrhythmia (anticoagulant)

Subacute bacterial endocarditis (medical)

Hypertension

II. Blood Constituents

Clotting characteristics (including thrombocytosis)

Anticoagulant

Platelet antiagglutinating agents

Dipyridamole (Persantine)

Aspirin

Sulfinpyrazone (Anturane)

Polycythemia

Anemia

Hypoglycemia

Hyperlipidemia (diet, clofibrate, nicotinic acid)

III. Arterial Wall

Vasospasm

Vasodilators

Carbon dioxide

Papaverine

Hexobendine

Betahistine hydrochloride

Atherosclerosis

Surgery

Endarterectomy

Shunts (reversal of vertebral artery flow)

(superficial temporal-middle cerebral branch bypass)

IV. Parenchyma

(none necessary)

To evaluate how well the objectives of therapy for transient focal cerebral ischemic attacks have been accomplished, it is first necessary to understand fully the variable natural history of the disorder and realize the necessity to compare the results of any form of treatment with the observations of a similar group of patients not undergoing therapy. The natural history
of these attacks is so variable that no significant judgment can be made about the efficacy of a therapy from simple observations of an occasional patient. It should be added that there are now so many facets of potential treatment (including antihypertensive, antihyperlipidemic, cessation of smoking, and so forth) used by large segments of the population, that it is very difficult to construct a pure “natural history profile” of such attacks. However, a number of studies of the natural history of transient focal cerebral ischemic attacks have been published. The results of these studies are summarized in table 1. In 3 studies, less than 20 percent of patients with transient ischemic attacks developed cerebral infarction (completed stroke) during the follow-up period. Ziegler’s patients did not include individuals with severe heart disease or hypertension, and 62 percent of those having angiography had less than 10 percent stenosis of any cervical-cerebral artery. Pearce and associates followed the patients for less than a year. Their results suggest that had their patients been observed for 50 to 60 months, the percentage of those developing cerebral infarction might have been the highest recorded in table 1. The experience noted by Marshall is entirely different from any other report in the literature. This observation is particularly unusual, since earlier Marshall reported that 68 (43%) of 158 patients with TIA developed cerebral infarction during a follow-up period of nearly 5 years. It appears that the series reported by Marshall (in table 1) does not, in fact, represent the natural history of transient focal cerebral ischemic attacks. The study by Goldner et al. covered a 15-year follow-up of 150 patients who had transient cerebral ischemic attacks and were first seen by the Mayo Clinic for this complaint in 1950 through 1954. Follow-up data were complete on only 111 patients; with data complete enough to know whether there had been a stroke or not. Forty-three or 38% had had a stroke. Based on all available data, 25% to 40% of patients with transient ischemic attacks (assuming that each patient has had more than 1 attack) will eventually have cerebral infarction if followed as long as 5 years. This gives a 5-8% chance of infarction each year. Studies suggest that the chances of infarction are not evenly distributed over the 5-year period but are concentrated during the first portion of the first year following onset of TIA when the chances of stroke may be well over 15%.

Treatment Related to the Heart

Arrhythmia

When a causal relationship is found between transient change in cardiac rhythm (an arrhythmia) and a focal transient cerebral ischemic attack (TIA) the cardiac dysrhythmia should be corrected. However, it has now been established by Reed et al. that a causal interrelationship is rare between transient focal cerebral ischemic attacks and episodes of cardiac dysrhythmia of the type associated with significant reduction in cardiac output. They noted that of 290 patients who received pacemakers for disturbances of cardiac rhythm or conduction, only 4 had focal neurological symptoms or signs, and only 2 (1%) had focal cerebral symptoms that could be temporally related to a specific episode of cardiac dysfunction. They reported that significant bradycardias and tachycardias commonly are associated with syncope, near syncope, jerking, or convulsions — all related to diffuse cerebral ischemia rather than focal ischemia.

It is necessary to make the distinction between the transient diffuse cerebral ischemia commonly associated with cardiac dysrhythmia in contrast to transient focal cerebral ischemia. Walter et al. studied 10-hour tape-recorded electrocardiograms in 39 ambulatory patients with “symptoms of cerebral ischemia.” Ten of these had transient cardiac arrhythmias or conduction abnormalities; 8 of these 10 “positives” occurred in the group of patients with symptoms of diffuse cerebral vascular insufficiency. The authors comment that “a transient cardiac arrhythmia is more likely to produce symptoms of diffuse cerebrovascular insufficiency.” Analysis of the material presented in other papers leads to a similar conclusion.

It is important to detect the existence of cardiac dysrhythmia as a cause of TIA and institute appropriate treatment.
Emboli

The role of various sources of emboli (other than from the carotid or verteobasilar arteries) including prosthetic cardiac valves, myocardial infarction, cardiac dysrhythmia and subacute bacterial endocarditis in the pathogenesis of TIA is not fully documented. In many instances cerebral emboli from these sources cause actual cerebral infarction, often of very severe degree.

The usual treatment for prevention of recurrent cerebral emboli from prosthetic heart valves has been the administration of oral anticoagulant on a long-term basis following surgery. However, Sullivan et al., reported that only 1 patient of 2 (553 months follow up) had 2 embolic events while receiving dipryidamole, whereas 9 of 50 patients (695 months follow up) had 17 embolic events while receiving anticoagulant and a placebo. Duvoisin et al. studied the risk of thromboembolism after insertion of prosthetic cardiac valves by constructing actuarial curves showing the proportion of patients with embolism at increasing time intervals postoperatively. This study suggests that the risk of thromboembolism diminishes with time, particularly by the third postoperative year. The risk of fatality averaged 15%; only 7% of the non-fatal embolisms resulted in significant continuing disability. Anticoagulation exerted a protective effect against emboli in patients having replacement of the aortic valve with a ball valve prosthesis, particularly when anticoagulant therapy was carefully controlled. The use of anticoagulant continues to be the recommendation made at Mayo Clinic except for homograft replacement valves where postoperative embolism is not as significant a problem as it is with prosthetic cardiac valves. The triad of rheumatic heart disease, mitral stenosis, and atrial fibrillation has long been associated with emboli to various organs, often the brain. Repeated episodes of many small emboli from the left auricle may produce transient episodes of cerebral ischemia as well as cerebral infarction. Although Askey and Cherry and Cosgriff reported anticoagulant therapy in recurrent thromboembolic events from a cardiac source, it is mainly on the basis of the observations by Wright and McDevitt that internists and neurologists administer oral anticoagulants to prevent recurrent thromboembolic events in patients with rheumatic cardiac disease. Wright and McDevitt found that the administration of coumadin anticoagulant to patients with rheumatic heart disease significantly reduced the chances of future cerebral emboli. Treatment is generally started after the first embolic event (wherever the site of the embolus) and continued for the life of the patient. Carter reported the recurrence rate after embolism (from a cardiac source) is about 50% in the first year and that this incidence could be significantly reduced in the first 6 months by using anticoagulant therapy. He noted that if rheumatic atrial fibrillation is the source of cerebral embolism, the anticoagulant therapy must be continued indefinitely unless normal rhythm is restored.

TIAs are frequent in subacute bacterial endocarditis and may be the initial symptom. Patients dying with subacute bacterial endocarditis usually have evidence of multiple small cerebral infarctions at autopsy. Cerebral infarction is a frequent cause of death in this condition. Treatment primarily consists of the administration of a suitable antibiotic. In 1945 Loewe reported that concurrent administration of penicillin and heparin appeared to be successful in the treatment of bacterial endocarditis. Dawson and Hunter noted no significant difference between a group of patients receiving penicillin alone and a group receiving penicillin and heparin. Thill and Meyer reported a significant incidence of fatal cerebral hemorrhage when penicillin and anticoagulants were used together to treat subacute bacterial endocarditis. This view continued until challenged by Lerner and Weinstein who believed it wise to use antibiotic and anticoagulant. In 1974, Kanis reported a patient with bacterial endocarditis who died from embolic cerebral damage after treatment with heparin. It would appear that it continues to be unwise to use anticoagulant in this situation.

Hypertension

It is clear that there is a highly significant interrelationship between hypertension and the frequency of stroke; hypertension has been categorized as a primary risk factor for stroke. However, the following data suggest that this is primarily a relationship between hypertension and the cause of stroke, and it is not known whether patients having transient ischemic attacks and hypertension are more likely to have stroke than patients with transient ischemic attacks who are normotensive. This does not reduce the importance of long-term control of hypertension in people with high blood pressure.

In the Veterans Administration Cooperative Study, evaluating the long-term effects of treatment of hypertension, in the subgroup of 143 patients with diastolic blood pressures of 115 through 129 mm Hg, the study was terminated after an average follow up of 18 months because of the high incidence of complications associated with hypertension occurring in the placebo group. In these 70 patients, there was 1 who had cerebral hemorrhage, 3 who had cerebral infarction, and 1 developed TIAs. In the 73 treated patients, there was 1 with cerebral infarction.

In the second Veterans Administration Cooperative Study, 31 of 380 patients with blood pressures averaging between 90 and 114 mm Hg diastolic, there were 19 cardiovascular deaths in the control group and 8 in the treated group. Seven of the deaths in the control group were due to stroke (4 hemorrhage, 3 infarction). In the treated group, there were no deaths due to brain hemorrhage and only 1 due to cerebral infarction. There were 20 patients total in the (both fatal and non-fatal) placebo group and 5 in the treated
An example of the confusion produced when dis-

group who had a stroke, a ratio of 4 to 1. Twelve

High blood pressure, of essentially any degree,

Treatmen Related to Blood Constituents

Clotting Characteristics — Anticoagulant

As is usual in therapeutic medicine, one must weigh

Accuracy of TIA categorization is fundamental to

would not be aware, when simply viewing the table, that

would be properly diagnosed and treated so that the

The average reader should be properly diagnosed and treated so that the patient is normotensive.

Treatment Related to Blood Constituents

Clotting Characteristics — Anticoagulant

As is usual in therapeutic medicine, one must weigh the beneficial results from treatment against the complications and other problems associated with the therapy. Because of the inherent danger in the production of hypoprothrombinemia, the following criteria must be present before short-term or long-term anticoagulant therapy is instituted in a hospital setting:

1. Accurate diagnosis of the category of cerebrovascular disease
2. A physician knowledgeable concerning the use of anticoagulants
3. A laboratory facility available which produces accurate clotting tests, and
4. No significant contraindications to the treatment.

In a hospital setting, active bleeding is the primary or absolute contraindication to the treatment. If there is any bleeding tendency, hepatic disease, renal disease, or extraordinarily severe hypertension, anticoagulants should be given only with extreme caution and high blood pressure must be prudently reduced. Out of hospital setting, if anticoagulant is to be administered for a longer period of time, additional qualifications must be met. These include:

1. Absolute cooperation of the patient and relatives in following instructions accurately and
2. Optimal control of arterial hypertension.

If these criteria are met, the serious complication rate is acceptable. There is no uniformity of opinion on the incidence of complications when anticoagulant is used to treat TIA. In the study of focal transient cerebral ischemic attacks reported by Baker and colleagues, there were no serious complications of anticoagulant therapy. In 5-year follow up studies at Mayo Clinic, 5% of treated patients developed intracerebral hemorrhage; however, 4% of patients not receiving anticoagulant also died of an intracerebral bleed. These observations suggest that the patient population being studied is one in which there is very significant chance of intracerebral hemorrhage (without any special form of therapy).

Accuracy of TIA categorization is fundamental to an attempt to evaluate realistically any therapy. This is especially true of any effort to define the natural history of transient focal cerebral ischemic attacks. An example of the confusion produced when dissimilar categories are lumped together is seen in “Anticoagulants and Cerebrovascular Disease — A Critical Review of Studies”, in which table 1 (Summary of Studies Evaluating Anticoagulant Therapy) lists 16 articles as sources of data. The average reader

Table 2 shows the data in 9 reports in which a direct attempt has been made to compare untreated patients suffering from transient ischemic attacks with those receiving anticoagulant drugs. It is recognized that variations occur in the individual patient responses to the effect of an anticoagulant. In each of these studies the anticoagulant was administered by personnel expert in controlling such treatment; even so, there must have been an unknown number of times when each patient probably had too much anticoagulant action or too little. The problem is somewhat similar to the precision with which it is possible to control diabetes mellitus or arterial hypertension. It is important to note the number of months of follow up in each study, to recall the long-term nature of the problem of observing the complications of atherosclerosis, and to reflect on the meaning of short periods of follow up. Some of the reports listed in table 2 are based on random selection of patients for treatment or no treatment and others rely on the assessment of large numbers of patients over long periods. The actual number of patients in 5 of the studies in table 2 is so small as to make comparison between the treated and untreated groups of only relative statistical significance. It is of interest that the percentage of individuals developing cerebral infarction was similar (spread from 3% to 7%) in all of the treated groups of each study except that of Toole et al. who reported that 13% (7) of 56 untreated TIA patients had a stroke compared to 29% (6) of 21 patients receiving anticoagulant. The authors add, “Of our 21 patients treated with sodium warfarin for periods ranging from six weeks to four years (average 27 months), 71% were asymptomatic during follow up, compared with 45% in the nontreated group.” More variation occurred in the percentage of individuals developing cerebral infarction in the control groups and only Pearce et al. reported a figure less than 23% with follow up that was under a year. Cerebral hemorrhage was the complication most feared. It occurred in 7% of the male patients receiving anticoagulant (Mayo series). During 5 years observation of similar untreated patients in an unrando...
Clotting Characteristics — Platelet Antiagglutinating Agents

Therapy must be considered, including thrombendarterectomy and the administration of antiplatelet agents; the greatest chance of cerebral infarction. When evaluating patients for treatment other types of platelet antiagglutinating agents are indicated.

Control value. The duration of treatment is uncertain; but rarely do patients with transient ischemic attacks stop while the patient is receiving anticoagulant. Untreated patients, in many instances, continue to have such transient episodes.

From the observations of cessation of transient ischemic attacks in patients receiving anticoagulant and, particularly, the lowered incidence of cerebral infarction while taking the drug, it is concluded on the basis of the combined reported experience that anticoagulant therapy decreases the risk of cerebral infarction in patients with transient ischemic attacks. In a carefully selected group of such patients, anticoagulant therapy is very worthwhile, provided the anticoagulant program is so managed as to keep the number of complications at a minimum. Today, aspirin, dipyridamole (Persantine) and sulfinpyrazone (Anturane) have been investigated in the laboratory and in some human clinical settings because of the effect on preventing blood platelet aggregation and/or adhesiveness. A direct relationship between these characteristics of platelets and the pathogenesis of transient ischemic attacks has not yet been firmly established except in the rare instance of thrombocytosis as reported by Levine and Swanson. Another instance of this rare disorder (actually treated with aspirin) was described by Mundall et al. When the clinician is confronted with idiopathic thrombocytosis, a trial of treatment with aspirin seems indicated.

Acheson et al. reported a controlled double-blind study of the effect of dipyridamole in 169 patients with known cerebrovascular disease. Each patient had partially or completely recovered from a clinical episode of focal cerebral ischemia. Eighty-five patients received dipyridamole and 84 received the placebo. The duration of the disease before the study was started ranged from 3 months to 5 years in both groups; the average period of observation was 11 months. No significant difference in the incidence of cerebral ischemic episodes was found when the drug-treated group was compared with the placebo-treated group.

**Table 2. Anticoagulant Therapy and Transient Ischemic Attacks**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Follow-up months</th>
<th>Cerebral Infarcts (Total)</th>
<th>Cerebral Infarcts (Late)</th>
<th>Cerebral Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Group</td>
<td>1963</td>
<td>160</td>
<td>60 mo.</td>
<td>51 (33%)</td>
<td>18 (11%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>175</td>
<td>60 mo.</td>
<td>7 (4%)</td>
<td></td>
<td>3 (2%)</td>
<td>13 (7%)</td>
</tr>
<tr>
<td>Cooperative Study</td>
<td>1962</td>
<td>20</td>
<td>20 mo.</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>24</td>
<td>18 mo.</td>
<td>1 (4%)</td>
<td></td>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Cooperative Study VA</td>
<td>1961</td>
<td>15</td>
<td>12.8 mo.</td>
<td>78 (53%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>22</td>
<td>9.5 mo.</td>
<td>71 (4.5%)</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Pearse, et al.</td>
<td>1965</td>
<td>20</td>
<td>10.6 mo.</td>
<td>2 (10%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>17</td>
<td>11.1 mo.</td>
<td>1 (5%)</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Baker, et al.</td>
<td>1966</td>
<td>30</td>
<td>40.6 mo.</td>
<td>*7 (23%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>30</td>
<td>37.9 mo.</td>
<td>2 (7%)</td>
<td>?</td>
<td>0**</td>
<td></td>
</tr>
<tr>
<td>Fisher</td>
<td>1958</td>
<td>23</td>
<td></td>
<td>8 (34%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>29</td>
<td>30 mo.</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Friedman, et al.</td>
<td>1969</td>
<td>23</td>
<td>27.4 mo.</td>
<td>**8 (35%)</td>
<td>0</td>
<td>1 (4%) SAH</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>21</td>
<td>27.4 mo.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Toole, et al.</td>
<td>1975</td>
<td>56</td>
<td>46 mo.</td>
<td>7 (13%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>21</td>
<td>46 mo.</td>
<td>6 (29%)</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Olson, et al.</td>
<td>1976</td>
<td>124</td>
<td>21 mo.</td>
<td>19 (51%)</td>
<td>3 (2.4%)</td>
<td>?</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>163</td>
<td>25 mo.</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

*Three patients randomized as treated had CI after A/C stopped.

**One cerebral hemorrhage in treated group but while on anticoagulant.

***One patient had been on A/C, but A/C was discontinued before the cerebral infarction.

Acheson et al. reported that 4% had brain hemorrhage. In table 2 no record is made of the number of transient ischemic attacks reported by treated and untreated patients. All reports indicate that for all practical purposes transient ischemic attacks stop while the patient is receiving anticoagulant; untreated patients, in many instances, continue to have such transient episodes.

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From the observations of cessation of transient ischemic attacks in patients receiving anticoagulant and, particularly, the lowered incidence of cerebral infarction while taking the drug, it is concluded on the basis of the combined reported experience that anticoagulant therapy decreases the risk of cerebral infarction in patients with transient ischemic attacks. In a carefully selected group of such patients, anticoagulant therapy is very worthwhile, provided the anticoagulant program is so managed as to keep the number of complications at a minimum. When patients with transient ischemic attacks are given coumadin anticoagulants, dosage should be regulated to keep prothrombin times approximately 2 times the control value. The duration of treatment is uncertain; but rarely do patients with transient ischemic attacks stop while the patient is receiving anticoagulant. Untreated patients, in many instances, continue to have such transient episodes.

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Harrison et al.38 treated 2 patients with amaurosis fugax attacks with 600 mg of aspirin daily. It was noted that in both patients the frequency of the attacks was decreased; this response appeared to be due to the effect of the aspirin.

In 1972, Evans39 described a randomized double-blind 6-week crossover trial of sulfinpyrazone in 20 patients with amaurosis fugax. Patients with greater than 70% carotid stenosis by angiography were excluded from the trial and treated surgically. All patients had eye symptoms, but 6 (3 from each group), in addition, had symptoms of weakness or paresthesias of the arms or legs. Thirteen patients showed a reduction in symptoms on sulfinpyrazone when compared with placebo. Two patients (1 in each group) had no reduction in the incidence of symptoms while taking sulfinpyrazone. These patients had only 30% narrowing of the carotid artery but in both there was an ulcerated plaque. These 2 patients were eventually treated surgically with relief of symptoms. This report suggested that the drug was effective for short-term reduction in the number of a certain type of transient cerebral ischemic attack — the study was not continued for a duration sufficient to answer the question about the prevention of cerebral infarction.

Dyken et al.40 described 26 patients in a retrospective study, 15 of whom were treated with aspirin (300 mg b.i.d.); the remaining 11 were not. No difference was noted in the incidence of cerebral infarction or death but only those who did not receive aspirin had subsequent TIA. The authors stressed that this study did not prove the effectiveness of aspirin but pointed to the need for a prospective investigation of the subject. Two cooperative studies of platelet antiaggregating agents' effect on transient ischemic attacks have been carried out — one in Canada and one in the United States.

The report of the American cooperative study of the effects of aspirin on cerebral ischemia41 is based on the analysis of 178 patients with TIAs who were randomly allocated to either treatment or placebo groups. Compliance with treatment was monitored as was evidence of patients in the control group taking aspirin or unknowingly using compounds with aspirin. After 6 months of follow up there was evidence of significant benefit in stopping TIAs in patients with multiple TIAs and in those with carotid artery lesions appropriate to the TIA symptom. "It cannot be inferred from this study that aspirin prevents stroke because when end points were restricted to death or cerebral or retinal infarction, there was no statistically significant differential between the aspirin and placebo treatments." It is of interest that when all study end points were grouped (TIAs, death, retinal and cerebral infarction) aspirin seemed to provide a significant benefit.

The Canadian cooperative study42 analyzed 585 patients with TIAs randomly allocated into 4 treatment groups: placebo, aspirin, aspirin with dipyridamole (Persantin) and dipyridamole alone, who were followed for 1,003 days. The study found significant evidence that aspirin protects against recurrent TIAs and ultimate cerebral infarction in men when compared to treatment with placebo or dipyridamole. There was no protective effect in women.

A second report is available from the Aspirin in Transient Ischemic Attack study.43 One hundred twenty-five patients with carotid TIAs had carotid surgery and were then randomized to aspirin or placebo treatment. Within 24 months 8 of 60 (13%) died who received aspirin after the carotid surgery. Six cardiovascular deaths occurred in the latter group; none in the former. It was concluded that "life table analysis that eliminated deaths which were not stroke-related revealed a significant difference in favor of aspirin." Thus, there is a different result in the 2 groups (medical and surgical) of patients in this study. The "aspirin question" remained uncertain. The physician may well ask: Is there any difference in the effectiveness of aspirin if: Cholesterol or other emboli are detected in the retina? The only symptom is amaurosis fugax? A bruit is present? The carotid or vertebrobasilar system is the site of the TIA?

**Polycythemia, Anemia, Hypoglycemia**

Millikan et al.44 reported 22 patients with some form of polycythemia and transient ischemic attacks. If found, polycythemia should be accurately diagnosed and promptly brought under control. It may be necessary to administer anticoagulants for a variable period depending upon the frequency and severity of the transient ischemic attacks. Siekert et al.45 noted a relationship in unusual instances between severe anemia and TIA, suggesting that the anemia be promptly treated and whatever additional study seems appropriate be conducted concerning the cause of the TIA. This same admonition applies to episodes of hypoglycemia.

**Transient Ischemic Attacks — Blood Constituents**

**Hyperlipidemia**

No direct relationship has been established between hyperlipidemia and TIAs or progressing stroke. Clofibrate (Atromid) is an agent which lowers cholesterol and triglycerides. In a short (7 months) clinical trial of clofibrate in patients with cerebrovascular disease, Acheson and Hutchinson46 suggested that its use reduced the incidence of transient ischemic attacks and recurrent cerebral infarction. A cooperative study47 in 20 Veterans Administration hospitals investigated the effect of clofibrate on morbidity and mortality due to atherosclerotic vascular disease in man with either an established cerebral infarction or TIAs. Recurrence of cerebral infarction was increased in patients receiving clofibrate as compared to controls while the incidence of new myocardial infarction and new TIA was similar in both groups. There was no correlation between pretreatment lipid (cholesterol and triglyceride) values and the results of therapy. There were too few cases with TIA for satisfactory analysis; however, the trends were similar to those of the entire group, with a failure to reduce recurrent vascular events but with an unexplained lowering in mor-
sitivity. There was nothing in this carefully designed study to suggest that the ingestion of clofibrate is directly effective in the treatment of occlusive cerebrovascular disease.

Treatment Related to the Arterial Wall

Vasospasm — Vasodilators

In 1891 Peabody observed a 56-year-old man who had 5 or 6 transient attacks of right hemiparesis. At autopsy there was neither cerebral infarction nor occlusion of a cerebral artery. Peabody wrote: “There might have been a spasmodic contraction of the muscular coat of the middle cerebral artery, or of several of its branches ... that this had occurred several times, causing each time temporary ischemia of important brain centers; and that in the final attack it had lasted long enough to produce death, but that it was not complete enough, or of long enough duration, to cause softening.” The term “vasospastic attacks” was used until the current concepts of TIA were developed. Vasospasm is thought to be the cause of the focal neurological phenomena in migraine; however, transient vasospasm has not been accepted as a common cause of TIA. Little has been written about vasodilators as treatment for TIA. Meyer et al. reported that papaverine, given orally in doses of 150 mg 3 times daily, was effective in preventing vertebrobasilar TIA. They recommended the long-term oral use of papaverine for patients with TIA's in the carotid system who are not suitable candidates for surgical excision of atherosclerotic plaques. Experience with carbon dioxide inhalation, hexobendine, and betahistine hydrochloride for TIA is inadequate.

Atherosclerosis — Surgery — Endarterectomy

Eastcott et al. were the first to report carotid surgery as treatment for TIA. Over 2 decades later the risk of carotid surgery and the results (stroke prevention) remain uncertain. Fields et al. studied 316 patients having transient ischemic attacks; 169 received surgical treatment and 147 received medical treatment. The follow up period averaged 42 months. Fifteen percent of the surgically treated patients had cerebral infarction (including postoperative complications) while 14% of those medically treated had cerebral infarction. The best results were in a subgroup of 94 patients with unilateral carotid stenosis; 45 were operated upon and 49 were treated medically. Six percent of the surgically treated patients had cerebral infarction while 12% of the medically treated group had cerebral infarction. Bauer et al. concluded that “1) surgical treatment appeared more beneficial for unilateral carotid stenosis in patients with transient ischemic attacks or a mild to moderate neurological deficit, 2) nonsurgical treatment produced better results for unilateral carotid artery stenosis in patients with a moderate to severe neurological deficit, 3) nonsurgical treatment appeared more beneficial for combined unilateral carotid artery stenosis and contralateral carotid artery occlusion of patients who had a moderate to severe neurological deficit, 4) nonsurgical treatment appeared more beneficial for patients with completed strokes who had a marked and persistent neurological deficit.”

The results of carotid surgery for TIA reported in 8 papers in the last decade are shown in Table 3. Combined operative mortality and morbidity rates vary from 0 to 23 percent. Total deaths, although there is some variation in the follow up period, are quite similar; in each report the most common cause of death was myocardial infarction or some form of heart disease. If one subtracts the number of patients (for each report in the table) having operative morbidity from the total number suffering cerebral infarction, the number of patients having cerebral infarction during the period of follow up is obtained.

Physicians active in the clinical cerebrovascular field are moderately to greatly enthusiastic about surgical treatment for carotid system TIA when an appropriate carotid lesion is discovered. However, greater uncertainty exists concerning the value of carotid endarterectomy for nonhemispheric transient ischemic attacks as reported by Ford et al. Fifty carotid endarterectomies were performed on 46 patients. Dizziness was the most common symptom while some patients had drop attacks, others bilateral visual blurring, syncope or dysarthria. Ninety-five percent of the patients were said to be improved and at follow up (average, 15 months) 31 (67%) of the 46 patients were asymptomatic, 13 (28%) improved and 2 (4%) unchanged. Easton and Sherman found considerable risk from carotid endarterectomy. They analyzed 228 consecutive operations done in 2 large community hospitals in a midwestern community. Surgery was performed by either certified neurologist or vascular surgeons. There was a combined stroke morbidity and mortality rate of 21.1%. Among the 57 patients with

![Table 3: Surgical Therapy and Transient Ischemic Attacks](https://www.ahajournals.org/doi/abs/10.1161/01.STR.9.4.306?journalCode=stro)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Operative deaths</th>
<th>Operative morbidity</th>
<th>Follow-up (Months)</th>
<th>Normal</th>
<th>Total cerebral infarct</th>
<th>Total deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson</td>
<td>1968</td>
<td>151</td>
<td>0</td>
<td>0</td>
<td>48</td>
<td>?</td>
<td>?</td>
<td>36 (28%)</td>
</tr>
<tr>
<td>Fields, et al.</td>
<td>1970</td>
<td>169</td>
<td>6 (3%)</td>
<td>13 (8%)</td>
<td>42</td>
<td>70 (41%)</td>
<td>25 (15%)</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Wylie and Ehrenfeld</td>
<td>1970</td>
<td>129</td>
<td>0</td>
<td>0</td>
<td>48</td>
<td>?</td>
<td>?</td>
<td>36 (28%)</td>
</tr>
<tr>
<td>DeWeese, et al.</td>
<td>1971</td>
<td>187</td>
<td>4 (2%)</td>
<td>19 (10%)</td>
<td>24</td>
<td>190 (58%)</td>
<td>157 (20%)</td>
<td>30 (27%)</td>
</tr>
<tr>
<td>Nunn</td>
<td>1972</td>
<td>103</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
<td>60</td>
<td>53 (53%)</td>
<td>17 (17%)</td>
<td>33 (34%)</td>
</tr>
<tr>
<td>Toole, et al.</td>
<td>1973</td>
<td>82</td>
<td>3 (6%)</td>
<td>14 (17%)</td>
<td>46</td>
<td>31/72 (71%)</td>
<td>13 (16%)</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Easton and Sherman</td>
<td>1977</td>
<td>24</td>
<td>4 (17%)</td>
<td>13 (87%)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*57 patients had the operation on the symptomatic carotid; 16 on the contralateral carotid.
TIAs the stroke morbidity and mortality rate was 21%. Eleven patients operated on for asymptomatic carotid bruit had a stroke morbidity rate of 18.2%. This report suggests that the general risk of carotid surgery is higher than that found in large medical centers where patient selection is more rigorous than in the country as a whole.

The subject of neurosurgical microsurgical anastomosis for cerebrovascular disease, principally connecting a superficial temporal artery to a branch of the middle cerebral artery, is being actively explored in a number of institutions. Thus far no statement can be made about the efficacy of this procedure. Reichman recommended a collaborative study of such procedures using randomized selection of patients. He suggested that some indications (for the operated group) might be: middle cerebral artery occlusion, intracranial carotid stenosis or occlusion with TIA, as well as some less frequent items such as giant aneurysm and small branch occlusions. Reichman had performed the operation on 78 patients and, in many of them, had been able to document an increased rate of flow in the territories supplied by the surgically anastomosed vessel.

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