A PROGRESSING STROKE refers to that temporal clinical category where progression or an increase of severity of the neurological signs has occurred within recent minutes. This diagnosis is made from analysis of the patient's history and by repeated examination. When a patient is admitted to the hospital with a moderate neurological deficit in his right arm, who on re-examination is worse, his stroke is considered to be progressing. If the deficit is the same, progress may be completed, and if the defect has disappeared, the diagnosis is usually a transient ischemic attack (TIA). When an area of the brain believed to be ischemic or infarcted is supplied by the carotid arterial system, 18 to 24 hours without progression is needed to be sure that further progression is unlikely. Then the patient's clinical temporal status is no longer categorized as "progressing stroke." When an area of the brain believed to be ischemic or infarcted is supplied by the vertebrobasilar system, a longer period (up to 72 hours) should pass before the patient is believed to have no further chance of progressing and is diagnosed as having a "completed stroke." Progression may be periodic and episodes of progression may be separated by hours or minutes, especially when circulation to the brainstem is impaired.

Diagnosis

The physician confronted with a patient whose paresis or speech impairment is worsening over minutes or a few hours, needs to have a clear program for action. The highest priority must be given to precise diagnosis. If a diagnosis of progressing stroke is made (stroke-in-evolution) immediate action to stop progression is indicated, as once such progression is apparent there is no evidence that cerebral infarction is reversible. Preventive therapy, if available, is the most important action.

In the diagnosis of progressing stroke it is desirable to differentiate between impaired brain function due to a decreased blood supply from the carotid arterial system and impaired function caused by decreased blood supply in the vertebrobasilar arterial systems. The clinical situation for progressing stroke due to carotid artery insufficiency generally includes some evidence of monoparesis or hemiplegia with or without a homonymous visual field defect and includes often some degree of impairment of speech and language and evidence of partial to full sensory perception loss on the opposite side of the body. The combination of symptoms and signs associated with vertebrobasilar occlusive events is more complex. The most common symptoms include impaired motor functions such as weakness, clumsiness, or paralysis involving any combination of the limbs with evident signs of cortico-spinal tract dysfunction associated with unilateral or sometimes bilateral cranial nerve paralysis, most often oculomotor, or evidence of trigeminal or facial nerve impaired function. A "crossed" defect (motor or sensory on the one side of the face and opposite side of the body) is considered unequivocal evidence of impaired brainstem function until proven otherwise. If motor or sensory abnormalities are bilateral and impaired with cranial nerve function, this too indicates brainstem involvement.

Physical Examination

The physical examination of a patient suspected of having an acute progressing stroke must proceed immediately. It is important to emphasize the neurovascular examination, which includes:

1. Inspection of peripheral vessels (i.e., temporal, radial, pedal arteries)
2. Palpation of vessels
3. Auscultation over vessels at cranial and cervical sites to detect bruit
4. Ophthalmoscopy
5. Ophthalmodynamometry

1. Inspection of Peripheral Vessels. A prominent, tortuous temporal artery often indicates cranial arteritis, which is a possible but an unusual cause of stroke. Significant arterial change can be detected by inspecting the superficial temporal arteries, coupled with palpation.

2. Palpation. The superficial temporal artery, the cerebral vessels in the neck, the radial and the pedal arteries should always be palpated. When palpating the cervical cerebral vessels, this should be performed gently to discover changes of arterial pulsations. Minor differences in the pulses from the 2 sides may be difficult to interpret. It is possible but difficult to distinguish a pulse coming from the first portion of the internal carotid or from the external carotid artery. Atherosclerotic lesions in cervical vessels may be ul-
cerated or covered by thrombi; both situations carry the risk of dislodging emboli during manipulation of the arteries.

3. Auscultation. Auscultation over cervical vessels may detect evidence of altered patterns of blood flow. A bell stethoscope is most useful. First the aortic valve is auscultated and then the stethoscope is moved (1 cm or less at a time) upwards. This is needed to determine if cardiac sounds are transmitted to the innominate, subclavian, common carotid or internal carotid arteries. The patient should be sitting or lying supine with face forward. This position is less likely to create sounds which are difficult to interpret. When respiratory sounds make auscultation difficult the patient is told to “stop” breathing for a few seconds. Bruits localized over extracranial cerebral vessels, such as the common and internal carotid arteries, are reliable indicators of sites of turbulent flow caused by arterial obstruction.4•

4. Ophthalmoscopy. This provides an opportunity to inspect blood vessels that are a direct continuation of the internal carotid arterial system. Sometimes, little use is made of this simple method of obtaining important clinical data. The retina must be inspected carefully for arterial or venous occlusion, including emboli, such as cholesterol, platelet-fibrin, calcific (mixed or foreign body), and changes such as hemorrhages, cotton wool patches, venous stasis, microaneurysms, vessel narrowing associated with arterial hypertension, papilledema, and ischemic retinopathy.5 The importance of detecting a retinal embolus or emboli in the diagnosis of TIA or progressing stroke has been demonstrated. The most common observed emboli are made up of cholesterol crystals which appear as shiny orange-yellow plaques, often localized at the bifurcation of retinal arterioles.6• The cholesterol plaque may appear wider than the arteriole as one is looking at the outer dimension of the column of red blood cells, rather than the wall of the arteriole. Pressure on the eye may change the position of the embolus and the material may then appear to glisten or change shade, a characteristic sometimes referred to as a heliographic reflection. These bright, orange-yellow plaques do not seem to impede blood flow. Such emboli move distally and disappear. One or more cholesterol retinal emboli usually signifies an ulcerated atheromatous carotid (internal) lesion until proved otherwise. An important embolus in retinal vessels consists of blood platelets and fibrin, and is usually grey-white in color. These may be long and move through an arteriole but are commonly stationary.6• Eye pressure does not cause this type of embolus to move and there is no heliographic reflection. These emboli block flow and there may be retinal infarction. The source for retinal emboli is usually an atheromatous plaque at the origin of the internal carotid artery.

Another type of retinal embolus may consist of calcium particles which are white in color and stationary. Calcium emboli are believed to come from heart valve lesions. Other observed retinal emboli consist of septic material such as talc and cornstarch.

5. Ophthalmodynamometry. This measures arterial pressures both systolic and diastolic in the main retinal branches of the ophthalmic artery.10• 11 When the retinal artery pressures are different in the 2 eyes it becomes clinically significant. A difference in pressure between the eyes of 15 to 20 percent is a reliable sign of stenosis or occlusion of the internal carotid artery on the side of the lower pressure. Retinal arterial pressures can be equal and normal with unilateral carotid stenosis or occlusion because collateral blood supply develops. Following internal carotid artery occlusion, the ipsilateral retinal arterial pressure is reduced and the return of retinal artery pressure depends on how rapidly collateral circulation develops. If retinal pressure decreases significantly while brachial arterial pressure remains normal as a patient stands up (ocular orthostatism), this is important evidence of carotid occlusive disease.

Laboratory Examination

The need for laboratory tests is determined by the initial history and physical examination. Recent precardial pain and cardiac dysrhythmia should prompt an electrocardiogram as the first test performed. Computer assisted tomography (CAT scan) has radically altered the program of differential diagnosis of stroke.12 A CAT scan should be done in the first hours following the admission of the patient with progressing stroke. The scan may be normal unless the infarction is hemorrhagic—an important clinical distinction. This diagnostic method has become so useful that it is common practice to perform a scan before the patient is admitted to a hospital bed.

Urine is collected for urinalysis and blood tests started. Basic laboratory tests, including red blood count, white blood count, differential blood count, blood hemoglobin, hematocrit, platelet count, sedimentation rate, fasting blood sugar, creatinine or urea, prothrombin time, cholesterol, triglycerides, uric acid and a test for syphilis should be promptly performed. The patient should be screened for renal dysfunction and a prothrombin time determined for baseline values. This laboratory screen will make it possible to diagnose such disorders as polycythemia which are known to carry the risk of a high incidence of focal cerebral vascular disease. Recently, questions have been raised about the role of even moderate elevations of hemoglobin and hematocrit as risk factors for stroke.

If cranial arteritis is present the sedimentation rate is almost always elevated. A diagnosis of cranial arteritis must be made quickly as there is a risk of permanent impairment of vision if treatment is delayed.

Where CAT scanning is available, examination of the cerebrospinal fluid is carried out only if meningitis or abscess are suspected or where the scan shows small amounts of bleeding.

In the usual patient with progressing stroke, the electroencephalogram does not add significant information and is not necessary in the work-up of the patient.
Non-invasive studies using Doppler flowmeters and ultrasound, however, may indicate extracranial carotid stenosis or occlusion but they rarely give significant information concerning the nature of the brain lesion and they are not accurate enough to replace arteriography.12-14

In hospitals where CAT scanning is available, the static brain scan in the differential diagnosis of progressing stroke is not useful.

Cerebral Angiography

In hospitals where arteriography has a low complication rate (complications less than 1/2 of 1%), the indications for its use in progressing stroke are:15-17

1. If there is a question about the differential diagnosis of the brain pathology not settled by the CAT scan.
2. In early progressing stroke (or very frequent TIAs) in the carotid system, where there is a history of amaurosis fugax, an appropriate bruit, retinal emboli, etc. suggesting the development of increasing carotid stenosis or an ulcerated atherosclerotic plaque.
3. When there is difficulty in making a clear clinical distinction between the carotid and vertebrobasilar system circulatory failure causing the progressing stroke.
4. When the clinical diagnosis of progressing stroke is not accurate and the patient is believed to have had a lengthy carotid TIA, then angiography needs to be done to identify the site of the lesion.
5. CAT scan evidence of brain edema, shift or intracranial or intracerebral bleeding.

Angiography should not be performed if the patient has:

1. decreased level of consciousness.
2. a severe, focal neurological deficit.
3. clearly an evident cardiac source for emboli.
4. acutely defective heart function.
5. CAT scan evidence of brain edema, shift or intracranial or intracerebral bleeding.

Prognosis

Little has been written about prognosis for patients with progressing stroke. Mortality statistics for patients with progressing stroke vary, depending on the type of hospital where treatment is given, the population being hospitalized and availability of intensive care units. The natural history of acute progressing stroke is quite variable which makes it desirable to compare treated and untreated patients. In 195516 204 consecutive patients with acute onset of progressing stroke believed to be due to disease in the carotid arterial system were reported. Within 2 weeks after onset, 12% of the patients were normal, 5% had some degree of monoparesis, 60% had some degree of hemiparesis and 14% died.

In the literature, usually little or no distinction is made between patients who have progressing stroke in the parts of the brain supplied by the vertebrobasilar artery and in parts of the brain supplied by the carotid artery. Treatment with anticoagulant indicated* that 8.5% of patients with acute progressing stroke in the brainstem died, but among untreated patients 58.9% died.

In studies where treatments are compared, it is necessary to include only those with onset of symptoms in the preceding hours. Patients included in a study with an onset of a focal neurologic focal deficit beginning 48 or 72 hours prior, will contain many in whom the process has reached its maximum degree and who could not be considered as having progressing stroke. From that point the natural history is one of improvement. Including such patients in a study of treatment biases the results in favor of the treatment. Jones and Millikan18 reviewed the records of 179 consecutive patients with acute cerebral infarction due to carotid artery system disease in order to analyze the clinical events during the first week. Patients admitted to the hospital within 26 hours of the onset of the first symptom were included. At the end of the first week, 39% were stable (unchanged) and 35% had gradually improved. In 19%, a progressing neurological deficit occurred which stopped within 48 hours of the onset. A remitting-relapsing course during the first 36 hours was observed in 6 patients (3%) and 8 patients (4%) became worse after 48 hours after being stable or improving. For the entire group, the mortality was 11%. A "high risk of death" group was identified in which the mortality was 41% for patients with any evidence of a decreased level of consciousness and hemiplegia on admission. Among the 67 patients with hemiplegia or a similar neurological deficit, who had normal consciousness when admitted, only one died giving a mortality of less than 2%. These percentages are useful in comparing a possible new therapy to earlier treatments. In medical centers, if there is a large population of patients with acute cerebral infarction, it is desirable to determine similar percentages, as such data can be used to compare new treatments in that particular hospital.

Treatment

When confronted with a patient with progressing stroke what treatment can be offered? Treatment is divided into general and specific therapy.

General Therapy

General therapeutic measures available for the patient with a progressing stroke are similar to those given to other ill patients. The nature of the treatment is governed by whether there are alterations in the level of consciousness. Patients with progressing stroke usually have no depression of consciousness but some with progressing stroke in the vertebrobasilar system can become comatose and will require special measures including careful attention to the airway and removal of excessive secretions. Patients with brainstem infarction may have respiratory insufficiency and may need assisted ventilation. The need for assistance is determined by the ventilatory rate and depth and arterial oxygenation.

The patient should be examined to determine ab-
normalities in heart size and rhythm and signs of congestive heart failure. When present, these conditions must be treated rapidly during the evaluation of the patient’s neurologic defect with suitable anti-arrhythmic drugs and diuretics.

Measurement of blood pressure on several occasions is essential to determine if progressing stroke is due to hypertensive encephalopathy. Patients with progressive stroke may be known to be hypertensive before the onset and at times hypertension becomes evident during the acute episode. If the blood pressure is not excessively elevated, it is usually not necessary to lower it but if the decision is made to reduce blood pressure, it must be done slowly. Precipitious lowering of blood pressure can increase cerebral ischemia by reducing cerebral blood flow in parts of the brain with deficient vascular autoregulation.

Patients who become comatose need careful attention to pressure areas on the skin. This problem should not be overlooked as bedfast patients easily develop ischemic ulceration of the skin which is difficult to heal.

A patient with a brainstem stroke may develop urinary retention or incontinence. Preferable treatment is intermittent catheterization with sterile techniques carried out through the acute phase rather than to use an indwelling catheter with its attendant risk of infection.

Patients with progressive stroke may vomit and they must be protected from aspiration, if the level of consciousness is depressed. Acute stroke may lead to gastro-intestinal ulceration and bleeding. If this occurs, suitable anti-acid medications should be used.

Bowel action is often impaired and patients easily become impacted which requires prompt attention, especially if the patient becomes obtunded.

When brainstem infarction results in paralysis of eye closure, attention must be paid to protect the corneal surface and keep it from drying or ulcerating. Usually taping the eyes shut is the only treatment needed.

Nutrition and adequate fluid and caloric intake require approximately 2,000 cc's of fluid per day and a 1,000 calorie intake per day. This should be given in small feedings but it may be necessary to give food and fluids intravenously.

If patients become febrile during an acute progressive stroke, it is important not to overlook an infection. The physician should never miss the possibility that the patient has an undiagnosed infectious disease. Elevations in body temperatures should not be dismissed as being solely due to neurologic deficits when seizures occur during a progressing stroke, anticonvulsive medication should be used.

Patients who have pain as they develop an acute stroke can be managed by careful positioning and frequent changes of position. Small amounts of aspirin can be given or a small amount of codeine usually relieves the patient of discomfort.

Specific Therapeutic Measures

The aim of therapy in progressing stroke is to stop progression. This is attempted by maintaining substrates for tissue metabolism through maintenance of blood delivered and removed from brain tissue. To attain this goal treatment may be directed at a number of factors which include:

1. Interference with the capacity of the heart to provide normal cerebral blood flow.

2. Conditions which alter blood and reduce neurometabolic substrate; conditions which cause thrombus formation and alterations in blood constituents — anemia, polycythemia, hyperlipidemia and hyponatremia.

3. Arterial lesions which cause occlusion or thrombus formation (these include atherosclerosis, arteritis, etc.).

4. Protection of neuronal metabolism by methods such as hypothermia, steroids, etc.

1. Cardiac Disorders

Cardiac disorders may interfere with cerebral perfusion by cardiac failure, cardiac dysrhythmia, embolus formation and excessive elevations of blood pressure. Cardiac arrhythmia occurring in a patient with progressing stroke may be associated with a recent myocardial infarction, an independent entity, or be associated with valvular disease. The physician must determine whether an arrhythmia has pathogenetic significance in the development of progressing stroke, particularly in producing a cerebral embolus. If there is a causal relationship, the change in cardiac rhythm should be corrected.

Cardiac emboli may be a more frequent cause of progressing stroke than suspected. Carter has reported that usually cerebral emboli are caused by mitral stenosis, myocardial infarction or atrial fibrillation or a combination of these. Cerebral embolism occurs most commonly within the first 6 weeks after a myocardial infarction. Anticoagulant therapy has been recommended to prevent emboli in these situations but it also acts to improve the cerebral lesion itself. Such treatment is reported to decrease overall mortality (Carter, Wells, McDevitt). All reports conclude that the reason for using anticoagulant therapy is to prevent further emboli from forming and going to the brain. Whether anticoagulant therapy should be started immediately for patients with progressing stroke caused by an embolus from the heart is a difficult clinical question which arises because of the possibility of increased risk of bleeding into the infarcted tissue, with bleeding made more likely by anticoagulant treatment. Experimental studies in dogs have shown that cerebral infarction is more hemorrhagic when anticoagulants were given after embolization as contrasted to a control group. Recurrent embolization can happen within a few hours after the first clinically evident embolus, so there is reason to begin anticoagulant therapy as early...
as possible when there is evidence that progressing stroke is not accompanied by gross intracerebral bleeding. This question can be settled by using the CAT (head) scan and by examination of the spinal fluid for blood.

Chronic rheumatic heart disease is a frequent source of cerebral embolism when there is atrial fibrillation. The incidence of embolism is reported to be 1.5% per patient year for a group of 754 patients with chronic rheumatic heart disease. When atrial fibrillation was present, it was 7 times higher than when there was normal sinus rhythm, but "anticoagulant treatment reduced the incidence of embolic recurrences." Freeman and Wexler reported the effect of treatment with anticoagulants on morbidity and mortality associated with chronic atrial fibrillation and organic heart disease. Among 300 hospitalized patients with decompensated hearts and atrial fibrillation for more than 18 days, 100 patients served as a control group, 100 patients received quinidine sulfate and bishydroxycoumarin (Dicumarol) and 100 received only anticoagulant. Death and non-fatal emboli were decreased most in the patients who were given anticoagulant alone. The report concludes that, "anticoagulant and conversion to normal sinus rhythm would seem to offer the best prognosis for patients with organic heart disease and chronic atrial fibrillation."

If an embolus comes from prosthetic heart valves, the usual means of prevention of recurrence has been oral anticoagulant medication. Sullivan et al. have reported one patient of 42 (553 months follow up) with 2 emboli who received dipyramidole and anticoagulant, and 9/50 patients (695 months follow up) with 17 emboli who received anticoagulant and a placebo. Duvoisin reports the risk of thromboembolism from prosthetic heart valves declines over time, particularly by the third postoperative year. A physician with a patient having a progressing stroke from this cause should consider giving anticoagulants to prevent additional emboli.

Patients with rheumatic heart disease with mitral stenosis (with or without atrial fibrillation) have emboli to various organs, often the brain. Giving oral anticoagulant to such patients has been found to be the preventive treatment of choice through the work of Owren, McDevitt, Fleming and Bailey, Adams et al. and Wright and McDevitt. Treatment is started after the first embolus, whatever the site. A physician must make a decision on the time to begin anticoagulant therapy since the need is to prevent further emboli. Carter reported that the recurrence rate for this type of embolism is about 50% during the first year but that the incidence can be reduced in the first 6 months by giving anticoagulants. When rheumatic atrial fibrillation is the cause of cerebral emboli, anticoagulant treatment must be continued indefinitely unless sinus rhythm returns. Generally, anticoagulant therapy is begun immediately by giving intravenous heparin if the neurological defect is associated with normal consciousness and mild hemiparesis. When a neurological deficit is marked, it is better to wait 3 to 5 days before beginning treatment as in this instance an embolic infarction can be hemorrhagic and could be made worse by immediate anticoagulation.

Progressing stroke can be caused by emboli following bacterial endocarditis. In this situation the role of anticoagulation is unclear. Loewe found that administration of penicillin and heparin was successful in the treatment of bacterial endocarditis, but Dawson and Hunter found no difference between patients receiving penicillin alone and those given penicillin and heparin. Thill and Meyer reported an increased incidence of fatal cerebral hemorrhage when penicillin and anticoagulants together were used as treatment for subacute bacterial endocarditis. Lernere and Weinstein believed that antibiotics and anticoagulants should be used for the same reasons that they are considered for persons not having endocarditis. In 1974 a patient with bacterial endocarditis with emboli, who died from cerebral damage after treatment with heparin, was reported by Kanis. It is generally considered to be unwise to give anticoagulants to such patients.

When cardiac output is impaired from primary cardiac failure or from hypertension, the cardiac output should be returned to normal, if possible, by suitable treatment.

Hypertensive encephalopathy is, in fact, a form of progressive stroke. The diagnosis of "hypertensive encephalopathy," is specifically reserved for patients with a stereotyped sequence of clinical events of serious, important, and dramatic development. It occurs in patients with moderate or severe hypertension and is associated with an increase in severity of the high blood pressure in a few hours time. The usual symptoms include intense headache, often associated with nausea and/or vomiting, and alterations in consciousness with semi-stupor or stupor progressing to coma and convulsions. Hypertensive retinopathy is generally found, as is some degree of renal impairment. The cerebrospinal fluid pressure is increased but examination of the fluid is commonly normal. To these basic features of hypertensive encephalopathy are usually added focal neurological signs, which on repeated examination may increase, thus constituting a progressing stroke. The addition of these focal neurological signs must be found with the syndrome described. Immediate control of the hypertension is needed and constitutes a medical emergency. The arterial pressure should be lowered before decreased consciousness begins because hypertensive encephalopathy treated can reverse all symptoms. The patient who becomes stuporous or comatose may respond slowly or not at all to a reduction of blood pressure. Sodium nitroprusside, prepared for intravenous use, is the most suitable treatment and is now widely available. This medication can produce a satisfactory lowering of blood pressure, but using it re-
quires constant monitoring of the patient by experienced personnel. Blood pressure should be reduced promptly, but it should not be precipitously reduced as brain ischemia and/or myocardial ischemia can result, especially if the diagnosis is not correct. Continued careful attention to blood pressure control is mandatory, usually for the remainder of the patient's life. For the patient with the usual progressing cerebral infarction, hypertension should be treated cautiously and the blood pressure should not be reduced as quickly as for hypertensive encephalopathy.

**Blood Constituents**

Treatment of progressing stroke may involve changing the characteristics of the blood constituents by the use of anticoagulant, platelet antiagglutinating agents, agents such as low molecular weight dextran, and fibrinolytic drugs. In addition, care should be given for a variety of phenomena, including polycythemia, anemia, hypoglycemia, etc.

**Anticoagulant Medication**

For the patient with an acute progressing stroke who is to be treated with anticoagulants there is often uncertainty about whether intracerebral bleeding is present. The question can be answered with satisfactory accuracy, as the CT head scan is nearly 100% accurate in determining an intracranial hemorrhage and it should be used in the initial evaluation. When there is no evidence of bleeding, heparin is started intravenously because of the acute, usually emergency nature of a progressing stroke. High blood pressure must be appropriately and carefully controlled. When the patient is hemiplegic and/or has a depressed level of consciousness, it can be assumed that maximum ischemia is probably present and progression of focal ischemia is unlikely. In this situation, it is not advisable to start heparin. Where treatment with heparin is initiated, it is usual to continue therapy with an oral anticoagulant. Treatment with anticoagulant is continued during the period of hospitalization and sometimes for 1-2 months after.

Table I summarizes the studies reported in the literature of the use of anticoagulants in progressing stroke. These studies are relatively comparable. In each study an evaluation was made of the patient as to whether progression of the neurologic deficit had occurred in the preceding few minutes. Frequent re-evaluations were made and later comparison between the maximal neurologic deficit which developed and the neurologic deficit evident at the start of the study was made. The number of patients having progression of their neurologic deficit in both groups, control and treated, for each study reported is shown. In every report, the patients treated with anticoagulant fared better than those who did not receive the anticoagulant. In one report 20% of those treated with anticoagulant progressed after entry into the study and 52% of those who did not receive anticoagulant progressed. The report of the National study is difficult to interpret but it is included since patients were randomized for treatment of control. In Fisher's personal study, the number of patients is small for statistically significant results, but the trend is definite, as 21% of the treated patients progressed, and 64% of those not receiving anticoagulant progressed.

The report of the cooperative group also supports this trend, as twice as many non-treated patients progressed as compared to patients receiving anticoagulant. In reports it is often difficult to find a detailed description of anticoagulant treatment. The recent report from Massachusetts General Hospital concerning symptomatic middle cerebral artery stenosis in 16 patients indicates that medical therapy, including anticoagulant, should be initiated early, before the occurrence of complete occlusion but the duration of therapy is unclear. The chance of in-

### Table 1: Treatment of Progressing Stroke With Anticoagulants

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<td>Percent progressive</td>
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tracerebral hemorrhage associated with anticoagulant treatment increases greatly after one year of treatment and it is reported as being small during acute treatment. In a report of 9 patients who developed intracerebral hemorrhage while taking anticoagulant, 8 had been on treatment for more than one year.

If hypertension is present, it must be controlled at the time anticoagulants are considered during treatment and should continue to be controlled. The report of Marshall and Shaw on a controlled trial of anticoagulant therapy in 51 patients with acute nonembolic, non-hemorrhagic cerebral vascular accident concluded that anticoagulants were not of value. All of the patients included in this trial had severe and persistent damage to brain function during the 72 hours before admission, and the extent of the neurologic damage was not reported. It is likely that many of those included had completed stroke which does not respond to treatment with anticoagulants when begun 72 hours after onset of symptoms. It is possible that many patients with severe neurological damage had cerebral edema and there is no effective means to reverse this catastrophic situation.

In the carefully performed investigations of acute progressing stroke treated with anticoagulant, each study points to fewer patients progressing when receiving anticoagulant, compared to those not getting such therapy.

**Platelet Antiaggregating Agents**

Unfortunately there are no current reports of the effectiveness or lack of it, in the use of platelet antiaggregating agents for progressing stroke.

**Dextran Therapy**

In a study by Gilroy, 100 patients with acute cerebral infarction or progressing stroke due to thromboembolism were assigned in a random manner to receive continuous intravenous treatment with dextran-40 for 3 days, or (the second group) an equal volume of fluid without the dextran-40. Each patient is reported to have had the onset of moderate to severe neurological deficit without improvement 24 to 72 hours before being accepted into the study. This report did not separate out progressing stroke. The patients were not divided into those who had their stroke 70 hours before treatment or 6 hours before. Successive evaluation of the neurologic status of each patient indicated that the group treated with dextran-40 had a lower mortality and better "quality of survival" than the untreated patients. Anaphylactic reaction to an intravenous infusion of dextran-40 has been reported.

Spudis et al. randomly treated 50 patients with dextran-40 who had onset of moderate to severe unimproving weakness or paralysis of less than 24 hours duration. They reported that "a greater percentage of dextran-treated patients improved with respect to consciousness and strength in upper and lower extremities but showed less restoration of language than the untreated patients." However, the differences in the 2 groups were not significant.

Kaste et al. performed a double blind trial by selecting 2 groups of patients with acute stroke. In each patient treatment started 24-29 hours after the onset of symptoms. The group that received intramuscular dexamethasone combined with intravenous low-molecular weight dextran showed no difference in mortality or neurologic status compared to the other group that received placebo. Random selection by Matthews of 2 groups of patients, 52 treated with dextran-40 and 48 in a control group, who were thought to have had a cerebral infarction during the previous 48 hours, indicated that, "in the treatment group mortality in the acute stage of patients with severe strokes was significantly reduced but survivors were severely disabled and 6 months later no significant benefits could be detected. In less severe strokes no effect of treatment was found." The results of these many reports indicate that no wide-spread enthusiasm for this treatment has developed and, most important, it should never be the exclusive treatment for progressing stroke.

**Fibrinolytic Agents**

The possibility that a thrombolytic drug could lyse a clot which obstructed arterial flow has always been an attractive one. This form of treatment should be possible for progressing stroke. Meyer et al. reported a study of the effect of an intravenous infusion of streptokinase, treating 73 patients. The study was terminated because the therapy was found to be detrimental to patients with progressing stroke. Fletcher et al. studied 31 patients with acute cerebral infarction and treated them with urokinase, each for about 10 hours. He found a prompt sustained increase of plasma thrombolytic activity but hemorrhagic complications occurred in several patients. He did not indicate a favorable therapeutic effect. Hannaway et al. reported in detail the clinical and pathological studies of 4 patients in Fletcher's series who developed cerebral hemorrhage during or within 24 hours of urokinase treatment. The ability to make a more accurate diagnosis of acute cerebral arterial obstruction due to thrombus and improved technology to administer and measure thrombolytic agents, might make this form of treatment feasible in the future.

**Alterations in Circulating Blood Constituents**

**Polycythemia**

There are no comparative studies to guide treatment of polycythemia, anemia and hypoglycemia in patients with an acute progressing stroke. Kannel et al. have reported, "men with hemoglobin values of 15 gm or greater and women with 14 gm or more had twice as many cerebral infarctions as did their cohorts with lower values." Tohgi reported on the relationship between the incidence of cerebral infarction and the level of the hematocrit in 432 consecutive
patients who came to autopsy. These patients had an average age of 77.1 years. If the hematocrit was above 46%, the incidence of cerebral infarction was higher. He also noted an increase in the frequency of stroke in patients with severe atherosclerosis when compared with those with small amounts of atherosclerosis. Thrombotic cerebral events have been reported to occur in 7 to 15 or more percent of patients with polycythemia vera; polycythemia must be actively treated if it is detected in a patient with progressive stroke. The availability of CAT head scanning has assisted in differentiating a focal ischemic lesion from one which is markedly hemorrhagic or from a frank intracerebral hemorrhage — which can also occur with polycythemia vera.

**Hyperlipidemia**

In the usual patient with acute progressing stroke, hyperlipidemia has not received any special therapeutic attention during the acute hospital admission.

**Hyponatremia Treatment**

At times with progressing stroke, the syndrome of inappropriate antidiuretic hormone secretion may occur with fluid retention and hyponatremia. The symptoms are irritability, confusion, unexplained muscular weakness and decrease in tendon reflexes. If hyponatremia is found with hyponatremia and increased osmolality inappropriately high for the serum osmolality, the patient's fluid intake should be restricted to about 1,000 cc a day until the abnormalities have disappeared.

**Arterial Lesions**

**Vasospasm**

Vasospasm has been considered as a possible cause of progressing stroke and vasodilating drugs have been used with uneven reports of effectiveness.

Mackey and Scott reported on the treatment of "apoplexy" by procaine infiltration of the stellate ganglion and found a marked benefit. Denny-Brown could not confirm these observations when he similarly treated 8 patients. Millikan et al. studied the effect in 27 patients who had stellate ganglion block and compared them to 60 patients who did not have the treatment and no benefit was found.

The inhalation of 5% CO₂ will cause 50% to 75% increase in cerebral blood flow. Utilizing this great increase in cerebral blood flow following CO₂ inhalation, Millikan studied its effect on acute focal cerebral infarction in 50 patients and compared them to 225 untreated patients. No statistically significant difference in the results in the 2 groups was found. Meyer et al. reported that "intermittent inhalation of 5% CO₂ may be beneficial in patients with TIAs and in mild and moderate cerebral infarctions, as evidenced by the clinical state of the patient and diagnostic and laboratory findings (lumbar puncture, arteriography, isotope brain scan). Inhalation of 5 percent CO₂ can cause a rise in cardiac work and cardiac output and is contraindicated in patients with coronary artery disease, congestive heart failure and systemic and pulmonary arterial hypertension." Despite these reported effects this treatment of progressing infarction is not generally regarded as useful.

Other agents which are believed to cause cerebral vasodilation include papaverine, isoxsuprine, and acetazolamide. Gilroy and Meyer treated 70 patients with progressing stroke; 34 of them received intravenous papaverine and 36 made up a control group. Statistical analysis of the results showed that improvement in the treated group was significantly greater than in controls. Gilroy and Meyer also studied 33 patients, of whom 17 received intravenous acetazolamide and 16 did not receive it. For this treatment there was no difference in outcome between the 2 groups.

There has been no further indication of usefulness for this mode of therapy.

Meyer et al. reported clinical improvement and increased cerebral blood flow in patients given dimethyl trimethoxybenzoloxo propylethylendiamine (hexobendine) by either the intravenous, intramuscular or oral routes. This form of treatment is not currently used in the United States.

**Vasconstrictors**

Hypocarbia has been evaluated as therapy for acute cerebral infarction by Paulson who measured cerebral circulation in patients with acute cerebral infarction and found that focal vasoparalysis often occurred during the acute phase. He also found that often there was a focal loss of autoregulation and elsewhere a normal response to changes of arterial PCO₂ and to the application of vasoconstricting or vasodilating drugs. Paulson also found paradoxical responses; focal flow decreases in response to hypercarbia which normally causes a flow increase. At times there was a focal flow increase following stimuli which cause a flow decrease. These various reactions led him to treat a group of 50 patients with severe acute cerebral infarction by using artificial ventilation to produce hypocarbia. This was started within the first 24 hours after the stroke began and continued for 72 hours. To serve as a control group, 21 patients with severe cerebral infarction not treated by hypocarbia were observed. No significant benefit was found when the clinical course of the 2 groups was analyzed later but he found that during the first few weeks the clinical response of the non-ventilated group was statistically better than that of the ventilated group. This method of treatment has not been studied further and is not used.

**Inflammatory Lesions**

If cerebral infarction follows an arterial obstruction caused by any form of arteritis or meningitis, pri-
mary attention must be paid to treatment of the disease causing the inflammation of the arterial wall. Patients with panarteritis (polyarteritis nodosa), lupus erythematosus, cranial arteritis, etc. should receive steroid therapy and patients with meningitis (bacterial, etc.) suitable antibiotic treatment, depending upon the organism producing the inflammation.

Surgical Therapy

Blaisdell found that patients with progressing stroke should not have cerebral angiograms because of the high risk of surgery and the possibility of an unfavorable surgical result. The Joint Study of Extracranial Arterial Occlusion found a mortality of 42% in 50 patients operated upon within 2 weeks following an acute stroke. The mortality was only 20% for patients in the same category not having surgery. Bruetman et al. and Wiley et al. reported intra-cerebral hemorrhage as a complication of carotid surgery and believe that the opening of carotid occlusion and re-establishing a normal head of perfusion pressure into an area of acute softening produced the intracerebral bleeding. Millikan reported a patient for whom emergency anticoagulant treatment and surgery appeared to be beneficial. The indications for surgical therapy for progressing stroke are as follows:

A. Clinical Events. 1) A cluster of frequent, severe carotid arterial system TIAs (a persisting mild neurological deficit may eventually become a mild progressing stroke); 2) a recent small cerebral infarction in brain supplied by the carotid arterial system followed by a cluster of TIAs; 3) onset of a focal neurological deficit during or soon after arteriography or sometimes immediately after carotid thromboendarterectomy.

B. Physical Signs. (These added to the clinical events, suggest the basic pathologic process is current and active) and include: 1) retinal emboli, 2) long systolic or systolic-diastolic bruit of grade 2 or 3 or more heard over the carotid bifurcation, 3) ipsilateral decrease in the retinal arterial pressure.

Fisher reported: "we have continued to operate on patients with the progressive stroke, with extremely good results. We operate on these patients on an emergency basis if emergency arteriography has shown that their problem is in the carotid territory. The results are extremely good, just as good as for patients with ischemic attacks. I would like to emphasize that surgery for acute stroke must be reconsidered."

Goldstone and Moore described the results in 26 patients, 8 of whom had a cluster of transient ischemic attacks from the carotid arterial system and 18 of whom had a stroke in evolution. They found that "each of the 26 patients made a dramatic, complete, and so far permanent neurological recovery following operation. There was no morbidity from either the angiographic or surgical procedures." They did not include patients for angiography and operation who had acutely developed severe focal neurological deficits (hemiplegia, etc.) or patients with a depressed level of consciousness. Siekert and Miltiak reported that a changing carotid bruit can indicate a change in the morphology of the carotid lesion and this should be added to the list of physical signs.

The risk factors for carotid surgery reported by Sundet should be carefully reviewed when evaluating indications for thromboendarterectomy in patients with progressing cerebral infarction. Careful evaluation and selection of patients with a progressing stroke will undoubtedly reveal some for whom emergency surgery is indicated. Consideration for surgery must be prompt and should not delay anticoagulant treatment.

Treatment To Protect Brain Parenchyma

The cerebral edema which can follow cerebral infarction is the most serious threat to life. It begins soon after an ischemic event, but usually it is impossible to predict who will have this complication and should have treatment. Edema causing lethal cerebral infarction begins in the first few hours after the start of a progressing stroke. Bounds reported a study of the records of all patients who came to autopsy at Mayo Clinic from January 1966 through September 1975. He found 100 patients with acute cerebral infarction in the brain in the distribution of the internal carotid artery. Sixty percent of the deaths occurred during the first week with brain herniation, cardiac abnormalities and pulmonary embolus the usual causes. Brain herniation was always secondary to brain edema following cerebral infarction. The sequence of edema formation should be understood when reviewing the literature reporting clinical trials of antiedema agents.

Glycerol Therapy For Edema

Meyer et al. investigated treatment of cerebral edema after acute cerebral infarction giving glycerol intravenously in doses of 1.2 gm per kg of body weight every 24 hours, and in some instances orally in doses of 1.5 gm per kg of body weight. Therapy was initiated within 72 hours of the onset of infarction. They found that glycerol "given within 5 days of onset of severe, progressive or sustained neurological deficit has been of benefit in patients with acute cerebral infarction." Matthew et al. conducted a double blind evaluation of glycerol therapy given intravenously with 54 patients who had an acute onset of cerebral infarction and 8 patients with hypertensive intracerebral hemorrhage. Patients were admitted to the study up to 4 days after the onset. They reported that "patients with cerebral infarction treated with glycerol..."
showed significant improvement in neurological status compared with the patients treated with placebo. They did not find any benefit with glycerol therapy for the patients with spontaneous intracerebral hemorrhage. Gilsanz\textsuperscript{93} compared 6 days of treatment with 10% glycerol in 30 patients who had acute cerebral infarction to dexamethasone treatment in 31 similar patients. All patients entered the study only if onset of their stroke was within 36 hours of beginning treatment. One patient treated with glycerol had hemoglobinuria and acute renal failure and died. Six patients given dexamethasone died. Gilsanz found that improvement was significantly greater in the group treated with glycerol at 8 and 15 days. Fritz et al.\textsuperscript{94} studied 106 patients with acute stroke. Fifty received intravenous glycerol and 56 did not receive this treatment. Using a scoring system devised for grading the neurological deficits, they found that those patients with the "highest and lowest scores did not improve from glycerol infusion." Patients with intermediate scores were found to improve significantly when compared with the patients treated with placebo. All patients had developed sudden focal neurological deficits within 6 hours before randomization. They found that "there was no difference in mortality or improvement of neurological score between the 2 groups."

Infused glycerol must be administered with caution, especially to patients with diabetes or patients with marked dehydration because the serum glucose can be elevated to dangerously high levels and non-ketogenic hyperosmolar hyperglycemia can be produced.\textsuperscript{96}

The results of the various studies of glycerol therapy are, unfortunately, inconsistent. When the reports are evaluated, the importance of the temporal profile must be considered as we suspect that glycerol, given a week after the onset of cerebral infarction, will not have a significant effect on edema. Few complications of this treatment have been reported, which should encourage further investigation. It may have a definite role in treating patients with progressing stroke who rapidly develop marked neurologic deficits and then, within 36 hours or less, have a marked reduction in their level of consciousness. Table 2 compares the reported results of treatment of edema with various hyperosmolar agents.

**Steroid Therapy**

Since the study of Russek et al.\textsuperscript{77} there have been few positive reports and enthusiasm for steroid therapy in patients with acute stroke to protect them from cerebral edema associated with cerebral infarction. Table 3 shows the results of 11 reports in the literature. Mulley and Wilcox\textsuperscript{97} evaluated 118 patients with acute stroke allocated for treatment with either dexamethasone or placebo and found that one year later there was no significant difference in the outcome of the 2 groups, i.e., the number of survivors or the quality of life. They concluded that there was no indication for treatment with steroids for patients with cerebral infarction.

Ottonello and Primavera\textsuperscript{98} studied postmortem examinations of 73 patients dying with acute stroke and found that the frequency of gastric erosion, gastric ulcer, duodenal ulcer and multiple erosions in the steroid treated group was significantly higher than in those who did not receive corticosteroids.

In our experience there has been no startling or dramatic improvement in patients who have been given steroid. Jones and Millikan\textsuperscript{99} found a mortality rate of 41% for patients with acute cerebral infarction with hemiplegia and a decrease in the level of consciousness. The results of the various studies of glycerol therapy are, unfortunately, inconsistent. When the reports are evaluated, the importance of the temporal profile must be considered as we suspect that glycerol, given a week after the onset of cerebral infarction, will not have a significant effect on edema. Few complications of this treatment have been reported, which should encourage further investigation. It may have a definite role in treating patients with progressing stroke who rapidly develop marked neurologic deficits and then, within 36 hours or less, have a marked reduction in their level of consciousness. Table 2 compares the reported results of treatment of edema with various hyperosmolar agents.

### TABLE 2 Treatment for Acute Cerebral Infarction With Hyperosmolar Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Onset to Treatment Maximum Interval (days)</th>
<th>No. of Patients</th>
<th>Better</th>
<th>Unchanged</th>
<th>Worse</th>
<th>Dead</th>
<th>No. of Patients Improved</th>
<th>Unchanged</th>
<th>Worse</th>
<th>Dead</th>
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</thead>
<tbody>
<tr>
<td>Meyer et al.\textsuperscript{91} 1971</td>
<td>Glycerol</td>
<td>3</td>
<td>36</td>
<td>30</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Mathew et al.\textsuperscript{92} 1975</td>
<td>Glycerol</td>
<td>4</td>
<td>29</td>
<td>22</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>25*</td>
<td>14</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Candelise et al.\textsuperscript{94} 1975</td>
<td>Mannitol + Dexamethasone</td>
<td>1</td>
<td>75</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>35</td>
<td>64*</td>
<td>-</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Fritz et al.\textsuperscript{95} 1975</td>
<td>Glycerol</td>
<td>1</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>56</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Gilsanz et al.\textsuperscript{96} 1975</td>
<td>Glycerol or Dexamethasone</td>
<td>1.5</td>
<td>30</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>31</td>
<td>12</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Larsson et al.\textsuperscript{97} 1976</td>
<td>Glycerol</td>
<td>1</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>15*</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Santambrogio et al.\textsuperscript{98} 1978</td>
<td>Mannitol</td>
<td>1</td>
<td>28</td>
<td>12</td>
<td>-</td>
<td>16</td>
<td>32*</td>
<td>14</td>
<td>-</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

*Placebo
TREATMENT OF PROGRESSING STROKE/Millikan and McDowell

Table 3  Treatment of Progressing Stroke and Acute Cerebral Infarction With Steroids

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Onset to Treatment (hours)</th>
<th>Placebo Improved</th>
<th>Placebo Died</th>
<th>Treated Improved</th>
<th>Treated Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyken &amp; White97 1956</td>
<td>36 24</td>
<td>— 10/19</td>
<td>—</td>
<td>13/17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubenstein95 1965</td>
<td>19 24</td>
<td>— 4/6</td>
<td>—</td>
<td>4/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putten et al.96 1972</td>
<td>31 24</td>
<td>41% 0</td>
<td>64%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candelise &amp; Spinelli95 1972</td>
<td>49 24</td>
<td>— 10/25</td>
<td>—</td>
<td>13/24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauer &amp; Tellez81</td>
<td>54 48</td>
<td>16/22 9/26</td>
<td>13/28</td>
<td>5/28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candelise et al.83 1975</td>
<td>152 24</td>
<td>42/64 22/64</td>
<td>55/88</td>
<td>33/88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norris85 1976</td>
<td>53 24</td>
<td>5/27</td>
<td>—</td>
<td>7/26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santambrogio et al.86 1978</td>
<td>66 24</td>
<td>14/32 18/32</td>
<td>15/34</td>
<td>19/34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment with Hypothermia, Anesthesia (Sedation), Hyperbaric Oxygenation, Normobaric Oxygenation and An--ticonvulsants

Although hypothermia, anesthesia, hyperbaric oxygenation and normobaric oxygenation should theoretically change metabolism or provide a favorable metabolic substrate for focal areas of brain ischemia, none of these treatments has been reported as useful for progressing stroke.

Hypothermia is cumbersome, requiring a large personnel effort, has many serious complications, and has produced little benefit.

The suggestion has been repeatedly made that the brain is not as vulnerable to hypoxia as clinicians have traditionally believed.97 Yatsu et al.96 report that "results of our investigation support a growing body of evidence showing the energy state (of brain) to be relatively stable to ischemia." No practical way has been found to acutely protect the brain from anoxia despite these hopeful reports. Anesthetic agents (forms of sedation including barbiturates) have been found to change the metabolic requirement of brain, but their practical application has not been studied in stroke in the human except indirectly. In Paulson's95,97 studies the patients who were hyperventilated were also under heavy sedation (essentially anesthetized) for the many hours of hypocarbia, and no benefit resulted.

Ingvar and Lassen96 studied the use of hyperbaric oxygen as treatment of focal cerebral ischemia in 4 patients. They were exposed to pure oxygen at a pressure of 2.0 to 2.5 atmospheres for periods of 1.5 to 2.5 hours. Three of the patients appeared to be benefited and in 2 this was objectively demonstrated in the EEG. Heyman et al.100 studied the therapeutic usefulness of hyperbaric oxygenation in 22 patients with recent focal cerebrovascular damage. He found that 4 patients had remarkable improvement and in 2 the improvement persisted, but in 2 others the neurological deficit recurred. Repeated exposure to high pressures of oxygen produced only temporary improvement. The problems of the mechanics of hyperbaric oxygenation, as well as possible complications, taken with the lack of enthusiasm for the treatment, even by those reporting some benefit from it, has resulted in a situation where hyperbaric oxygenation is not used in treatment.

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Treatment of progressing stroke.
C H Millikan and F H McDowell

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