The Pathogenesis of Transient Focal Cerebral Ischemia

The Lewis A. Conner Memorial Lecture

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"W"ith the growing appreciation of the vast clinical importance of coronary thrombosis the question is being asked more and more whether the atherosclerotic changes in the vessel wall are the chief causal factor or whether there are other factors, such as changes in the character of the blood itself, that play an important role. Unfortunately the question cannot be answered at present. There are various reasons for thinking that other factors may play a part in the production of thrombosis, but upon the evidence at present available we are forced to believe that atherosclerotic changes in the arterial wall are an essential, and probably are the chief, prerequisite for the formation of the thrombus."1 This statement was written by Dr. Lewis A. Conner, editor of the American Heart Journal, and appeared in an article in the American Journal of the Medical Sciences in 1933. If one were to change the word "coronary" to "cerebral," this statement would be directly applicable to our current knowledge of the pathogenesis of focal cerebral ischemia. As a clinician, Dr. Conner may have wondered why knowledge of occlusive cerebrovascular disease lagged behind that concerning coronary occlusive disease. This lag was probably explained in part by the neurologists' and neuropathologists' intense interest in cerebral morbid anatomy and in efforts to describe fully the physical counterpart of focal types of structural brain damage; at any rate, there has been relatively little concentration on efforts to explain the mechanisms that might produce clinical focal cerebral ischemia. In fact, there was little in the descriptive literature concerning occlusive disease of the cerebral circulation outside the head until the last decade. In 1875 Gowers2 described a patient who had right hemiplegia and blindness in the left eye. He attributed the difficulty to occlusion of the left carotid artery in the neck. In 1908 Guthrie3 and in 1912 Cadwalader4 each described two similar patients. In 1914 Hunt5 wrote concerning 20 patients with hemiplegia, four of whom had diminished carotid pulsations in the neck on the appropriate side. There were also two patients who had occlusion of the carotid in the neck associated with local trauma. For some reason, Hunt's articles did not make a great impression on internists and neurologists and was largely ignored for almost 40 years. In 1937 Moniz and collaborators6 described occlusion of the cervical portion of the internal carotid artery demonstrated by arteriography. However, once again, this description seemed to have little impact on the clinical medical public. However, in 1946 the picture began to change with Kubik and Adams7 study of occlusion of the basilar artery. In the case protocols listed in the article, almost half of the patients apparently had warning events before the beginning of occlusion of the basilar artery. However, Kubik and Adams did not comment on the possible use of such warnings as prognostic aid in detecting oncoming thrombosis of the basilar artery. That same year Risteen and Volpittio8 advised the use of stellate ganglion block in the therapy of cerebral infarction, and 2 years later Gilbert and de Takats9 recommended the same treatment. These enthusiastic articles concerning a possible therapeutic method stimulated in-

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terest in the subject. Further interest was aroused by Kety's work in cerebral blood flow published in 1948. Since the description of the nitrous oxide method for determining cerebral blood flow, many interesting observations have been made concerning cerebrovascular physiology in health and disease. However, the method is of no practical value for the study of focal cerebrovascular disease in individual patients, since it reports only concerning blood flow per 100 Gm. of brain per unit of time and cannot give any evaluation of the state of the circulation in a specific local area of the cerebrum.

In the last decade, events have moved much more rapidly in our studies of occlusive cerebrovascular disease. To date, occlusions in cervical portions of cerebral circulation have been emphasized and described more accurately; a clinical temporal classification of cerebral occlusive disease has been developed; the syndromes of intermittent carotid and vertebral basilar insufficiency have been described and their natural history has been studied; the administration of anticoagulants for certain types of cerebrovascular disease has been initiated and is now widely used; ophthalmodynamometry has become a valuable clinical tool in diagnosis; the importance of bruits in the carotid circulation has been emphasized; new angiographic technics have been developed; and study concerning the possible surgical reconstruction of extracranial brain vessels has got underway. In addition, numerous laboratory workers have been engaged in investigating certain aspects of the cerebral circulation in a variety of species of experimental animals; however, as these last-mentioned studies have added little to our certain knowledge of human cerebrovascular disease, no special comment is made concerning them at this time.

The fundamental question that awaits answer is, What is the pathogenesis of focal cerebral ischemia in cerebral occlusive disease? Any self-respecting vascular surgeon will state simply that the pathogenesis of focal cerebral ischemia is atherosclerosis of the extracranial cerebral vessels. As such a statement contains at least partial truth, it merits further scrutiny. In 1942 Hultquist examined the entire carotid system and brain in 3,500 consecutive autopsies. He found 91 instances of occlusion of the carotid artery. In 1954 Fisher described the findings in 432 consecutive autopsies in adults. There were 28 cases of occlusion and 13 of severe narrowing. It is interesting that seven of the patients had unilateral occlusion of the carotid without symptoms. In 1957 Hutchinson and Yates reported a study of patients who had clinical evidence of cerebrovascular disease and were ultimately examined at autopsy. Of 83 patients examined, 40 had at least half of the lumen of either a carotid or a vertebral artery, or both, obliterated.

In 1960 Martin and associates studied the pathologic anatomy of the extracranial carotid and vertebral arteries along with the arch of the aorta, its branches, and their ostia in 100 unselected patients more than 50 years of age who came to autopsy. Figure 1 shows the 15 occlusions that were detected and the

![Oclusions diagram](http://circ.ahajournals.org/)

**Figure 1**

*Number and sites of occlusions; I.C., internal carotid; E.C., external carotid; C.S., carotid sinus; C.C., common carotid; V., vertebral; subcl., subclavian; and innom., innominate.*

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sites of these occlusions. These occurred in 11 patients. It is of special importance that six of these patients had no symptoms or signs of cerebrovascular disease. Two patients had ancient cerebral infarction, and two patients who died of cerebral infarction had an occlusion which consisted of atherosclerosis plus fresh thrombosis. One patient had a recent intracerebral hemorrhage. Figure 2 shows the sites and numbers of stenoses involving 50 per cent or more of the lumen. Seventy-seven such lesions were detected and occurred in 29 patients. Eighteen of the 29 patients had no symptoms or signs referable to the central nervous system. Figure 3 indicates the sites and number of kinked arteries, seven in all. These seven kinks occurred in four patients. One artery was occluded by mild atherosclerosis plus fresh thrombosis of the kinks; the patient had cerebral infarction. Thus, of 40 patients with significant stenosis or occlusion, 24 had no symptoms or signs of cerebrovascular disease.

The primary question that comes to mind, of course, is whether the atherosclerosis has anything to do with the symptomatology or the cerebral infarction (or both). Parenthetically, it can be stated that in patients having cerebral infarction in which there is no evidence of a cardiac source for an embolus, it is almost universally true that there is atherosclerotic disease of the intracranial or extracranial cerebral arteries. However, it is glaringly apparent that there is no one-to-one relationship between atherosclerosis and symptomatology; in the study by Martin and associates, more than half of the patients with severe and widespread atherosclerosis were entirely free from symptoms and signs of brain disease. Is there some difference between the atherosclerosis in those patients who had cerebral symptoms and in those patients who were free from symptoms? Whisnant and co-workers have studied this group of patients and found a higher incidence of high-grade cervical arterial stenosis in those patients who had a history of focal cerebral ischemia with or without infarction as compared with those patients who had no symptoms of cerebrovascular disease. A meticulous search was not made for distal occlusion in

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**Figure 2**

Number and sites of stenoses involving 50 per cent or more of lumen. For explanation of letters see legend for figure 1.

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**Figure 3**

Number and sites of kinked arteries. For explanation of letters see legend for figure 1.
smaller vessels due to emboli or other material, and no special study was performed concerning the surface characteristics of the atherosclerotic lesions in the cervical portions of the arteries.

From all of these studies, it appears an inescapable conclusion that atherosclerosis is not the sole pathogenetic factor in the production of focal cerebral ischemia of either short or long duration. The commonness of such atherosclerotic lesions will provide the vascular surgeon a massive amount of operative material until such time as we have more accurate knowledge concerning the actual role played by these lesions.

Factors Other Than Atherosclerosis That Could Contribute to Focal Cerebral Ischemia

What factor or factors if added to atherosclerosis could influence the production of focal cerebral ischemia? These factors are discussed in the following order: vasospasm, transitory systemic hypotension, kinking and external compression of vessels, polycythemia, anemia, transitory hypoglycemia, transitory shunts, and thrombosis and multiple emboli from atherosclerotic lesions.

Vasospasm

The factor of vasospasm was championed as a cause so effectively for so many decades that some comments concerning this pathogenetic mechanism are indicated. In 1891 Peabody observed a 56-year-old man who had had five or six transient attacks of right hemiparesis and found neither a cerebral infarct nor a complete occlusion of the cerebral artery at autopsy. The author believed that there "... might perhaps 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 ischaemia of important brain centres; 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." Since that time, vasospasm has actually been observed by many neurosurgeons and it has been inferentially demonstrated by angiographic methods. However, the body of evidence that vasospasm is of any importance in the pathogenesis of cerebral infarction due to occlusive cerebrovascular disease is small indeed. It has long been known that the nerve supply to the intracranial cerebral vessels beyond the meninges is poor and that the muscular coat and elastic laminae do not appear to have potential for spasmic contraction when contrasted to similar-sized vessels elsewhere in the body. In the early observations of Forbes and Wolff, vasospasm in pial vessels was found to be weak compared with that of similar-sized vessels elsewhere in the body. Studies of blood flow by the nitrous oxide method following stellate ganglion block showed no significant change in blood flow and implied that there is little alteration in vessel diameter. Likewise, it has now been repeatedly demonstrated that stellate ganglion block does not influence attacks of intermittent carotid insufficiency or intermittent vertebral basilar insufficiency as should be the case if such episodes were in fact due to vasospasm. Similarly, the most efficient cerebral vasodilator known, carbon dioxide, when administered to patients with episodes of intermittent insufficiency, does not influence the natural history of the phenomena. This is a strong implication that vasospasm is not playing any significant part in the cause of the episodes. It is also true that strokes are most common during the decades of life when the changes of aging and atherosclerosis most significantly interfere with the anatomy of the intracranial and extracranial cerebral vessels and apparently decrease greatly the capacity of the vessels to change diameter due to contraction of the muscular coat. It is interesting to note that patients with the aural phenomena of migraine, which are thought to be due to arterial spasm, no longer experience the phenomena as they enter the age period in which the changes of aging and arteriosclerosis alter arterial structure. The phenomena are most common and disconcerting during those years when the vessel walls are least involved.
by aging and disease. The implication, of course, is that phenomena secondary to spasm disappear as the population ages. Likewise, in amaurosis fugax the phenomena appear to be due to occlusion by an intraluminal blocking material rather than secondary to vasospasm. Pool, one of the champions of the theory of vasospasm as an important mechanism, himself says, "Before rupture of an intracranial aneurysm, angiographic evidence of vasospasm and secondary neurologic signs are extremely rare. In angiograms, for example, showing an aneurysm that has never bled, I have seen no evidence of vasospasm." The evidence is overwhelming that vasospasm primarily or added to atherosclerosis is of relatively little importance in the pathogenesis of most instances of focal cerebral ischemia.

Transitory Systemic Hypotension

Rothenberg and Corday, Denny-Brown, and Meyer have all supported the idea that atherosclerotic stenosis or occlusion associated with a transitory relative systemic hypotension produced significant ischemia in the brain supplied by the affected artery. If the alleged hypotension is very brief, a transient ischemic episode occurs; longer periods of systemic hypotension can cause cerebral infarction. Recently, Meyer wrote, "In our experience the most common form of hemodynamic crisis, however, is due to a fall in blood pressure, sometimes resulting from the unwise use of hypotensive drugs in the hypertensive patient, or to postural hypotension particularly in diabetic subjects." There seems little question that this mechanism can produce significant focal cerebral ischemia. Elderly patients undergoing major operative procedures and experiencing significant decrease in blood pressure rarely have clinical evidence of focal brain damage during the immediate postoperative recovery period. However, at autopsy, infarction may be demonstrated only in the area supplied by a diseased artery. Meyer's statement does not appear tenable for a variety of reasons. Since the experience of Eastcott and associates, investigators, including Fisher, Denny-Brown, and Meyer and co-workers, have been unable to induce attacks by lowering the blood pressure by use of the tilt table. Attacks of cerebrovascular focal insufficiency are uncommon in patients receiving antihypertensive therapy in clinics where large numbers of such patients are treated. This is true in spite of the fact that these patients very commonly have a brief but sharp fall in the blood pressure. Likewise, cerebral infarction associated with major general surgical procedures in elderly patients is uncommon. Transitory systemic hypotension is common under such circumstances. Experience with many patients teaches that attacks can begin while the individual is recumbent, sitting, and standing quietly as well as when he is active. Blood-pressure recordings on many patients with actively advancing infarction remain at the usual values for that patient. Ligation of the carotid artery in the neck is not associated with attacks of intermittent carotid insufficiency such as would be expected if a transient lowering of blood pressure were the inciting factor. Most important is our experience in coincidentally observing the blood pressure in five patients (over 10 years' time) at the very onset of a typical episode of focal cerebrovascular insufficiency. In each instance the blood pressure remained unchanged for that patient. The following case history is of particular significance.

Report of Cases

Case 1. The patient was a 49-year-old man who complained of episodes of blindness and unsteadiness on his feet. He registered at the Mayo Clinic in June 1961. The past history included myocardial infarction in 1954 followed by angina and a second myocardial infarction in 1959. There were regurgitation and vomiting of food for 25 years and hematemesis about 1940. Treatment for a duodenal ulcer was started in 1942 and apparently was effective. In 1954 and subsequently he had difficulty with food "sticking" after it had been swallowed.

In June 1960 he began to have painless episodes of blindness in which his vision faded out in a matter of seconds and he was unsteady on his feet. The episodes lasted 5 to 10 minutes, and then vision and gait returned to normal. On July 14, 1960, he awakened at 3 a.m. with a "paralyzed" feeling in the right side of his face and right arm. There were weakness in the right part
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of the face and drooling from the right side of the mouth, mushy speech, and difficulty manipulating food with the tongue. Complete recovery occurred gradually over a period of 2 weeks. In January 1961 he first noted that he could precipitate episodes of visual loss by turning his head to the extreme right or left. Similar symptoms with unsteadiness occurred without turning of the head. He stopped driving his car and working because of the attacks. An anticoagulant was said to have been administered during a portion of 1960. He had no attacks during this treatment.

Results of general physical and neurologic examinations were normal except for slight weakness of the buccal angle on the right. Retinal artery pressures were equal and normal. A clinical diagnosis of esophageal stenosis and intermittent vertebral-basilar insufficiency was made.

The results of laboratory examination including urinalysis, concentration of hemoglobin, leukocyte count, erythrocyte count, blood urea, and cephalin-cholesterol flocculation were normal. Roentgenograms of the chest and head, an electroencephalogram, and visual-field examination also gave normal results. Roentgenograms of the esophagus and stomach revealed a short esophagus with 3 inches of stomach in an intrathoracic position and a severe stricture at the esophago-gastric junction. The electrocardiogram showed changes indicating a previous posterior myocardial infarction with an intraventricular conduction disturbance. The prothrombin time was 18 seconds (normal 17 to 19 seconds).

The patient was admitted to the hospital for observation, biopsy, and dilatation of the esophagus.

On June 25, 1961, severe dysarthria, severe quadraparesis (worse on the left), and bilateral Babinski signs developed. At the onset of the attack the blood pressure was 140 mm. of mercury systolic and 85 diastolic. Heparin was administered intravenously. Recovery was complete in 30 minutes. During the next 48 hours, the patient had six similar attacks. The blood pressure was measured 5 minutes before the onset, at onset, during, and between attacks. There was no decrease in blood pressure save for a slight (10 mm. Hg) decrease after 15 minutes of one episode. This is a characteristic example of the absence of hypotension as a factor in the pathogenesis of intermittent focal cerebrovascular insufficiency.

Patients with orthostatic hypotension may have intermittent focal cerebrovascular insufficiency. The following is an example.

Case 2. A 74-year-old man was admitted to the Mayo Clinic in June 1961 and was hospitalized because of cough and a question of pulmonary neoplasm. There had also been three unusual episodes of neural dysfunction. In October 1959 he had suddenly noted weakness of the right side of the face and right hand, drooling, and thickness of speech. He was normal again in 3 days. During January 1961 there were rapid onset of vertigo, nausea, ptosis of the left eyelid, and severe dysphagia. These phenomena cleared in 1 day. A similar attack occurred in May 1961 and recovery was complete in a few hours.

Results of general physical and neurologic examinations were normal, as were those of various laboratory procedures, roentgenograms of head and chest, and bronchoscopic examination. The cough abated. The patient was dismissed on June 19, 1961.

He returned to the Mayo Clinic and was admitted to the hospital on July 5, 1961. On June 20, while eating the noon meal, he experienced lightheadedness. Speech and swallowing as well as other functions were normal. The symptoms abated when he lay down. From that time until admission he experienced a similar sensation when he sat upright or stood up.

Examination revealed that his blood pressure while lying down was 120/70; while sitting it was 60/2 by palpation. A clinical diagnosis of ancient, intermittent vertebral-basilar insufficiency and current orthostatic hypotension was made.

Blood cortisol values and results of various other laboratory tests, including urinalysis, erythrocyte count, concentration of hemoglobin, hematocrit value, leukocyte count, and levels of blood urea and plasma cholesterol, were normal. Observations of blood pressure revealed a consistent severe orthostatic hypotension. On one occasion syncope was induced, but no focal neurologic symptoms or signs developed.

The administration of fludrocortisone acetate (Florine f Acetate tablets), 1 mg. twice daily, adequately controlled the orthostatic hypotension so that the patient was able to walk normally. He was dismissed on July 17, 1961.

This is a clear-cut example of a case in which severe transitory hypotension did not induce attacks of focal ischemia in a patient who had a cerebrovascular problem. Another similar patient was recently studied. The episodes of severe orthostatic hypotension were associated with syncope, but in no instance did an attack of vertebral-basilar insufficiency occur. An attack came only while the patient was sitting and the blood pressure was stable.

It seems plausible that intermittent systemic
hypotension is a factor in those instances in which there is a distally located occlusion in a small artery with a collateral supply of borderline quality. Instances in which there are multiple occlusions or narrowings of a large vessel may also be adversely affected by transient systemic hypotension. Clinically, one always searches for a cause for transient hypotension when studying patients with focal intermittent cerebrovascular insufficiency, but such a clearly defined cause is seldom detected.

Kinking or Compression

It has been attractive to speculate that transitory kinking or external compression of an extracranial cerebral artery could account for attacks of transient cerebral ischemia or produce cerebral infarction. Gegenbauer25 mentioned that flow through these vessels may vary with change of position of the head. De Kleyn and associates26, 27 suggested that phenomena precipitated by rotation of the head, including positional nystagmus and vertigo, could be due to decreased flow of blood through one vertebral artery. Many years later, Biemond28 described a patient whose apnea and hiccup could be induced by turning the head to a certain position. He believed that the vertebral artery was compressed at the time of cranial rotation. In 1956 Boldrey and associates29 reported a patient whose attacks of left carotid insufficiency were related to turning the head to the right. Boldrey turned the head to various positions during inspection of the arteries at operation and noted that the left lateral process of the atlas moved anteriorly when the head was turned to the right and compressed the left internal carotid artery from behind. Toole and Tucker30 described a method for the study of the patency of the carotid and vertebral arteries in the cadaver. They noted a frequent decrease in flow through these vessels when the head was turned to various positions. They emphasized the need for attempts to demonstrate these phenomena in the living. Bauer and associates31 performed panarteriography in 71 patients with a clinical diagnosis of occlusive cerebrovascular disease. One or both carotid or vertebral arteries were markedly tortuous, kinked, or rotated in 21 (30 per cent). However, in only one patient was kinking evidently the sole precipitating cause of cerebrovascular insufficiency.

At the Mayo Clinic it has been our practice for almost a decade to try to reproduce patients' attacks of focal cerebrovascular insufficiency by placing the head in various positions. Rarely has it been possible to induce attacks. It appears that kinking or compression of a cervical vessel is a potential but rare cause of focal cerebrovascular insufficiency, with or without atherosclerosis.

Polycythemia

Attention was directed by Millikan and coworkers32 to the association of various types of polycythemia and intermittent insufficiency of either the carotid or the vertebral-basilar artery. Episodic events had been included in various papers33–36 as portions of case histories but had not been discussed from the standpoint of significance or pathogenesis. Since these observations concerning 22 patients, the authors32 have seen more than 20 additional instances. The clinical phenomena observed in the cases described were essentially the same as those noted when polycythemia or focal cerebrovascular insufficiency occurs singly.

The pathogenesis of these attacks is not certain. The changes in blood viscosity, blood volume, cerebral blood flow, and cerebral vascular resistance are probably stable, at least from hour to hour. Another factor must be operative to cause attacks that come on very rapidly and persist for only a few minutes. Some cerebral atherosclerosis is likely in many, for the average age of the patients is well over 50 years. The atherosclerosis is also relatively stable. In case 10 reported by Millikan and associates,32 the blood pressure taken just before and during the onset of two separate attacks did not change, nor did the pulse rate or rhythm. No evidence of a cardiac lesion or other site of a distant source of emboli can be discovered in a majority of
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the patients, nor is there evidence of embolic phenomena in other parts of the body.

Brown and Gifin demonstrated that there was increased viscosity of the blood, and Kety showed that there is a marked decrease in cerebral blood flow and increased vascular resistance in polycythemia. These factors enhance the tendency toward the formation of thrombus. It appears likely that the increased tendency toward formation of thrombus, plus the atherosclerosis, can produce significant arterial stenosis at the site of the atherosclerosis or that particles of thrombus might become emboli which could produce transient occlusion distal to the atherosclerosis. The short duration of the attacks may be related to lysis of the thrombus or disintegration of the fragile emboli, or to the rapid opening of effective collateral channels. Observation of many cases, including arteriographic study, indicated that usually the main vascular channels open again. In such instances, it is logical to presume that failure of opening of collateral flow cannot constitute the only defect, since the flow through the main vessels would prevent episodes of insufficiency. Pitts evaluated 23 cases of internal carotid artery occlusion for severity of neurologic signs and evidence of collateral circulation. Those patients with evidence of good ophthalmic artery flow had the most disability, a finding which suggests that this type of collateral flow provided poor protection against cerebral infarction. The almost uniform cessation of attacks with anticoagulation or successful treatment of the polycythemia adds weight to this hypothesis. Certainly the association of intermittent cerebrovascular insufficiency and polycythemia supplies one more bit of evidence implicating some part of the mechanism of thrombosis (with or without atherosclerosis) in the pathogenesis of focal transient cerebral ischemia.

Anemia

Another factor that may be operative in the pathogenesis of intermittent focal cerebral ischemia is severe hypochromic anemia. Siekert and associates reported on five patients who had intermittent cerebral arterial insufficiency during a period of anemia. Four were more than 60 years of age; a 50-year-old patient had angiographically demonstrable occlusion of the right internal carotid artery and stenosis of the left internal carotid artery. Attacks ceased in all instances when the anemia was corrected. While stenosis or occlusion of an arterial channel supplying the disturbed area appears to be one important factor, the transient quality of these episodes remains unexplained. Additional elements such as temporary hypoglycemia or systemic hypotension were not demonstrated. In this situation it appears less likely that transient alteration in the dynamics of the clotting mechanism of the blood played a role, as contrasted to the situation in polycythemia. The association of severe anemia with such attacks is rare, and this suggests that no universal mechanism is involved in this association which would apply to most attacks of transient ischemia.

Transitory Hypoglycemia

Rarely, transitory hypoglycemia is associated with clinical evidence of a focal neurologic lesion, probably ischemic in nature. These patients have attacks that are indistinguishable from episodes of transitory focal cerebral ischemia. The temporal relationship of the complaints to the ingestion of food suggests an abnormality of glucose metabolism. Appropriate study may reveal the source of metabolic defect; rarely, it is an islet-cell tumor. The focal character of the neurologic defect is theoretically explained by stenosis of the artery supplying blood to the defective neural tissue. The metabolic requirements of such an area would not be satisfied, compared with those of the remainder of the brain, and this would account for the focal nature of the symptoms. In clinical experience such cases are extraordinarily unusual.

Transitory Shunts

Sudden shunting of blood from one section of the cerebral circulation to another unusual area, thus producing relative ischemia in the unusual region, is another theoretical patho-
genetic mechanism of transient ischemic attacks. However, no significant evidence suggests the existence of such a mechanism. At the Mayo Clinic, shunting of such massive amounts of blood as actually to occasion reversal of flow in a major channel has been observed. There is reversal of blood in an internal carotid artery when the ipsilateral common carotid is ligated for an intracranial aneurysm; and there is reversal of flow in the vertebral artery associated with occlusion of the ipsilateral subclavian artery proximal to the origin of the vertebral artery. In the former, evidence of focal cerebral ischemia does not generally appear. Instances of proximal subclavian artery occlusion are seldom associated with cerebral phenomena of any type. The rare exception is that in which there is atheromatous involvement of multiple extracranial and intracranial arteries, thus making accurate assessment of the role of each artery impossible. After such shunts are established, a "steady state" of flow once again obtains. Subsequent episodic events must be explained on the basis of interposition of some new transient causative factor. Exercise of the ipsilateral extremity in proximal occlusion of the subclavian artery should increase demand for blood flow to that extremity, but in such circumstances specific evidence of focal ischemia of the brain stem or hemispheres in the form of a discrete episodic neural deficit rarely is noted.

**Thrombosis or Embol Secondary to Atherosclerosis**

The most plausible theory of pathogenesis in most instances of focal cerebral ischemia includes the basic arterial lesion (atherosclerosis at one or more sites) plus some thrombotic or embolic event that is capable of changing focal cerebral blood flow very quickly. Such a mechanism could operate with a number of variables for the initiation and the spontaneous relief of focal ischemia. Thrombus formation, in all possible stages of development, could produce symptoms by (1) occluding flow at the site of the thrombosis, (2) producing eddy currents and turbulence secondary to stenosis (particularly in the basilar artery), thus decreasing flow into the orifice of a small but important artery, and (3) generating embolic fragments (material from an ulcerated atherosclerotic plaque may also embolize) which impair flow in a peripheral portion of the system. If focal ischemia has not been in a duration-quantity ratio such as to produce sustained change in neural function, relief of symptoms could be due to (1) dissolution of the thrombus by lytic action, (2) an occluding embolus dissolved or fragmented at a bifurcation with fragments traveling to more distal branches and ultimately disappearing or no longer producing focal ischemia, and (3) occlusion remaining but effective collateral channels opening in seconds or minutes. The evidence for the existence of some combination of these possibilities is discussed.

In recent years autopsy study of patients with cerebral infarction has frequently included examination of the extracranial cerebral arteries. In almost every instance occlusive disease is found. When the cerebral infarction is recent, the occlusive disease is often found to be atherosclerosis plus fresh thrombosis. Two patients dying of cerebral infarction in the study of Martin and associates are examples. No attempt has been made to ascertain how frequently distal embolization is concurrent with atherosclerosis plus fresh thrombosis. In general, pathologists have been content to ascribe any cerebral infarct to any lesion in the arterial supply to the diseased area. The study of Martin and associates demonstrated a much higher incidence of high-grade cervical arterial stenosis in patients who had a history of focal cerebral ischemia with or without infarction. However, most patients who have atherosclerosis alone are without symptoms. An example of the important combination of atherosclerosis and thrombosis is the patient who has attacks of intermittent vertebral-basilar insufficiency and who ultimately dies of basilar thrombosis. Careful study of the occlusion often discloses that the thrombosis is laminated, having built up in increments at different times.

The transportation of embolic particles to
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distant reaches of the cerebral circulation as a potential mechanism for transient episodes of focal cerebral ischemia is given sharp emphasis by the observations of Hollenhorst.41 Bright, orange-colored plaques were found at bifurcations of the retinal arteries in 27 of 235 patients with occlusive disease within the carotid arterial system. Some of these plaques later disappeared from the retina, some remained stationary, and still others were observed to move distally. An occasional plaque caused occlusion of the arteriole. These plaques apparently consist of embolic material from atheromatous lesions in the aorta or carotid arteries. Hollenhorst has also observed another type of embolus in the retina. It appeared as an irregular, extremely white body unaccompanied by orange-yellow plaques. It appears highly probable that emboli of both types travel to the cerebral portion of the cranial circulation as well as to the retina. The analogy may well extend to the disappearance of some emboli and to the fact that many do not actually occlude the vessel. Parenthetically, it has been shown in experimental animals by Meyer42 that clumps of platelets alone or mixed with red blood cells do move in small cortical vessels and under certain circumstances disperse and disappear.

The contents (neurologic phenomena) of most transient ischemic attacks suggest that pathologic decrease in blood flow is distal in one of the two main-stem arterial channels. It is common in episodes involving the carotid system to have the patient describe a moderate defect in speech with moderate decrease in function of the right hand. It is rare that an episode involving the carotid will include hemiplegia, hemianopsia, hemianesthesia, and loss of speech. This is also true of transient ischemic attacks in the vertebral-basilar system.

If emboli from a thrombus in the first part of the internal carotid artery do at times produce distal occlusion, one would expect that manipulation of the internal carotid would at times be associated with cerebral infarction on the appropriate side. And such is the case. In 1946 Askey43 collected seven cases of contralateral hemiplegia associated with carotid sinus massage or pressure. In several instances there was no coincident bradycardia or hypotension. It seems unlikely that cerebral infarction would always occur on the side of carotid pressure if the mechanism were a simple general decrease in cerebral blood flow. Since the report of Calverley and Millikan,44 the latter has observed three additional patients in whom cerebral infarction developed on the same side while the carotid artery was being palpated but not occluded. There was no change in pulse or blood pressure. The immediate onset of the neurologic defect was characteristic of the picture in cerebral embolism. It is plausible that such an embolus could result from the dislodging of atheromatous or thrombotic material from the wall of the carotid artery.

Expansion of this evidence should include direction of attention to the complications that occur with direct carotid arteriography for the delineation of the site and degree of occlusive disease in patients in whom there is strong clinical evidence of internal carotid atherosclerosis. Baker45 pointed out that the permanent cerebral complications in five of 70 patients were associated with injection of contrast material into the left carotid artery. None occurred on the right where the contrast material reached the carotid system via subclavian puncture and injection into the innominate artery. The most common neurologic defect was a parietal lobe syndrome, a strong implication that the manipulation had dislodged an embolic fragment which traveled to the far reaches of the carotid system before producing significant arterial occlusion.

It is also intriguing to note that certain relatively young patients who undergo surgical occlusion of the cervical portion of the internal carotid artery for the purpose of lowering arterial pressure in the presence of a berry aneurysm suddenly show signs of cerebral infarction hours or days after the occlusion. In this particular situation, opening the surgical occlusion is generally not associated with improvement of the neurologic defect. Once again, the most likely mechanism is
distal embolization from a source at or near the proximal occlusion.

A final and important piece of evidence supporting the intraluminal thrombosis-embolism theory is provided in the reported experience of clinical investigators who have administered anticoagulants to patients with intermittent insufficiency in the carotid or vertebral-basilar arterial systems. After the initial favorable reports by Millikan and associates,46, 47 Fisher23 recorded observations on 29 cases. "Transient ischemic attacks," he reported, "stopped in 28 of the 29 patients. In only one case did a stroke or worsening of the neurologic picture occur and that occurred after a favorable response for almost three years. In 12 of 20 cases symptoms which had stopped during treatment-recurred when anticoagulant therapy was interrupted." Fisher48 summarized the cerebral vascular events following randomization in 15 untreated and 17 treated subjects. Follow-up averaged less than 9 months per patient. Eleven of 15 patients in the control group continued to have transient ischemic attacks in contrast to five of 17 treated patients. In the average follow-up, three of the untreated patients and one treated patient were found to have had cerebral infarction. Siekert and associates49 followed 230 patients an average of 40 months. One hundred fifteen were treated and 115 were untreated. Eight per cent of the treated patients and 29 per cent of those not treated were normal at the conclusion of the average follow-up time; 3.5 per cent of the treated and 34 per cent of the untreated patients had suffered an incapacitating or lethal cerebral infarction. These reports clearly suggest that long-term anticoagulation is of benefit as shown by a decrease in the number of transient attacks and the lowered incidence of cerebral infarction. The fundamental action of the anticoagulants strongly suggests that some aspect of thrombosis is a principal factor in the pathogenesis of the attacks and of many instances of cerebral infarction.

**Summary**

The pathogenesis of certain types of focal cerebral ischemia, particularly episodes of focal cerebrovascular insufficiency, is not fully understood. Atherosclerosis, a relatively static process, commonly occurs without producing any neurologic phenomena. However, such episodes rarely occur in cerebral vascular systems unaffected by atherosclerosis. Atherosclerosis plus some transitory pathophysiologic event would explain the clinical events. A list of such events includes vasospasm, transitory systemic hypotension, kinking and external compression of vessels, transitory hypoglycemia, temporary shunts, and thrombosis and multiple emboli. The roles of polycythemia and anemia are mentioned. Evidence is presented that incriminates thrombosis or embolus formation (or both) as the process, secondary to atherosclerosis or associated with atherosclerosis, that produces the focal cerebral ischemia.

**References**

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John Snow

John Snow was in general practice throughout his professional life. Snow was the son of a Yorkshire farmer. Born in 1813, at an early age he determined to become a doctor. He was apprenticed to a doctor near Newcastle upon Tyne and quite early in his career had experience of a cholera epidemic at Killingworth colliery. . . .

Probably from observations made when at Killingworth, Snow had formed the idea that the infection of cholera could be conveyed by polluted water, and that the mode of infection was by drinking such infected water. Observation of an epidemic of cholera in Soho confirmed him in these views and in 1849 he published a pamphlet on the subject. Then, in 1854, there occurred another epidemic in South London which gave him an excellent opportunity to test his theory. There were two water companies which supplied the area in which the epidemic of cholera was rampant—the Lambeth Company and the Vauxhall Company. The Lambeth Company obtained its water from an upper reach of the Thames where there was no contamination; the Vauxhall Company got their water from a lower and badly contaminated part of the Thames. Snow followed up every case of cholera in the affected area and found that though both water supplies provided water to the same streets, nearly all the cases of cholera occurred in those houses supplied by the Vauxhall Company. A person drinking water supplied by the Vauxhall Company had fourteen times greater probability of suffering from cholera than those who drank the water supplied by the Lambeth Company. This investigation has always been taken as a perfect example of field epidemiology and I can do no better than quote the words of Bradfield Hill—

"To those who hold that statistics are dull I commend that simple comparison; to those who hold that the statistical approach is barren and unprofitable I commend Snow on cholera." "This disease," Snow concluded, "may be rendered extremely rare, if indeed it may not be altogether banished from civilized countries." How right he was. In close on a hundred years we have been free in this country from epidemic cholera and it is a freedom which basically we owe to the logical thinking, acute observation and simple sums of John Snow.—ZACHARY COPE, Kt. Some Famous General Practitioners and other Medical Historical Essays. London, Pitman Medical Publishing Co., Ltd.. 1961, p. 12.
The Pathogenesis of Transient Focal Cerebral Ischemia: The Lewis A. Conner Memorial Lecture

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