Medical Management of Cerebral Vascular Disease*

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I shall begin with two axioms and a few definitions and, subsequently, offer conclusions and a few words to the medical lexicon. Axiom #1—there is no such thing as a CVA. In the year 1974, with cerebral angiography widely available and with computerized axial transverse tomography coming into its own, CVA can only stand for "confused vascular analysis." Axiom #2—the best time to treat a stroke is before it happens or at the very least, before it significantly disables the patient.

Ultimately, there are two fundamental kinds of stroke: cerebral infarction or ischemia and cerebral hemorrhage. The first relates to a focal cerebral dysfunction due to transient or persistent insufficiency of blood in a given cerebral vascular territory. The second relates to the often massive escape of blood into the brain parenchyma, the subarachnoid space, or both locations. From a practical standpoint, a lumbar puncture which fails to reveal blood, and particularly xanthochromia, effectively rules out almost all cerebral hemorrhages and suggests the process of cerebral ischemia or infarction. The two major kinds of stroke can be differentiated clinically without too much difficulty. On the other hand, the problems of etiology, pathogenesis, and management continue to challenge the clinician. Since strokes due to cerebral ischemia and/or infarction account for 75% or more of all observed strokes, and because of the preponderance of strokes of this variety and the limits of space, we will confine our attention here entirely to the problem of cerebral ischemia and infarction.

If one is to classify strokes due to cerebral ischemia, one may do so in terms of the nature and duration of the episode, on the one hand, and the vascular territory of involvement, on the other hand. When an episode of focal cerebral dysfunction occurs which is related to a given vascular territory, persists for minutes to at most 12–24 hours, and then vanishes completely, we say that the patient has had a transient ischemic cerebral attack. If the episode involves the vision of one or the other eye (patients often state that it seemed as though a shade was drawn across the vision of the eye), we state that the patient has had a transient retinal ischemic attack or amaurosis fugax. Onset over a period of a few seconds to a few minutes characterizes these episodes. If an episode develops either quickly or over a period of minutes to hours and if the focal deficit persists for many days and then largely but not completely clears, we say that the patient has had a transient ischemic episode with incomplete recovery. From a pathogenic and treatment standpoint, the transient ischemic episodes and transient ischemic episodes with incomplete recovery are considered to be a single entity. If the focal deficit appears over minutes to hours or sometimes even days and persists, severely disabling the patient, we say that the patient has suffered from a completed stroke. In this situation, cerebral infarction, characteristically, is the underlying cerebral pathology.

Quite frankly, most neurologists in the field at this time can point to no satisfactory treatment for the completed stroke, except for good medical care with attention to cardiopulmonary function, management of blood pressure, withholding of oral intake, and treatment entirely by intravenous fluids during the acute period, particularly when the patient is mildly obtunded. These efforts have stood the test of time. More specific therapy, such as stellate ganglion block and CO_2 inhalation, as well as streptokinase and urokinase, have fallen by the wayside, some buried by their own initial advocates. Nevertheless, the search must go on. In only one area, that of stroke in evolution involving the brain stem, has a specific form of therapy, anticoagulation,

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reduced mortality and morbidity to a degree—tenfold—which causes the Mayo group to advocate its use with vigor in this specific instance.

Ischemic strokes are also defined in terms of territory of presumed blood vessel involvement. The two major territories are those of the carotid middle cerebral–anterior cerebral system and the vertebrobasilar system. Carotid territory dysfunction is characterized by one or more of the following: ipsilateral, transient or rarely persistent visual loss due to the fact that the ophthalmic artery is the first branch of the carotid artery, contralateral weakness, contralateral cortical sensory dysfunction, contralateral hemianopia, and in almost all of the right-handed individuals and in some 60% of left-handed individuals, aphasia or dysphasia—the impairment of the faculty of language when the left internal carotid artery territory and left cerebral hemisphere are involved. The words of the psalmist, "If I forget thee, O' Jerusalem, let my right hand forget its cunning and let my tongue cleave to the roof of my mouth," characterize the classic dominant carotid territory lesion.

Strokes due to vertebrobasilar involvement rarely give rise to the classic crossed syndromes so familiar in neuroanatomy texts, such as Weber's syndrome, characterized by an ipsilateral third nerve palsy and a contralateral hemiplegia. More often, one or more of the following characterize ischemia in the vertebrobasilar territory: alternating hemiparesis, ataxia, diplopia, dysarthria, hiccup, alterations in respiratory pattern, nausea and vomiting, and pupillary changes.

Many things can cause transient or persistent focal cerebral or retinal ischemia. Particularly when ischemia is encountered in younger individuals, one may suspect a primary cardiac source involving the valves as in rheumatic endocarditis or verrucous endocarditis, left atrial thrombosis in rheumatic heart disease with mitral stenosis and atrial myxoma. Changing pulses and/or chest pain should suggest a dissecting aneurysm. Atrial fibrillation should always suggest a primary cardiac source. A variety of systemic diseases including polycythemia, thrombotic thrombocytopenic purpura, idiopathic thrombocytosis, and granulomatous angiitis, as well as disseminated intravascular coagulation should be thought of in all cases; but the garden variety of transient or persistent stroke due to focal cerebral ischemia, as seen in the hospital, usually appears in a seemingly healthy male at an average age of 62. The incidence of what is still fashionably called "cerebral thrombosis" in this patient population approaches 1% per year in the age group 65–74. Almost 40% of these patients have a history of increased blood pressure, 20% a history of diabetes, and at least 50% will give a history of a previous transient cerebral ischemic episode. Hypertension, diabetes, and previous TIA's constitute the triad of the stroke-prone profile; indeed, 30–37% of patients with transient ischemic episodes will exhibit a full-blown completed stroke within five years if untreated.

Our New York University (NYU) study of the surgical treatment of transient and persistent focal cerebral ischemia revealed approximately one-third of the patients with transient ischemic attacks, one-third with transient ischemic attacks and incomplete recovery, and one-third with completed strokes. Arteriographic studies had borne out the fact, first extensively studied by Hutchinson and Yates, that the garden variety of transient or persistent focal cerebral ischemia is related more to observable extracranial atheromatous arterial disease, particularly in the carotid arteries than to *primary* intracranial occlusive disease and indeed, more to stenosis than to occlusion.

Various studies have defined the preferred sites of atheromatous disease in the surgically approachable areas of the brachiocephalic system. Predominance of the carotid bifurcation involvement is apparent with stenosis of greater than 30% being present in more than one-third of all right and one-third of all left carotid arteries. Frank occlusion is much less common. In the intracranial circulation, observable stenotic lesions in the carotid territory fall tenfold. The values for occlusion in the distal carotid artery are inflated because in many cases occlusion is taken to represent propagation of clot from the origin of the internal carotid artery. Proximal vertebral artery involvement has been seen in approximately 20% of all vertebral origins on the right and left. Considerably less often, but probably symptomatically much more important, is stenosis which is seen distally in the vertebrobasilar system.

There is no clear-cut relationship between frank carotid occlusion and the degree of neurological deficit. Another problem encountered is that patients often do not present with a single high grade stenotic lesion in the artery appropriate to their cerebral symptoms; rather they present with a complex mixture of arterial lesions which may give rise to the exact same symptomatology.

In our NYU experience with 400 patients, we tried to group all of the cases into a meaningful framework. It is understood that every patient's vascular fingerprint is individual and that there are almost as many patterns of lesions as there are symptomatic patients. It was interesting that when we classified a lesion as a lesion, if the stenosis occupied more than 30% of the vascular lumen in any x-ray plane, 17% of the patients showed no lesions which occupied 30% or more of a vessel lumen after four-vessel angiography. The existence of this pleomorphic pattern of vascular lesions, paired with the fact that 50% of all individuals over the age of 50 have a major stenosis of at least one of the four major vessels (two carotid and two vertebrals, all leading to the brain), and that only 10% ultimately become symptomatic, offered numerous roadblocks to our eventual understanding of the pathogenesis of at least most of the carotid territory transient and persistent strokes.

Until the 1960's, it had been customary to attribute the patient's symptoms to the degree of stenosis or occlusion of the vessel developing by one or more pathogenic processes, which led to marked luminal compromise and then, presumably, to symptoms which developed in proportion to the degree of collateral circulation possessed by the patient. Surgical studies compared with angiographic observations, however, began to question this stenotic theory of pathogenesis of strokes. A new concept of pathogenesis, best characterized as the embolic theory, arose.

The sources of arterial emboli from lesions, which may occupy less than 30% of the vascular lumen formerly considered to be insignificant, were as follows: necrotic plaque, clot from ulcer, and platelet emboli from ulcer. Ulcerations can easily be seen on angiography, in the initial phases associated often with high grade stenosis, and the dye can also be seen hung up in the ulcer crater. Distal propagation of thrombus, significantly compromising the internal carotid lumen, can be seen. Radiologic evidence from NYU disclosed 24 ulcerative and 22 irregular lesions at the origin of the internal carotid arteries of the neck in the cerebral angiograms of 71 patients with history of cerebral vascular occlusive disease. Further, the incidence of middle cerebral branch occlusion associated with either irregular or ulcerative lesions of the extracranial carotid arteries was 33%, compared to 16% of patients with angiographically "normal" or smoothly stenosed extracranial carotid arteries. More and more evidence, therefore, implicates the process of arterial–arterial embolization as a major one, particularly in transient and often in persistent focal cerebral ischemia.

Thus we have a process of arterial–arterial embolization as distinct from cardiac–cerebral artery embolization, which apears to be a major pathogenic factor in ischemic strokes toward which treatment should be aimed before the stroke occurs, when we are warned by the presence of a transient episode. Since the term embolus is overextended and usually implies cardiac source, muddying our thinking about cerebral ischemia, I have long felt that to require the term "cerebral embolus" to include in its embrace the widespread process of arterial embolization would be like asking a mouse to extend its amorous interests to an elephant; it would confound confusion where too much confusion already exists. I have proposed, therefore, the acronym, "artarem," to describe an embolus which arises in an artery (art-) and lodges in a distal artery (-ar-) by a process of embolization (-em). The process can be described as being artaremic. On the other hand, if the embolus, from clinical evidence, appears to arise from the heart, the term "cardiarem" will serve, and the process of heart-to-artery embolization might be described as "cardiaremic." Adjectival modifiers such as cerebral fibrinoplatelet artarem or myxomatous cerebral cardiarem could give rise to further diagnostic precision.

Having noted angiographic and operative evidence of the artaremic process, research began for a safe medication which could delay or inhibit the first step in fibrinoplatelet emboli. Surgical studies had already clearly revealed that the neck lesion often was related to visual and cerebral symptoms since these symptoms disappeared after surgery, whereas control patients who were not surgically treated with known similar lesions often developed stroke or permanent visual defect. The experience of the Cooperative Study of Extracranial Arterial Occlusion showed a tenfold reduction in the appearance of frank stroke in the territory of the operated artery in the neck. There can be no doubt, therefore, that the source of the patient's difficulty was most often in the prominent lesion at the carotid bifurcation. Surgery, however, has its drawbacks and random studies of surgery have failed to precisely define the role of arterial surgery.

Our own NYU random study reveals one rea-

son for the confusion. In patients who were not randomized, the nonsurgical patients showed a considerably smaller initial long-term survival than the surgical patients, suggesting a significant measure of surgical selection. Where the patients were randomized, long-term survival was equal in both groups; initial surgical mortality, however, was significantly greater.

Our figures show that in patients with full recovery from transient cerebral ischemic attacks, surgical mortality is down to 3% and long-term survival is greater than in the nonsurgical group (numbers too small for statistical significance). Transient ischemic attacks in patients with incomplete recovery are characterized by a greater degree of surgical mortality; but in the proportion surviving, a larger percentage survived five years. The other major point of the surgical study was that in patients with completed stroke, surgical mortality is prohibitive, particularly in patients who are obtunded, and long-term survival is significantly better in the nonsurgical group. Mortality over the long term, however, is not simply a function of cerebral vascular disease. Associated atherosclerotic disease is characteristic of this group of patients. While the major cause of death in the postoperative period after surgery is stroke, over the long term, cardiac causes account for as many deaths as stroke, and the number of deaths in the surgical and the nonsurgical series approach one another.

Since stroke surgery is prophylactic, the major question remains—will stroke surgery in selected patients significantly diminish the proportion of stroke and significantly improve survival? No data from randomized studies have yet settled this issue completely satisfactorily. Thus, the search has gone on for safe medications which will depress the tendency for fibrinoplatelet emboli to form on ulcerated or irregular plaques. Obviously nothing can be done for the initial process of disengorgement of gummatous and cholesterol material from the broken down plaque. Anticoagulants have proven to be successful in depressing the number of transient ischemic episodes; however, anticoagulants can be given only to a reliable, stable patient population, and such therapy would be much more successful in Rochester, Minnesota for Dr. Millikan's and Dr. Whisnant's patients than for our patients at Bellevue Hospital.

In the 1960's, Frasier Mustard's group in Canada (1, 2) noted inhibition of the platelet aggregation release reaction by sulfinpyrazone. Subsequent studies have shown that anti-inflammatory drugs, such as butazoladine derivatives and aspirin, the pyridopyramidine compounds such as Persantine® and the tricyclic antidepressant drugs, have an effect on platelets. The most profound inhibition of ADP or collagen-induced platelet aggregation is shown by aspirin. In the in vitro studies, 37% of serotonin is released with no aspirin, as compared to no release with aspirin. A tenfold increase in ADP reveals that aspirin can no longer be effective against aggregation, but that there is continuing inhibition of serotonin release. Similarly, aspirin inhibits connective tissue induced aggregation as well as serotonin release from platelets. This effect of aspirin is not confined only to the test tube, but it has been shown in dogs that arterial thrombus is retarded when the intimal surface of an artery is mechanically or chemically damaged and similar results have been shown after endarterectomy in patients receiving aspirin (3). While it is known that as little as 5 gr of aspirin may depress the aggregation release reaction for as long as five days in man, as judged by the epinephrine challenge to platelet rich plasma as well as with most in vitro tests, this association of inhibition of aggregation is not clearly related to observed inhibition of transient ischemic episodes. It has been noted, however, that aspirin will stop transient retinal ischemic attacks, amaurosis fugax. We have been able to follow a most instructive patient at NYU who had as many as nine attacks daily of amaurosis fugax, with response to increasing doses of aspirin in terms of attacks and effect on platelet aggregation release reaction. This unusual patient demonstrated that the optimal dose of aspirin for amaurosis fugax appears to be 5 gr qid. A retrospective study recently published in *Stroke* by Dyken (3) shows a relative diminution of transient cerebral ischemic attacks in aspirin-treated patients. It is of interest that in some of his cases the attacks responded better to four aspirin tablets per day than to two. Prospective studies of aspirin, directed toward not only the question of aspirin inhibition of transient attacks, but also to the more important question of prophylaxis against completed stroke, are in process in the United States and in Canada and no definitive statement will be made on this subject for at least another year.

The judicious mixture of surgical therapy and prophylactic therapy with a safe platelet antiag-

gregant appears at this time to be the best combination of approaches to the axiom: The best time to treat a stroke is before it happens.

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