EDITORIAL

Treatment of Impending Stroke

THE TREATMENT options available to the physician who wishes to prevent impending stroke are limited. This is because over half of the patients who have a cerebral infarction, have it without prior warning so that there is no time for a physician to provide anything in the way of prevention. Among those patients who do have warning symptoms suggesting impending stroke, the natural history of such symptoms is quite variable. Some patients immediately have a cerebral infarction; some have spontaneous cessation of such warning symptoms and some continue to have symptoms without a stroke. These phenomena narrow the available population for which stroke could conceivably be prevented to a relatively small percentage of patients, probably less than 25% of the total population who will have a stroke. Efforts directed toward the prevention of cerebral infarction have been directed to this group.

Because of the limits and dangers of available therapeutic methods to prevent stroke (anticoagulants or surgery) any new suggestion for treatment is greeted with enthusiasm and often utilized in a large number of patients before a clear therapeutic or prophylactic effect is demonstrated. A current example is extracranial/intracranial bypass surgery. The recent demonstration that the circulating platelet and its adherence to atherosclerotic plaques has a meaningful role in the production of warning signs of impending stroke, has opened a new avenue for suggestions for therapy. Agents which prevent platelet adherence are available, safe to use and, in some instances, such as aspirin, are in common use for other reasons by much of the population of the United States.

The study of the effectiveness of anti-platelet adherent agents including aspirin and sulfinpyrazone has been carried out by several groups, Canadian, American and German, and is being continued in studies in Great Britain and Denmark. The American study could only conclude that aspirin prevented or reduced the frequency of transient ischemic attacks (TIA). The data did not demonstrate that aspirin could prevent subsequent cerebral infarction in patients with transient ischemic attacks. However, since transient ischemic attacks are linked to cerebral infarction, reducing the frequency of these attacks might also make it very likely that the ultimate chance of a stroke will be reduced.

In the Canadian report, the evidence presented by the cooperative study group indicated that aspirin alone, and aspirin with sulfinpyrazone, reduced the chances of death and cerebral infarction. Surprisingly, the beneficial results were demonstrable only in men. This report has caused controversy about the interpretation of its results, the selection of patients for study and concern generally about the conduct of clinical trials. The criticisms must be considered and should be heeded before there is a too ready acceptance of its results. The controversy overlooks the fact that a new therapeutic avenue has been opened for the possible prevention of cerebral infarction. There is now good evidence of the role of abnormal platelet adherence in the production of transient ischemic attacks. An approach for the prevention of such attacks, and probably stroke, by changing or blocking such adherence becomes possible.

In all likelihood, there is no such thing as the ideal clinical trial for this type of disorder. A staggering number of patients is needed to prove effectiveness of particular clinical agents when the incidence of the phenomenon desired to be prevented is relatively low. The need to involve large numbers of centers or physicians in collecting data adds the potential of important errors in patient selection. The lack of unanimity on which patients are to be studied, i.e. whether one includes patients with very mild neurological defects as well as those with no evidence of persistent neurological defect, has received much criticism.

Obtaining good evidence of an effective therapy for conditions which do not generally have either hard endpoints, such as death, or short distinct natural histories such as with infectious disease, makes the evaluation of any form of treatment difficult. Equally important in such studies are hard entry points which are very difficult to define for studies based on a history of patients' symptoms rather than on physical or laboratory findings.

Generally, there are two avenues to finding which patients will benefit from any specific treatment. The traditional method has been one of trial and error involving the reporting of individual patients or series of patients and the other controlled clinical trials. Over a long period of time, those patients who clearly benefit from therapy eventually sort themselves out. This phenomenon is clear in the example of those pa-
Patients who have been selected for surgical treatment of extracranial vascular disease for the treatment of stroke.\textsuperscript{12, 15} The initial enthusiasm for this form of treatment prompted surgeons to apply it to virtually all types of patients with evidence of cerebrovascular disease, both threatened and completed. Now there is growing general agreement that those patients who have transient ischemic attacks with appropriately placed extracranial cerebral arterial lesions are the most successfully treated of the group. The results in those who are suffering from completed stroke and progressing stroke are viewed with less optimism. Endarterectomy is less often applied to this latter group of patients. Clearly, the same will be true for aspirin and other anti-platelet aggregating agents. From experience with these agents will emerge a specific group of patients who are clearly benefitted by the use of anti-platelet aggregating agents such as aspirin. There will be patients for whom aspirin fails to produce desired results and other forms of treatment become necessary. Shortly, we may be able to distinguish clinically between patients who would benefit from anti-platelet aggregating agents or be able to make a distinction on the basis of laboratory evidence. We may be able to tell not only who would benefit but for how long such medication should be taken, as there is evidence that hyperaggregability of platelets is not a permanent phenomenon in patients with cerebral atherosclerosis; it may be transient.\textsuperscript{16}

What the controversies always leave open is how the practicing physician, who must deal with such patients primarily, should proceed when he makes a diagnosis of TIA. In this instance, should he use aspirin? should he use sulfinpyrazone? or should he use a combination of these drugs? and are these treatments preferable to anticoagulants or are they preferable to surgery? Those who conduct large scale studies of a particular medication or surgical treatment often do not address themselves to this particular facet of importance and leave the concerned physician dangling as to whether he should or should not use a particular form of therapy.

How then should one proceed — using all therapeutic means available to assure maximum chances of prevention of a cerebral infarction for patients who have evidence of danger of having stroke, such as a patient having transient ischemia attacks? The problem first and foremost is to educate patients to recognize such symptoms and to report them promptly to their physician. Unfortunately, even though transient ischemic attacks were relatively common in patients who have had a stroke, too few patients heeded these warnings and told their physicians about them. Also, unfortunately, many times when patients do report symptoms, they are overlooked as inconsequential by physicians and nothing is done about them. It is important to educate the patient about symptoms, especially for individuals beyond the age of 50 who have demonstrated other evidence of atherosclerotic vascular disease. Once the symptoms do occur, it is imperative for the physician to take them seriously and to evaluate the patient thoroughly. Current forms of clinical evaluation, including brain scanning and arteriography, carry with them acceptable risks if one considers the enormously devastating effect of a cerebral infarction, and its high morbidity and mortality. Patients who develop evidence of impending stroke, such as transient ischemic attacks, should be admitted to the hospital, carefully evaluated for hypertension, cardiac disease and peripheral vascular disease; for evidence of neurologic disability, carefully oscillated for cervical bruits and, when facilities are available, examined for changes in retinal artery pressure and for abnormal patterns of circulation from the external to the internal carotid artery. On the basis of these findings, selected patients should then have four-vessel angiography to determine whether or not there is a localized, extracranial, surgically accessible lesion which could be safely removed. In those patients where the atherosclerotic vascular lesion is inaccessible or where atherosclerosis is so extensive that surgery cannot be contemplated, the issue of further treatment becomes central for the physician who is anxious to prevent disaster. In this situation if there is evidence of an active process suggested by multiple recurrent transient ischemic attacks, it is probable that first a brief period on anticoagulation, starting with heparin followed by coumadin anticoagulants for a month to 6 weeks, is the preferred form of treatment in those patients who have no contraindication for its use. In patients with contraindications for coumadin anticoagulation and in those who require subsequent therapy for long periods of time, anti-platelet adherent agents, such as aspirin, should be utilized and, to be effective, require approximately 1200–1800 mg of aspirin per day in multiple doses for desired effect.

The stimulus provided by the possible usefulness of anti-platelet aggregating agents is promoting in-depth investigation of the phenomenon of platelet aggregation and its relation to attherosclerosis and to cerebral ischemia. It is also stimulating the development of more suitable and more effective agents for prevention. These new agents will require clinical trials to establish whether they are effective in the treatment of patients with threatened stroke. What is important is to recognize the need for a thorough study of the usefulness of such agents before they come into common use, recognizing the probability that such trials conducted without controversy about design or interpretation of data are unlikely. What does come out of such efforts is a better understanding of the varying mechanisms that produce transient cerebral ischemic symptoms and cerebral infarction and, in some instances, providing the physician with additional methods for preventing the tragic results of major neurologic disability which follows cerebral infarction.

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