In Answer to the Question: "As Compared to What?"

A Progress Report on the EC/IC Bypass Study

THE DEVASTATION of a major stroke for an individual and his family needs no elaboration for the readers of this journal. To reduce the incidence of this common catastrophe is the goal and preoccupation of many physicians and surgeons. Into the scientific appraisal of therapeutic measures a new element has entered — modern methodology. There is a growing demand by critical members of our profession for convincing accreditation of measures purported to be effective in stroke prevention. As a result medical, and also surgical, means of stroke prophylaxis have been submitted to this type of enquiry by clinical trials. Pitfalls in design, execution and analysis have been encountered in most studies to date, resulting in criticism and cynicism directed at these trials. Both are welcome as they will lead to improvement in methods for further studies. Critics and cynics can hamper, very seriously, the success of an attempt to validate a therapy because if their voices are authoritative they may persuade practitioners and the public that clinical judgement based on experience, well-remembered anecdotes of happy or unfortunate outcomes, or long series of uncontrolled studies with apparently reduced morbidity and mortality are adequate evidence of effective treatment and preferable to "experimenting on people."

The development of microsurgery followed the pioneering studies of Donaghey and Yasargil who demonstrated that the blood supply of the scalp could be successfully grafted onto that of the brain with safety and patency in humans as well as in the laboratory. Subsequently, such surgery has been done frequently enough to convince the most critical that it is a procedure of low morbidity and mortality and a large number of neurosurgeons now can perform EC/IC anastomosis with skill and operative success. Patency rates are high and cerebral blood flow studies often demonstrate quantitative improvement in regional cerebral blood flow.

Proposed Indications for EC/IC Anastomosis

As a sequel to this technical advance there are several potential clinical applications.

The first is the prevention of stroke resulting from deliberate surgical occlusion of cerebral arteries. A number of instances are known where a preliminary bypass has permitted deliberate ligation of middle cerebral or internal carotid arteries in dealing with giant aneurysms or tumors at the base of the brain. These observations have demonstrated that despite the small size of the anastomosis between branches of the superficial temporal artery and the middle cerebral artery sufficient blood can be supplied to prevent the development of the ischemia which would otherwise be the inevitable consequence of such a procedure. This situation is an acute one and a long-term randomized study is not required to assess the worth of a bypass under these circumstances.

Second, patients with a completed stroke may have a marginal zone of imperfectly functioning, yet viable tissue, in the periphery of a major infarction which could respond to an increased supply of blood by functional recovery. This has been attempted but the remarkable variability in spontaneous stroke recovery leaves in serious doubt any claims related to uncontrolled studies. Attempts have been made to sidestep the need for controlled trials in this situation by demonstrating better regional cerebral blood flow by selecting especially those cases which have EEG or clinical improvement under hyperbaric conditions. Unfortunately, the vital question as to whether or not the procedure convincingly produces clinical improvement by comparison with identical cases not dealt with in this way goes unanswered. To date, no clinical trial of rigorous design is known to have been initiated to substantiate the justification for this "indication."

Third, extracranial/intracranial anastomoses might reduce the incidence of stroke and death in patients with transient ischemic attack (TIA), reversible ischemic neurological deficit (RIND) or partial non-progressing stroke (PNS) in brain supplied by diseased carotid or middle cerebral arteries, not accessible to conventional extracranial artery surgery. The arterial lesions that appear to qualify are occlusion of the internal carotid artery, inaccessible stenosis (high...
cervical or intracranial) of the internal carotid artery, and stenosis or occlusion of the middle cerebral artery. By now, thousands of patients with these lesions have been subjected to the bypass procedure and there has been a plethora of reports of series, small and large. Most express cautious enthusiasm for the possible benefit of the procedure and reporting a low morbidity and mortality and very high postoperative patency rates. These series have constituted a necessary phase in the technical development of bypass surgery. If an acceptable denominator of unoperated patients were available for comparison, the large numbers operated upon to date would constitute an excellent numerator for evaluation of bypass surgery in stroke prevention. Such a denominator is needed to answer the question: "Compared to patients treated without this operation are the surgical results favorable?"

The only acceptable answer to this question would be that they had been compared to a group of patients, as closely identical as possible, who: 1) have been given, contemporaneously, similar base-line medical therapy, omitting only the unproven operative procedure, 2) have been randomized to achieve as equal a distribution of other variables as possible, 3) are in sufficient numbers to yield statistically significant results for defined end-points, 4) have been followed long enough to account for the chronicity of the disorder, and 5) have been lost to follow up as infrequently as ingenious methods can ensure. To date, such demanding prerequisites leave the question unanswered.

Patients with vertebral-basilar TIA, RIND or PNS may benefit from an anastomosis of the occipital artery to PICA or other branches of the posterior circulation. This procedure has been demonstrated to be technically feasible. It seems unjustified to allow patients to be submitted to this unproven procedure with apparently higher risk of death and morbidity until the seemingly safer procedure of STA-MCA anastomosis has been validated. When and if that stage is reached a major decision must be faced as to the reliability of extrapolating results to other vascular distributions.

The Denominators in the Conditions Afflicting Potential Candidates for EC/IC Bypass

The prerequisite of a denominator to calculations about benefits has plagued those concerned with the indications for coronary bypass. Not only is this essential in the aggregate of patients submitted to either coronary or cerebral bypass operations, but also, if possible, in the sub-groups. For patients with TIA, RIND and PNS in the EC/IC Bypass Study the radiological sub-groups are those with occluded internal carotid arteries, inaccessible carotid stenosis and middle cerebral stenosis or occlusion. Comparison of these specific situations with results from natural history studies or other treatment programs involving patients having other than these very particular lesions cannot be regarded as valid.

Knowledge of the prognosis in each of these varieties of lesions is presently inadequate. Internal carotid artery occlusion without major infarction may be followed by further ischemic events. A figure of 2% per year going on to stroke has been estimated recently in a retrospective study. Whether this prognosis varies with the time-lapse between the last TIA and the establishment of an occlusion by angiography is not known. The denominator here is imprecise.

No study can be found in the literature dealing with the natural history of intracranial or high cervical internal carotid stenosis. Possibly it is legitimate to equate it with the prognosis of TIA, RIND or PNS in a general collection of patients but this is a presumption without substantiating data. A control group of any kind for this comparison is totally wanting.

There is a recent study dealing with the prognosis of middle cerebral artery stenosis. This series is comprised of a scant 16 patients with a maximum follow up of 7 years. This review suggests that the outlook for this lesion may not be as grave as previously suspected. Stroke supervened in only 2 patients and TIAS recurred in only 1 after instituting medical therapy. A larger series with longer follow up might have altered this picture considerably but, to date, it is the only denominator available.

Middle cerebral artery occlusion develops for several reasons. Atherosclerosis confined to the middle cerebral artery may be complicated by thrombotic occlusion. Alternatively, the occlusion may be the result of embolism from the heart, aorta or the carotid artery. Even with the most diligent efforts, distinction between these varieties of middle cerebral artery occlusion may be difficult on clinical grounds. The prognosis for such patients is not known. Once more an alternative denominator to that provided by a random treatment study of these cases is non-existent.

Design of the EC/IC Bypass Study

In 1977, 20 North American centers agreed to a standardized protocol and began to enter patients into a collaborative study funded by NINCDS which was designed to test the hypothesis that infarction in the brain supplied by the internal carotid artery might be prevented by STA-MCA anastomosis. The patients to be randomized were in the particular categories described above, but the collective and sub-group prognosis was not accurately known. The patients chosen for entry into the study were similar to those currently being operated upon in an uncontrolled manner.

The biostatisticians and epidemiologists associated with the trial design used the data available for TIA, RIND and PNS prognosis in general (lacking a more precise base for these calculations). They concluded that 1000 patients must be randomized into surgical and medical groups and followed for an average of 5 years in order to detect a 50% reduction of stroke from the procedure. In order to reach this number of patients, the study has been expanded so that it now includes some 60 centers in North America, Europe.
and Japan. All centers were accredited when the study coordinators were satisfied of the expertise of the participating neurosurgeons as indicated by an 80% postoperative patency rate in a minimum of 10 consecutive patients. Postoperative angiograms were required in every patient in the surgical cadre. Continuing medical care (including risk factor management and platelet anti-aggregant therapy), documentation of patients and quarterly follow up visits were made the responsibility of the participating neurosurgeon. An agreement has been received from each center to submit for randomization all patients falling within the limits of the protocol. Obviously, freedom of choice rests with each patient but all participants have been encouraged to explain frankly to potential candidates that this study and their cooperation are important in the future of stroke prevention.

Patients are advised that the surgery is innovative, not experimental, but that its benefit is unproven. Furthermore, it is explained that no other method is known whereby proof of its value can be obtained.

Individual patients are excluded, as in any controlled trial, if they fail to meet the clinical or radiological demands of the protocol, if they are an "obligatory exclusion" (eg. associated serious illness, more than 3 months since last ischemic event, etc.) or if the patient cannot give informed consent. All patient data forms are reviewed in the Central Office (University Hospital, London, Ontario) again in the Methods Center (McMaster University, Hamilton, Ontario) and all pre-entry and post-operative angiograms are reviewed at the Central Office by the principal neuroradiologist.

Progress of the EC/IC Bypass Study

The first patient was entered in September, 1977, and by mid-December, 1979, a total of 545 had been randomized. This number is short of the original optimistic target by about 150, but the pace of entry in recent months has been steady. Indications are that the study will be completed within 12 months of the original target date. As expected, patients with carotid disease have been more common than those with middle cerebral artery lesions by a ratio of about 3.5 to 1. Overall, ICA occlusions constitute 61% of patients, inaccessible ICA stenosis 17%, MCA stenosis 12%, and MCA occlusion 10%.

North American centers have entered 339 patients, European centers 165, and Japanese centers 41.

The question has been raised and will be increasingly discussed as to the wisdom of expanding the study so that patients are now being entered from a total of 60 centers on 3 continents. This expansion has been deliberate and in response to the need to achieve a sufficient number of patients within a reasonable period of time. Quality control, however, has not been sacrificed. This is ensured by demanding proven expertise on the part of the individual neurosurgeon performing the bypass, by carefully scrutinizing operative morbidity and mortality and, most especially, the patency rates at postoperative angiography. A reassuring measure of the success of these stringent guidelines is the patency rate of 90% achieved for patients randomized to date for surgery.

Twelve patients have been later excluded because of erroneous clinical or radiological entry. Since each patient is closely monitored in the participating center, again at the Central Office, and finally in the Methods Center, this fine-combing is bound to yield a few errors which become apparent on repeated review. It is the opinion of those involved in this trial that a post-entry rejection rate of 2.2% is acceptable. None of the investigators involved in the scrutiny of raw data has any inkling of the trends, let alone the results of treatment to date. Results will remain unknown to the participants until the study is completed.

Problems Encountered

It is evident that the success of such a study demands attention to many factors. Two things have been difficult to achieve and are interrelated.

First, the number of patients entered must equal or exceed the estimate of 1000 arrived at prior to the study. Without this a great deal of patient confidence and a large amount of investigators' time and energy, as well as considerable taxpayer-dependent research money, will have been expended on an equivocal or dubious venture. The patient entry for the North American centers varies from 1 to 46, an average of 10 per center over the 2 years of the trial. Since about half of these centers joined the study late this represents an annual entry of about 7 per center. Entry for the European centers varies from 2 to 33, for an average of 10 patients per center. Since a majority of these centers started within the past year their annual entry is higher than in North America. As the Japanese centers entered later, their overall contribution and center breakdown cannot as yet be assessed. Patient entry in any major collaborative trial is always a problem but the half-way mark has already been passed.

The next problem concerns the requirement that every participating center attempt to randomize most if not all of the eligible patients. If this is not done, biased entry could distort the result. This possible bias is negated to some extent by the fact that any patient to be entered must still face randomization, a process which will help to restore the balance. If, however, a number of centers were to decide to operate, outside the study, on the less complicated patients and submit for randomization only the most serious ones, a group with a poor prognosis might be selected for entry and be sufficiently bad in outlook as to make any therapeutic advantage less obvious. Centers unwilling or unable to abide by challenges of randomization have been asked to withdraw from the study.

The patient entry rate per center is low for a variety of reasons. The study is not designed to test the benefit of bypass surgery in patients who have suffered a major infarct. Many patients who have had the operation and are reported in the literature have been of this type. Patients in the EC/IC study must have been in-
vestigated for TIA, RIND or PNS and found to have lesions inaccessible or not amenable to conventional surgical treatment. Such patients constitute about 15% of patients with these clinical presentations. There is no doubt that many centers initially over-estimated the number of eligible patients which they would encounter. Further, there is growing and indeed vigorous enthusiasm for the procedure, whether proven or not, which has reduced the referral to centers attempting to evaluate it. Participating surgeons are frequently instructed by their referring colleagues to “do a bypass.” Response in this situation is dependent on the determination of the center to deal with this operation as a challenge to be properly explored, or, alternatively, on a wish to oblige their referring neurologists, neurosurgeons, internists and vascular surgeons. The operation has become popular, many neurosurgeons are doing it, more are being trained to do it. Many courses, seminars, congresses and annual society meetings feature the cerebral revascularization story. “How do I do it” is more often the theme than “Why do I do it.” This is understandable. It is a theoretically attractive, elegant and richly satisfying operation requiring considerable neurosurgical craftsmanship. It has a low morbidity and mortality, and CBF studies may show an improved cerebral circulation. Its active promotion by a number of neurosurgeons and its passive acceptance and active solicitation by energetic neurologists is the major challenge to the success of this trial.

Conclusion

The randomized trial will continue and the determination is that it will be successful in its stated entry and follow up goals. Whether it will lend credibility to the suggestion that bypass surgery will prevent stroke remains to be seen. Whether the results, whatever they may be, will be accepted by the practicing members of the profession is equally unknown. It is a sobering and haunting thought, however, that this trial almost certainly represents the only opportunity that will ever exist to evaluate scientifically this promising mode of therapy.

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