Progress Report

The International EC/IC Bypass Study

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The actual rate of patient recruitment from North America fell somewhat short of the original target within the first year, so that centers in Europe and later from Japan were brought into the Study. After 48 months of entry, it was apparent that more than a third of the patients entered were afflicted with an occlusion of the internal carotid artery and that a substantial number of them had not had ischemic events since angiography demonstrated the occlusion. Because this subgroup may have an improved prognosis over patients with inaccessible internal carotid artery stenosis or with middle cerebral artery stenosis or occlusion, its over-representation threatened to dilute the possibility of finding a surgical benefit from the procedure even though a genuine benefit might be present. To obviate this possible error, the original number of 1000 patients has been increased to 1400 and the deadline for patient recruitment has been extended to August 1982.

The Bypass Study has entered 1,240 patients from August 1977 through November 1981. Approximately 20% of these patients have been enrolled for more than 36 months, and the mean time since randomization stands at 21 months. Clinical follow-up data is collected every three months on all patients. The randomization process, as would be expected with sufficiently large patient cohorts, has achieved an almost exact comparability between the medical and surgical groups in all important entry characteristics. An excellent balance has been achieved between the groups in respect to age, sex, race, systemic hypertension, cigarette consumption, diabetes, previous myocardial infarction and evidence of peripheral vascular disease. There has been no disproportionate intake in either group in respect to the type and duration of the preceding ischemic events, the vascular territory affected, the period of time between the last event and randomization, nor the time between the last event and therapy. History of prior antiplatelet therapy, neurological disability rating and employment status are evenly distributed between the two cohorts.

A wide spectrum of entries per center exists between the 57 collaborating units in North America, Europe and Japan: 9 have entered more than 30 cases while only 14 have entered fewer than 15. Despite doubts expressed about the quality of the contribution made by smaller centers in cooperative clinical trials in cancer therapy, discrepancies have not emerged in the

REVASCULARIZATION of the brain emerged several years ago as a potential prophylactic surgical procedure for certain patients threatened with ischemic stroke. It seemed particularly attractive for patients with ischemic events continuing to recur in the presence of middle cerebral artery and internal carotid artery lesions inaccessible or not appropriate to conventional surgical treatment. The prospect of yet another imperfectly defined form of putative therapy for stroke-threatened patients aroused sufficient concern among many of the neurosurgeons expert in microvascular surgery that a randomized clinical trial was launched designed to achieve a scientific evaluation of the hypothesis that an anastomosis between the superficial temporal and middle cerebral arteries will reduce the incidence of stroke in these selected groups of patients. The need for the trial and its modus operandi have been described in earlier reports. In due course, a collaborative study was suggested. This Study is approaching the end of patient-entry and a short progress report is considered appropriate for the readers of this journal.

The International Extracranial-Intracranial (EC/IC) Bypass Study has accepted patients with TIA or minor stroke and angiographic evidence of stenosis or occlusion of the middle cerebral artery, surgically inaccessible internal carotid stenosis, or occlusion of the internal carotid artery of atherosclerotic origin. The Study was designed to detect at least a one-third reduction in the rate of stroke for surgical compared with medical treatment. The sample-size calculations assumed a stroke rate of 24% for the medical group over five years, a 4% perioperative stroke rate for the surgical group, and a later stroke rate for the surgical group of no more than 12%. To demonstrate these findings, at least 1000 patients were required. According to initial planning, this number was to be recruited within three years.

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EC/IC Study were the larger and the smaller centers. All centers were obliged to document the fact that the participating neurosurgeon had expertise in performing the procedure with a minimum experience gained from operating on ten consecutive patients in whom a postoperative patency rate of at least 80% could be validated by angiography. Furthermore, to avoid assessment bias all follow-up neurologic examinations are the responsibility of the neurological participant in each of the centers. Up to the present time 93% of the patients in the Study have been submitted to postoperative angiography and the patency rate stands at 91%. This patency rate is shared by large and small centers. Further evidence that centers with a small contribution to the Study have not had a negative impact is a similar low rate of complications and high quality and consistency of patient follow-up.

Two problems which present major difficulties in the analysis of results have beset the conduct of many clinical trials. One is the loss of patients to follow-up. The organization of the EC/IC Bypass Study has been designed to keep this statistically-insoluble enigma at a minimum. At no time since it was inaugurated have the whereabouts of more than two patients been unknown to the Central Office. The fact that this figure usually refers to two different patients during any given six-month period is evidence of the ongoing nature of the detective work involved in the pursuit of the data. The second problem is more particular to surgical clinical trials and concerns the crossing over of patients from the medical category, into which they have been randomized, to the surgical category. This phenomenon has not yet been troublesome. During the first 18 months, while the participants were becoming familiar with the technique of discussing randomization with prospective patients, 12 patients elected to have surgery despite being randomized to the medical regimen. During the same 18-month period, 12 patients randomized into the surgical category, refused to have the operation and elected medical treatment. Thus the impact of one group breeching protocol in one direction was offset by the same number crossing over in the opposite direction. In the subsequent three years of randomization, only 8 more have declined surgery and 9 more have demanded it after being assigned to a medical treatment category. Thus the overall crossover rate has been kept down to an acceptable level of 3%. This reflects the discipline of the participating centers to make every effort to adhere to the protocol. The determination to validate the possible benefit of the procedure persists despite enthusiastic reports in the literature and at national and international gatherings proclaiming, by anecdotal and unsubstantiated evidence, the purported value of this procedure in stroke prevention.

The goals of the study for each subgroup will be met if patient entries continue at or above the present rate. Until the past few months patients were being recruited at an overall rate of approximately 1 per day. Since then the rate has dipped slightly. This progress review closes with an earnest plea to the many steadfast contributors, and to the neurologists and neurosurgeons in the wider community of North America, Europe and Japan, to continue or even exceed their present cooperative efforts to ensure the satisfactory completion of this once-only study. This Study is entering the home-stretch and it is patently obvious that it will never again be possible to assemble a team to repeat a credible evaluation of this procedure in sufficient numbers and with acceptable controls to validate the worth of this procedure.

References

The international EC/IC bypass study.
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