“THE VALUE OF carotid endarterectomy in the management of asymptomatic carotid stenosis remains controversial and poorly documented.” So begins the description of the Veterans Administration Cooperative Study in this issue of STROKE. 1 The statement would be just as true if “in the management of asymptomatic carotid stenosis” were deleted. To date no properly designed, prospective, blinded study has established that the procedure is better than medical therapy for any condition. Only three prospective random studies have ever been reported, 2 3 - 4 and only one of these involved more than one center.3

One was a study of patients who had asymptomatic bruits and abnormal ocular pneumoplethysmography.2 Fifteen of these patients had angiography and surgery, and 14 were treated with aspirin. Of course with these small numbers, no significant results were obtained. When 28 patients who had refused to enter the random study were added, those treated surgically had significantly more unfavorable results. These machinations destroyed the original design so that the conclusions must be considered anecdotal.

A second study of patients with transient ischemic attacks (TIAs), also confined to one institution, was aborted because of a high operative morbidity and mortality after only 20 patients had been operated upon.4 Three died and five had strokes. The major endpoints, stroke and death, were almost the same in each group. During a 5.6 year follow-up of the surgical group, 10 died, six had strokes, and one had a TIA. In the medical group, during 6.1 years, 10 of 21 died, five had strokes, and 11 had TIAs. As the study was initiated in 1965, it is unlikely that any of the patients received platelet antiaggregating agents. Also, the average follow-up period was six months longer in the medical group. Because of the high early death and stroke rate, only 12 patients were at risk for TIAs in the surgical group for the full 5.6 years compared to 21 in the medical group. In addition, although the death and stroke rates were about equal, using the IMPS (intact months of patient survival) analysis of Jonas,3 those in the medical group obviously had many more months of survival.

The third study was a large multicenter study of patients with TIAs.3 It was performed in the 1960s and published in 1970. If all deaths and strokes that occurred before discharge from the hospital were discarded, there was a trend in favor of endarterectomy. If one looked only at the deaths and strokes that occurred during hospitalization, endarterectomy was associated with an eight-fold increase which would have occurred by chance in less than two in 1,000 times. But, when all events were considered from time of randomization, there were no significant differences between the treatment groups. Of course, this study is no longer appropriate. Medical treatments such as platelet antiaggregating agents and better antihypertensive therapy are now available, and it is assumed that the complications of surgery have decreased.

The issue would not be so critical if all surgeons had the low complication rates reported in some individual series. But, a number of institution and community studies of all patients consecutively operated upon report higher mortality and permanent stroke rates (Easton and Sherman, 21%; Modit et al, 5%; Brott and Thalinger, 9.5%; Slavish et al, 4.4%; Muuronen, 10%; Fode et al, 6%; and the ACASS, 3%). These rates appear to be more reflective of the nation as a whole than the individual series. The National Hospital Discharge Survey13 reported that carotid endarterectomies performed in civilian hospitals in the United States jumped from 15,000 in 1971 to 82,000 in 1982. A recent update14 indicated the rise is continuing and was 103,000 in 1984. These data do not include the public health hospitals, the armed forces, or the Veterans Administration Hospitals. These increases are occurring despite evidence that around 2.8% of those submitted to surgery die as a result of the procedure.13 As in most published studies the stroke rate ranges from one to five times the death rate, it is likely that the combined death and stroke complication rates are 5.6 to 16.8%. Recently, a multicenter retrospective review of all carotid endarterectomies performed at 46 institutions during 198111 indicated that although the average combined mortality and stroke risk was 6%, the range was from 0 to 21%. Therefore, it appears that surgeons and institutions where the procedures could be performed with a low complication rate might be identified by audit.

Even if the operation was of minimal risk for the patient, it places a large financial burden on the health care system. For example, the Medicare Peer Review
Organization of Indiana reviewed all Medicare cases from August 1, 1984 to January 31, 1986.\textsuperscript{19} From a total of 270,000, 451 were for carotid endarterectomy. Of these 15 (3.33\%) were discharged dead. The average charges for hospital costs alone was $7,765. For professional costs, Blue Shield of Indiana\textsuperscript{6} reported that the average charge was $2,700 for the surgeon, $540 for the assistant, and $432 for the anesthesiologist. The Physicians Fee Reference\textsuperscript{17} estimated that the radiologists professional fee for angiography was $519. Not considering neurologists, cardiologists, pathologists, etc, the professional fees were $4,191. These, added to the hospital charges, totalled $11,951. As Indiana is below the median for Medicare fees in most categories\textsuperscript{18} it is quite likely that the cost to the nation ($11,951 times 103,000) was in excess of $1.2 billion.

For these reasons, it is critical to establish whether endarterectomy is truly beneficial and in what conditions, and if there is benefit, to determine if it outweighs the risk. This can only be accomplished by studies similar to The Veterans Administration Cooperative Study for Asymptomatic Stenosis.\textsuperscript{1}

The participants of the Veterans Administration Cooperative Study must be lauded for their integrity and for their courage to submit their preconceptions to the rigors of scientific investigation. As this is one of the few prospective random studies to test the value of any surgical procedure for ischemic disease of the brain,\textsuperscript{2,3,4,5} it is unfortunate that it is not possible to applaud the good intent and to pass it on without further comment. Unfortunately, only one of the previous studies has produced clear-cut results that can be accepted by the scientific medical community as answering the questions posed.\textsuperscript{19} It is also unlikely that this study will be definitive even though the data obtained will be more useful than the anecdotal reports heretofore. A number of observations about the design need to be made so that the medical community does not expect more from the study than it can be expected to give, and will not be surprised if additional studies are required.

First, the study is concerned only with asymptomatic patients who have much lower event rates than those with TIAs. Next, this study takes place entirely within the Veterans Administration hospitals, and therefore, may not be projected to private civilian hospitals. The surgeons, the length of hospital stay, the type of patients, the predominance of males and many other factors may be different. This is always true of single-institution or single-system studies, but as these are obvious and easily recognized, other problems may be more serious.

More important are the selection factors of the patients for the study groups, the endpoints and the verification of endpoints, the lack of attempts to blind evaluators, and the assumptions concerning the percentage of endpoints in each group upon which the determination of sample size was made.

The success of this study is dependent upon the accuracy of the numbers of predicted events in each of the two treatment groups. If these are far off, all the estimates of sample size are invalid. If the sample size is too small and no significant differences are present, it would be concluded that none exist even if they do, a type-II error.

The sample size is based on the assumption that 20\% of the medically treated group will have a primary endpoint during the five years of clinical follow-up and that a reduction to 5\% or less in the endarterectomy group would be of clinical importance and should not be missed. One might argue about whether a one-tailed test is appropriate, but this is not as critical as the number of patients required in each treatment group needed to show a reduction from 20\% to 5\% for an alpha significance level of 0.05 with a power of 0.9. If the authors are correct that the event rate in the medical group will be 20\%, it will be almost impossible to reduce this to less than 5\%. As background for this study, all participating institutions reviewed the previous 24-month experience with endarterectomy. The overall operative mortality was 1.9\%. Neurologic morbidity was transient in 2.2\%, and permanent in 1.8\%. This total 5.9\% complication rate already exceeds the maximum event rate for the entire five years. Therefore, unless the estimates are far afield, and the complications much less for asymptomatic stenosis patients than others, the study cannot show a benefit for surgery.

In addition, the numbers are quite dependent upon the primary endpoints. They are TIA, stroke, or death due to stroke. Although patients and physicians consider many things to be worse than death or stroke, TIA is not one of them. If the only endpoint that occurred with frequency was TIA, would this warrant the widespread use of an expensive, painful procedure with some inherent risk for stroke and death? Even when TIAs continue, they usually occur in flurries and seldom seriously interfere with life. The inclusion of TIA as a primary endpoint will create problems in a study when it is impossible to blind the patient or evaluators. Stroke and death are usually not contestable but the diagnosis of a TIA can be quite subjective. How does one interpret the complaint of a "weak" or "numb" extremity that so often occurs upon waking up in the morning or after sitting for awhile in a chair? If a large number of TIAs are diagnosed in the medical group, it is possible that many would have endarterectomy. Thus, the more important endpoints of stroke and death could never be determined.

Although death is the most easily established of all endpoints, in this instance the investigator must make the decision whether it was due to stroke. This could be a source of bias, particularly for those who die outside a hospital.

The predictions for event rates for patients with asymptomatic stenoses are based on three studies.\textsuperscript{20,21,22,23} Each of these concluded that neurologic events increased when stenosis reached a critical point (60\%,\textsuperscript{21} 75\%,\textsuperscript{22} or 80\%,\textsuperscript{23}) and it was on these data that the event rates for this study were estimated.

The Busutill study\textsuperscript{20,21} is not pertinent. In addition to
asymptomatic bruits, the patients studied had TIA and stroke, and 41% of these were selectively removed for a surgical procedure.

The endpoints for Chambers and Norris\(^2\) were any neurological event including TIAs and strokes. John Norris (personal communication) reports that for stenosis greater than 75% the event rate for patients is 5.5% per year. This is based upon five events in 94 patients. Only two of these were in the distribution of an artery with greater than 75% stenosis. Two were in the verteobasilar system and one was on the opposite side in the distribution of a carotid artery with less than 50% stenosis. Therefore, there was a poor correlation of stroke to treatable stenosis.

Roederer\(^2\) concluded that there was an increased risk for stroke when the stenosis was in excess of 80%. This was based on five TIAs and three strokes. Only five strokes occurred during the study. One patient had occlusion of a carotid artery upon entry. One with 20% stenosis had a stroke as a complication of angiography. Only three progressed to 80% or greater during follow-up, and one of these had an occlusion two months before the stroke. At entry only nine arteries had 80 to 99% stenosis, and in no case did a stroke occur. One had a TIA at six-month follow-up.

A number of studies have followed patients to determine whether there is a relationship between the degree of the stenosis and neurological events.\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\),\(^11\),\(^12\),\(^13\),\(^14\),\(^15\),\(^16\),\(^17\),\(^18\),\(^19\),\(^20\),\(^21\),\(^22\),\(^23\),\(^24\),\(^25\),\(^26\),\(^27\),\(^28\),\(^29\),\(^30\),\(^31\),\(^32\),\(^33\),\(^34\),\(^35\),\(^36\),\(^37\) but none have shown an independent relationship of stenosis to stroke alone. There is either no current relationship or the relationship is related to multiple risk factors or to just TIA.

These data suggest that an event rate that could be related causally to a critical stenosis is unlikely, or much lower than estimated. Regardless, in each case the reported critical stenosis was greater than the 50% used by the Veterans Administration Hospital study.

These editorial comments are not intended to be excessively critical of the Veterans Administration Hospital study, but are considered necessary to point out potential pitfalls so that at the end of the study unwarranted conclusions are not made. It is understood that whenever one mounts a complicated multicenter study with a large number of participating physicians originating from different disciplines and with different preconceptions and biases, a number of compromises are necessary. Obviously from the description of the study design, the participants have considered most or all of the points mentioned in this editorial, and the final result was to some degree such a compromise.

It is possible that some definitive answers might be obtained. For example, if the operative complication rate is much lower for patients with asymptomatic bruits than those operated upon for all conditions, and if the participants are able to resist performing endarterectomies on patients in the medical group that have TIAs and continue to follow them for stroke and death, the study could be extremely valuable. In that case a significant decrease in stroke and death in one group of patients would be strong evidence in favor of the type of treatment received. Even if there is only a trend, the study could serve as a pilot for other studies that could recruit larger numbers and test smaller clinically acceptable differences. Thus, the findings that result from this study may focus subsequent studies so that they can be designed to definitively establish benefit or lack of benefit. In addition, the study may help pioneer an approach to testing surgical procedures in the same objective, unemotional, scientific fashion that is required before any drug is released for general use in this country. Regardless, for the first time in almost 20 years, a large prospective random multicenter study has been mounted to test the impression that endarterectomy is of value. At last from the darkness there is a glimmering of science.

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The time has come for a consistent methodological approach in stroke outcome studies. In this issue of Stroke,1 Dombový, Sandok, and Basford, writing from the point of view of stroke rehabilitation, have provided a comprehensive review of the findings of recent stroke outcome research. They effectively emphasize the fact that, if important but controversial issues about stroke rehabilitation are to be resolved, greater attention must be given to the way in which stroke outcome studies are conducted.

Research about the outcomes of stroke is important for many reasons. First, it monitors the impact of the disease on society: survival and disability data must be added to incidence rates to provide the full picture. Second, it provides the basis for prognosis: our current appreciation of the positive, as well as the negative, probabilities facing stroke survivors has come from outcome studies done during the last two decades.2-3 Third, it provides a baseline to which controlled studies of interventions can legitimately be related. For example, much early functional improvement after stroke is really part of the natural history of the disease and only greater than expected functional levels should be attributed to an intervention. Finally, these data provide the basis for rational planning of health and human services for stroke survivors, both in type and magnitude.

As in all important clinical and epidemiological research, it is vital that stroke outcome studies be done with a methodologically rigorous approach. Anything less will only create more confusion and not answer the crucial questions that have been identified. The following consideration of some of these methodological issues will illustrate the complexities that must be effectively managed if future stroke outcome research is to be maximally productive.

There are at least five important methodological issues that must be dealt with in studies of stroke outcome. These are (1) appropriate study groups, (2) classification of neurological deficits, (3) identifying the role of comorbidity, (4) the outcome variables to be studied and how these are to be measured, and (5) allowing for the all-important factor of timing.

**Appropriate Study Groups.** Questions about the natural history of stroke are best answered by epidemiological studies that include all cases, not just those that happen to be referred to a specific hospital or rehabilitation center. The latter settings, however, are quite appropriate for a clinical trial of a new intervention, provided a prospective randomized design is used. At present, further purely descriptive studies of stroke inpatients are unlikely to produce useful new information unless a new outcome variable is used. Epidemiological studies, on the other hand, continue to provide needed data on differences in incidence and natural history in different populations.

**Classification of Neurological Deficits.** In stroke outcome research, it is important that the baseline neurological status of each study group be clearly identified. If the constellations of neurological deficits observed are unusual (e.g. more patients with left than right hemiparesis), the outcome determinations must be analyzed separately for each subset before inferences are made about stroke survivors as a whole. In general, stroke studies provide a paucity of information of this type even though it is of obvious importance in assessing outcomes. Any study that attempts to provide data that will enable more precise prognostication is particularly obliged to give close attention to the classification of neurological deficits at baseline.

**Outcome Variables to be Studied.** This is an area of...
Carotid endarterectomy studies: a glimmering of science.
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