Eighth Conference

CEREBRAL VASCULAR DISEASES

FLETCHER H. McDOWELL,
Chairman

FLETCHER H. McDOWELL and ROBERT W. BRENNAN,
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Published September 1958

THIRD CONFERENCE, January 4-6, 1961
C. H. Millikan, Chairman; R. G. Siekert and J. P. Whisnant, Editors
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FOURTH CONFERENCE, January 8-10, 1964
C. H. Millikan, Chairman; R. G. Siekert and J. P. Whisnant, Editors
Published April 1965

FIFTH CONFERENCE, January 5-7, 1966
C. H. Millikan, Chairman; R. G. Siekert and J. P. Whisnant, Editors
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SIXTH CONFERENCE, January 10-12, 1968
James F. Toole, Chairman; R. G. Siekert and J. P. Whisnant, Editors
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James F. Toole, Chairman; J. Moossy and R. Janeway, Editors
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Preface

The Eighth Princeton Conference on Cerebral Vascular Diseases took place on January 5, 6, and 7, 1972, with Dr. Fletcher H. McDoweil serving as chairman. On the Planning Committee for the conference were Drs. Jack P. Whisnant, Peritz Scheinberg, Eugene Braunwald, Robert W. Brennan, Robert A. Fishman and Oscar Reinmuth. The editors of the proceedings are Dr. Fletcher H. McDowell and Dr. Robert W. Brennan. The meeting as in the past was sponsored by the American Neurological Association and the American Heart Association Council on Cerebrovascular Disease.

We wish to express our gratitude for the continued support of the National Insitute of Neurological Diseases and Stroke and the National Heart and Lung Institute of the National Institutes of Health.

Only minor alterations have been made in the format of the edited transactions. When references to the medical literature were used in Open Discussion, they were listed at the end of each session if the participants furnished the proper citations to the editors. Some of the formal presentations contained a large number of illustrations and references, and these whenever possible have been included intact.

The editors wish to express their thanks to the trustees of the conference, Drs. Jack P. Whisnant, Peritz Scheinberg, Edwin B. Boldrey, Ray W. Gifford, Fletcher H. McDowell, and Eugene Braunwald, for their support and guidance.

The editors are especially pleased to offer their thanks to the many co-workers who have assisted them in the development of this latest Princeton Conference on Cerebral Vascular Disease. Mrs. Diana Carucci continually assumed a heavy burden of typing and planning for the program for this meeting. Her assistance in the preparation of the proceedings of this conference has been invaluable and her long and continued efforts on behalf of the conference are greatly appreciated. The recording of the conference was again ably handled by Mr. Cyril Lichtensteiger and his staff.

Fletcher H. McDowell
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Contents

Introductory Remarks

FLETCHER H. McDOWELL, M.D.

Cornell University Medical College
New York

It is my considerable pleasure to welcome all of you to this the Eighth Conference on Cerebral Vascular Disease held at the Nassau Inn in Princeton, New Jersey. The first of these conferences was held in January 1954, and subsequently they have been held at intervals of 2 to 4 years. In recent years, because of the rapid increase in new information about cerebral vascular disease, the conferences have become biennial.

In the audience this evening are several men who must be given special credit for the founding and perpetuation of this conference. Dr. Irving S. Wright, Emeritus Professor of Medicine at Cornell University Medical College, was the founder of this conference and has been instrumental in its perpetuation. Dr. Clark H. Millikan, of the Mayo Clinic, has been the mainstay in its continued development. Most recently, Dr. James F. Toole, Professor of Neurology at the Bowman Gray School of Medicine, has been its guiding light. In the audience as well are individuals who have loyally served as editors of the proceedings: Drs. Robert G. Siekert, Jack P. Whisnant, Richard Janeway, and John Moossy. I am also pleased to welcome members of the executive branch of the National Institutes of Health: Dr. Edward F. MacNichol, Jr., Director, National Institute of Neurologic Diseases and Stroke; Dr. Murray Goldstein, Associate Director, National Institute of Neurologic Diseases and Stroke; Dr. Jerome G. Green, Associate Director, National Heart and Lung Institute; and Dr. Gardner C. McMillan, Chief, Arteriosclerosis Branch, National Heart and Lung Institute.

I am pleased, as were the former conference chairmen, to welcome a number of distinguished foreign visitors. This evening we have with us Dr. James B. Brierley, Medical Research Council Laboratories, Carshalton, Surrey; Dr. Bryan Jennett, Division of Neurosurgery, University of Glasgow; Dr. Alan Richardson, Division of Neurosurgery, Atkinson Morley's Hospital, London; Dr. Olaf B. Paulson, Bispebjerg Hospital, Copenhagen; Dr. Bo K. Siesjö, University of Lund; and Dr. S. Pakarinen, Neurosurgery Division, University of Helsinki.

The character of each conference has been a little different and the subjects emphasized quite variable. Throughout, there has been a major endeavor to bring important problems in the pathophysiology, diagnosis, and treatment of cerebrovascular disease into sharp focus. There has always been an effort to look at the new, the old, and the neglected problems in the field of cerebral vascular disease. The first conference, for instance, was primarily devoted to a straight clinical and pathologic review of the various types of cerebrovascular disease. Subsequent conferences placed more emphasis on the physiology of cerebral circulation, its relation to symptoms and signs, and its role in production of brain pathology. Other conferences emphasized the importance of atherosclerosis—the substrate of cerebral infarction, the most common kind of cerebrovascular disease. Later conferences have emphasized the importance of identifying and treating premonitory or warning signs of developing stroke. In every conference there has been an emphasis on what can be done for the patient with cerebro-

vascular disease. In every instance, when treatment has been discussed there has been an effort to summarize and bring up to date the advantages and indications for a particular regimen and to relate it to observable changes in brain physiology. The goal of the conference in recent years has been to put in perspective advances in the understanding of cerebrovascular disease, pathophysiology, diagnosis, and treatment, and to review the important research contributions that make such statements possible.

This published proceedings have served a major role in providing definitive statements and excellent summaries of the various aspects of cerebral vascular disease. The conference has never discouraged the presentation of new information. The areas explored by a particular conference have always contained new and often unpublished information. With the vast increase in information being disseminated about cerebral vascular disease, it becomes harder and harder to provide, in the time allotted the conference, a comprehensive summary of progress to date. Each program committee must therefore select for emphasis those aspects of the problem which seem to have received most definitive attention in the interim and bring into view new problems and new ideas.

Another key reason for the conference is the opportunity to gather together, over a 3-day period, individuals interested in cerebral vascular disease, to allow them to become acquainted with one another, to exchange ideas and discuss problems of mutual interest. Because of the nature of the programs, time for this activity has not always been optimal, but the 3 days here at Princeton at this time of year have provided the isolation conducive to closer contacts among individuals interested in these problems. It has also been possible on each occasion to welcome young and new investigators into the field, to hear of their work, and to provide them the opportunity for contact with colleagues well established in this field.

This evening we will discuss the surgical treatment of stroke; tomorrow, the treatment of aneurysms by a variety of methods and the topic of cerebral ischemia; and on Friday, diagnostic methods and new suggestions for treatment. Several important things must be emphasized for the proper conduct of the program. If we are to cover all the material in the program, it will be necessary that speakers adhere strictly to the time allotted them and that open discussion be given as much time as possible. It is also of great importance that each individual who speaks before the conference clearly identify himself, as the conference is being recorded and it will be necessary to identify clearly who made each statement. I hope none of you think I am too rude when I insist on adherence to the allotted time and interrupt your speech when that time is up.

The first speaker of the evening will be Dr. F. William Blaisdell, who will discuss the surgical treatment of stroke.

Extracranial Arterial Surgery in the Treatment of Stroke

WILLIAM BLAISDELL, M.D.
University of California
San Francisco

The decision to organize the Joint Study of Extracranial Cerebrovascular Disease was made in January 1959. The original aims of the study were to determine the incidence of extracranial arterial disease in patients with symptoms of cerebrovascular disease, to evaluate the risks and advantages of angiography, and to determine the efficacy of arterial reconstructive surgery in modifying the natural history of the disease.[1-5] Accumulation of data began in July 1960, but the original protocol for compilation of data needed by the study was found to be inadequate. Formal collection of data began with distribution of a new protocol to the participants of the Cooperative Study on July 1, 1961.

Initially 10 institutions participated in the study. This number was later increased to 24. It soon became apparent that the determination of the efficacy of surgery in modifying the natural history of cerebrovascular disease required a controlled study.[6] In 1961, 5, and later 13, of the 24 institutions agreed to choose patients at random for surgery, using common criteria. Random allocation of comparable surgical candidates with symptoms of occlusive cerebrovascular disease into surgical and nonsurgical groups was officially introduced into the study, and information on the first such patients was submitted to the Central Registry in March 1962. From that time until the admission of new cases was terminated on July 1, 1969, 1,378 randomized cases were admitted to the study.

The incidence of extracranial cerebrovascular disease, the pattern of distribution of the lesions, and the results of angiography have been reported previously.[1,2,4] The results of surgery for extracranial cerebrovascular disease can be assessed by the effect on mortality, by the quality of survival, and by the prevention of stroke and transient ischemic attacks. The effect of surgery on transient ischemic attacks has been described previously.[7,8] Stroke prevention could not be analyzed independently of death because of the high initial mortality in the patients treated surgically. The quality of survival proved difficult to assess and was of necessity subjective. Moreover the interinstitutional variability in the quality of the outcome criteria in the protocols discouraged the use of this parameter. The present discussion, therefore, will compare the survival of patients who had operative removal of atherosclerotic lesions in extracranial arteries with the survival of patients treated in identical fashion medically, but who did not have surgery.

RESULTS

During the period of randomization, which extended from March 1962 to June 1969, 1,378 patients were selected randomly for medical or surgical therapy by criteria previously described.[9] Of these patients, 685 were treated with the best possible medical therapy (medical group) and 693 were treated with operation plus the best possible medical therapy (surgical

group). Of the 1,378 patients, 613 died during the period of the study. The principal cause of death was heart disease (36.5 percent); one-third of the deaths were due to stroke, and the remainder were due to a wide variety of causes.

The medical and surgical groups were analyzed separately (Table 1). The cause of death in the two groups was comparable, although there were more deaths from stroke in the surgical group owing to the high incidence of postoperative strokes. When the 43 postoperative deaths were excluded (Table 2), there was a dramatic difference in the deaths from stroke in the two groups: 96 in the medical group; 68 in the surgical group. The risk of vascular reconstruction carried out at the different anatomic sites varied widely. Table 3 presents the data for the study as a whole.

One of the problems inherent in a cooperative study is the need to pool data and draw conclusions therefrom. In our study there was considerable interinstitutional difference regarding surgical mortality. Figure 1 demonstrates the wide variability in data among the 24 hospitals. The mortality associated with operations at the carotid bifurcation ranged from zero in four centers to as high as 21 percent in other institutions. This wide variation must be taken into consideration when the data are interpreted. The surgical mortality progressively decreased during the study. The initial average mortality for carotid bifurcation endarterectomy was 9.5 percent but dropped to only 2.8 percent in the final year of the study (Fig. 2).

Since most of the operations were carried out at the carotid bifurcation, we have concentrated our evaluation of the effects of surgery at this level. Significant differences for operations at other sites were difficult to determine because there were relatively few patients in each category.

TABLE 1

Cause of Death in Medically and Surgically Treated Patients

Cause of death	Medical group	Surgical group
Cardiac disease	116	108 (5)*
Stroke	96	111 (43)
Infection	29	36 (6)
Cancer	16	26
Pulmonary embolism	7	11 (2)
Gastrointestinal or hepatic disease	9	6
Trauma or suicide	4	10 (1)
Other vascular disease	5	5 (1)
Renal disease	4	4
Unknown	4	6
Total	290	323

* Numbers in parentheses indicate postoperative deaths.

TABLE 2

Cause of Death (Excluding Postoperative Deaths) in Medically and Surgically Treated Patients

Cause of death	Medical group	Surgical group
Cardiac disease	116	103
Stroke	96	68
Infection	29	30
Pulmonary embolism	7	9
Other vascular disease	5	4
All other causes	37	51
Total	290	265

TABLE 3

Mortality Associated with Various Vascular Reconstructive Procedures

Location of operation	No. of patients	Mortality (%)
Carotid bifurcation (single procedure)	1,695	5.7
Carotid bifurcation (bilateral procedure)	395	12.0
Common carotid artery (single procedure)	155	9.0
Subclavian artery (single procedure)	38	5.3
Vertebral artery (single procedure)	130	6.2
Other (single procedure)	28	14.3
Other (multiple procedure)	216	12
Total	2,657	7.4

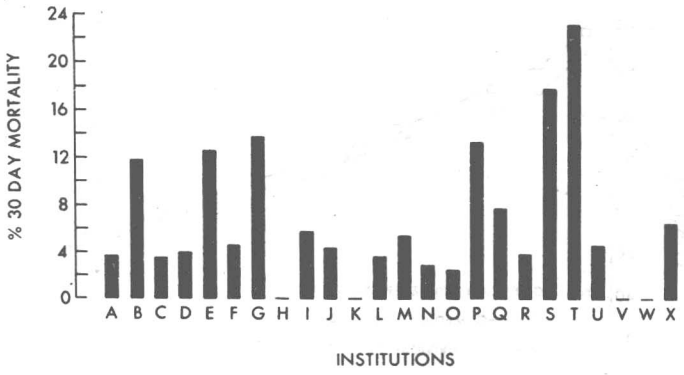

Fig. 1. Mortality associated with carotid bifurcation endarterectomy in the 24 participating institutions.

The patients who were operated upon at one carotid bifurcation only were observed for periods of up to 96 months and were analyzed by the life-table method. This represents 60 months of follow-up in almost all the figures presented. When the effective sample size in the two groups (medical and surgical) exceeded 30, a difference of greater than 1.96 indicated chance occurrence of less than 5 percent and was considered significant. Average follow-up was 36 months, and most of the patients were followed for 55 to 60 months; 111 patients were lost to follow-up (60 in the medical group, 51 in the surgical group).

Review of the randomized series as a whole shows that when the medical and surgical groups are compared, there is no significant difference in survival (Fig. 3). The initial mortality in our surgically treated patients was not compensated for by any detectable improvement in survival in this group during the period of follow-up.

Since most of the deaths were due to heart disease, and since hypertension is a well-documented risk factor in patients with stroke,[10] the data were analyzed with reference to these factors. Patients who did not have end-stage disease (defined as severe neurologic deficit at initial examination) were reviewed in the period when surgical mortality was the lowest (July 1965-1970). Patients were divided into groups with and without hypertension, the dividing line being a blood pressure value of 160/95 mm Hg. They were also divided into groups with and without heart disease. Those with heart disease were patients described in the protocol as having electrocardiographic abnormalities, angina, or myocardial infarction. This produced four categories: (1) normotensive patients without heart disease (Fig. 4), (2) normotensive patients with heart disease (Fig. 5), (3) hypertensive patients without heart disease (Fig. 6), and (4) hypertensive patients with heart disease (Fig. 7).

Normotensive patients with heart disease had a significantly greater survival rate if they were managed medically. Presumably the stress of surgery resulted in a much higher immediate

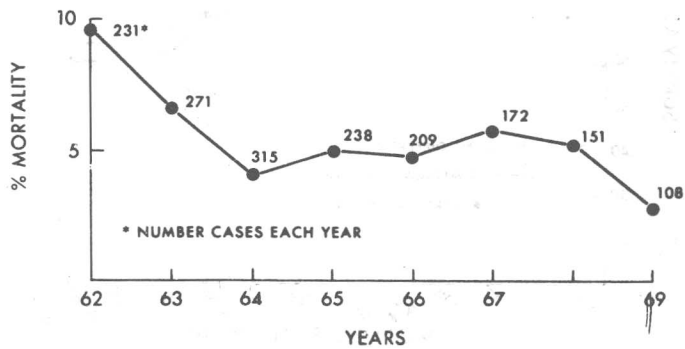

Fig. 2. Mortality associated with carotid bifurcation endarterectomy during each year of the study.

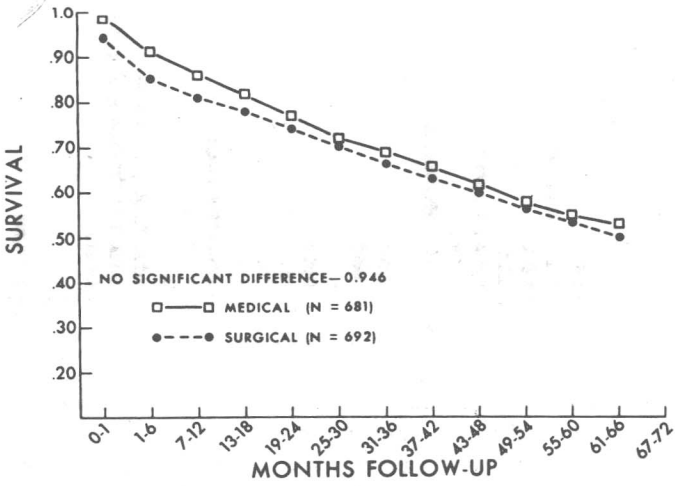

Fig. 3. Survival rates of medical and surgical groups, all patients.

mortality which was not compensated for by a lower death rate during the follow-up period. Conversely, normotensive surgically treated patients without evidence of heart disease showed a slight, but not statistically significant, increase in survival over those treated medically. Hypertensive patients without heart disease had a higher survival rate if they were treated surgically than if they were managed medically, although this difference was not statistically significant. Surgically treated patients with both hypertension and heart disease had a slightly higher survival rate than their medically managed counterparts, but this difference was not statistically significant.

The patients were also analyzed by lesions and by symptoms. This analysis was applicable only to the relatively common lesions, such as unilateral stenosis, bilateral stenosis, and stenosis plus occlusion of the internal carotid arteries. The number of patients with such lesions as unilateral and bilateral occlusions was too small to allow statistical evaluation.

There was no significant difference in mortality between the medically and surgically managed groups with unilateral carotid stenosis, although survival in the surgical group was slightly higher at almost all follow-up intervals (Fig. 8). When the patients with unilateral carotid stenosis were examined relative to

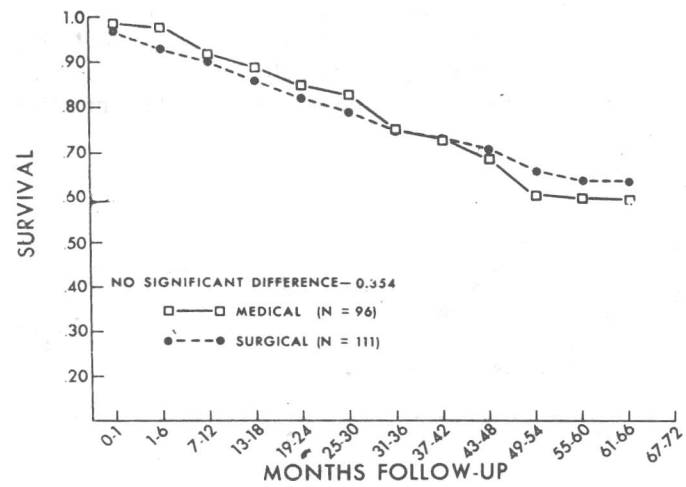

Fig. 4. Survival rates of medical and surgical groups, normotensive patients without heart disease.

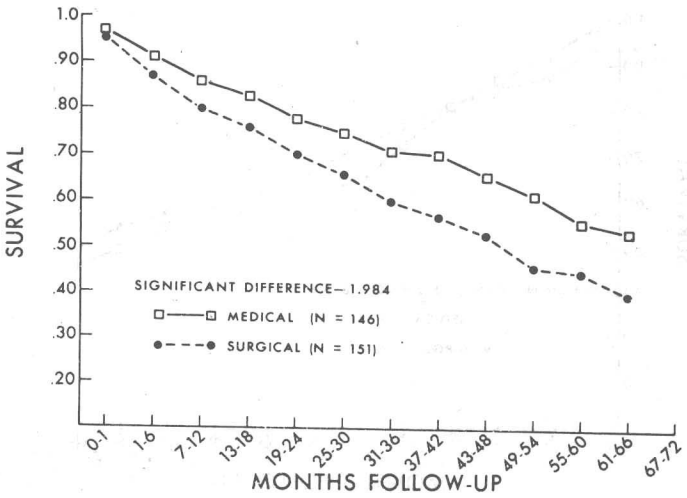

Fig. 5. Survival rates of medical and surgical groups, normotensive patients with heart disease.

symptoms, the differences in the two groups still were not striking. Patients with carotid symptoms and unilateral carotid stensois had a nearly identical survival rate, whether treated medically or surgically (Fig. 9). Among patients with unilateral carotid stenosis and vertebrobasilar symptoms, the difference in survival was not significant either, although the group treated surgically seemed to have a better 5-year survival rate (Fig. 10).

When patients with bilateral carotid stenosis were analyzed, a marked difference in survival in favor of the surgical group was noted. The difference was marked at all intervals of follow-up and was statistically significant at the 25- to 30-month interval (Fig. 11). Patients with bilateral carotid stenosis were also analyzed by symptoms. Patients who underwent surgery on the stenotic artery which supplied the area of brain considered responsible for symptoms showed even greater improvement in survival than the surgically treated group with bilateral carotid stenosis as a whole. Those who underwent surgery on a carotid artery which did not supply the area of the brain thought responsible for the symptoms had a lower survival rate than the surgically treated bilateral stenosis group as a whole (Fig. 12).

Improved survival was detected in patients with carotid stenosis plus occlusion of the

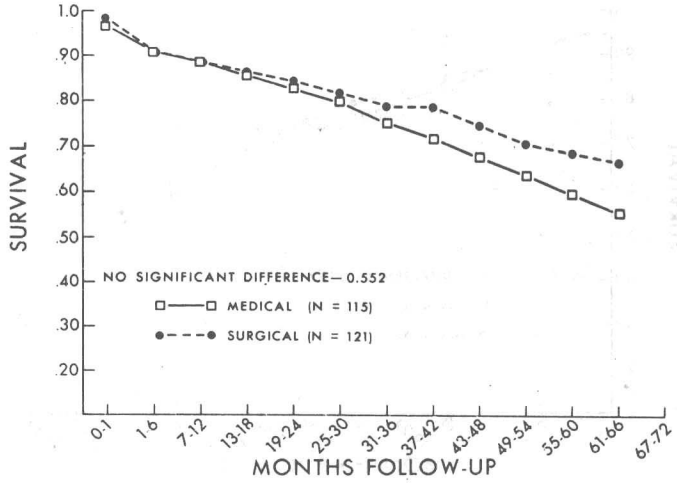

Fig. 6. Survival rates of medical and surgical groups, hypertensive patients without heart disease.

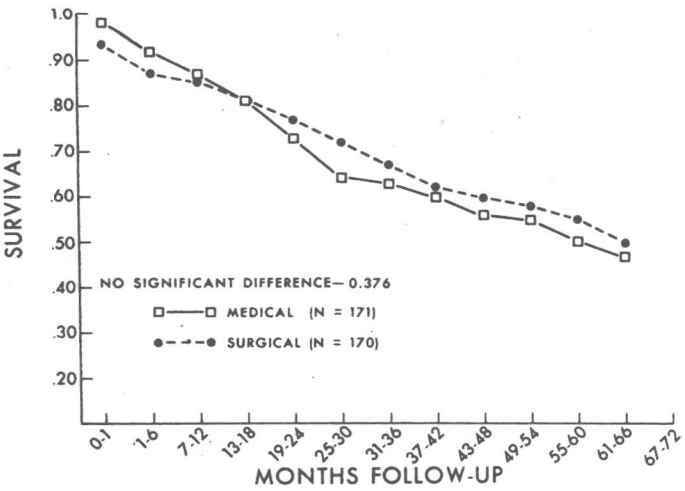

Fig. 7. Survival rates of medical and surgical groups, hypertensive patients with heart disease.

opposite carotid artery in the medically managed group. The difference was significant at every interval of follow-up and appeared to be related to the initial and unacceptably high surgical mortality (16 percent; Fig. 13). This group could not be divided further because of its small size. However, patients who were operated upon on the symptomatic side fared much better than those who were operated upon on the asymptomatic side. This finding was identical to that in the bilateral carotid stenosis group described above.

The patients with unilateral internal carotid occlusion and bilateral internal carotid occlusion were examined. Although neither group showed benefit from surgical treatment, both groups were too small for statistical evaluation.

DISCUSSION

The primary problem in randomization of patients for surgical treatment was that an operation is dramatic and potentially potent therapy and the decision to randomize surgical treatment provoked considerable controversy when initially proposed. Some participants in the study entered it with skepticism about the relation of extracranial arterial disease to the etiology of stroke and had serious reservations about the potential of surgical treatment. The

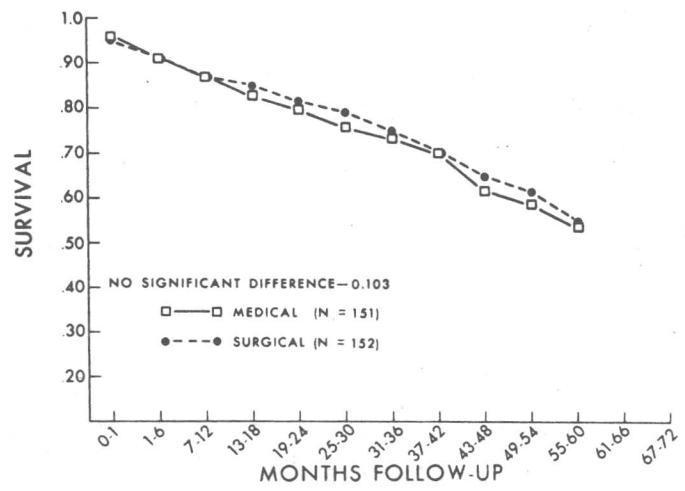

Fig. 8. Survival rates of medical and surgical groups, all patients with unilateral carotid stenosis.