CLINICAL PROGRESS

Recent Trends in Therapy of Cerebral Vascular Disease

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In the past decade great interest in the problems of cerebral vascular disease has developed. Increasing numbers of centers throughout the country have gained experience in the therapy of strokes, some of which offers considerable hope for the future.1,2 It is fitting at the close of this decade to review and assess what has been accomplished and ask what may we expect in the future.

Certain gaps in knowledge as well as definite variables are immediately obvious. Knowledge regarding the natural history of strokes is inadequate to assess fully the value of the therapeutic methods that have been advocated. In addition, the course of a stroke can be so variable from patient to patient that a large number of patients must be studied before any one given measure can be truly validated. All of us have seen many patients with stroke who appeared to be seriously ill at onset and who walked out of the hospital some weeks later, without "active" intervention on the part of the physician. Any disease with so inconsistent a picture must be most carefully investigated before final answers can be given.

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Conservative Therapy

It would appear that the attending physician's attitude toward his patient with stroke may play an important role in affecting the outcome. In a study of large numbers of patients with strokes, Nielsen3 found that the mortality rate could be reduced from 44 to 31 per cent merely by improving the nature of the general medical care these patients received. In cerebral thrombosis the mortality rate was reduced from 30.2 to 24 per cent. Thus, one must adhere to the following precepts. One cannot be certain of the prognosis at onset. Coma, while carrying serious implications, need not end in death or serious residual impairment. Therefore, all patients with strokes should be made ambulatory and exercised as soon as possible. Maintenance of an adequate cardiac output must be assured. Close attention must be paid to insure adequate pulmonary ventilation. Dehydration must be avoided. Hypoglycemia should never occur and polycythemia must be corrected as rapidly as possible.

Unfortunately, even with the most expert medical and nursing care, there is an irreducible minimum beyond which conservative therapy cannot go, and for this reason more active intervention has been attempted.

Cerebral Thrombosis

Therapy has been aimed at three stages in the life history of cerebral thrombosis (1) in the prodromal stage when the individual may be experiencing recurrent transient episodes; (2) during the acute phase; (3) in the recovery phase and thereafter for a definite or indeterminate period of time.
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Phase 1. The Period of Recurrent Transient Ischemic Episodes

The work of Kubik and Adams,4 Fisher,6 Denny-Brown,7 and Millikan and associates8,9 has done much to clarify our concepts of the pathogenesis of transient ischemic attacks. It is clear that these episodes are far more common than was previously suspected. They may be evanescent, however, and must be inquired for most carefully during history taking. Fisher10 found that of 125 patients with a diagnosis of cerebral thrombosis, 13 per cent had transient ischemic attacks as their only clinical manifestation of disease and 42 per cent had transient ischemic attacks progressing to persistent deficit. In a recent review of 57 patients with proved carotid artery occlusive disease, a history of transient ischemic episodes was obtained in 16 (25 per cent).11

A. Anticoagulant Therapy

In this variety of stroke, anticoagulant therapy has seemed to be quite efficacious. Dr. Millikan has been kind enough to allow us to give the most recent figures of the experience of the Mayo Clinic: in 163 patients with basilar artery insufficiency the use of anticoagulants has resulted in cessation of attacks in 148 patients. In patients with carotid artery insufficiency the attacks were stopped in 131 of 145 patients. Fisher10 has reported a similar experience with anticoagulants: of 29 patients with transient ischemic attacks, anticoagulant therapy achieved cessation of recurrent attacks in 28. Upon cessation of anticoagulants in 20 of these patients transient ischemic attacks recurred in 12.

These figures are so impressive that they almost do away with the need for controlled studies. However, since we have found patients with transient ischemic attacks in whom the episodes ceased spontaneously11 (as has Fisher),10 a controlled study is considered desirable. At present a cooperative study of cerebral vascular disease is in progress at several institutions and perhaps an answer will be forthcoming. Certainly one can say that the evidence in favor of the efficacy of anticoagulant drugs in therapy of this variety of stroke is strongly suggestive.

B. Surgery

In recent years surgeons have attempted to aid individuals with transient ischemic attacks. They have had considerable success in lowering operative morbidity and mortality while re-establishing circulation in obstructed cervical internal carotid arteries and somewhat less success in obstructed vertebral arteries.12,13 In some patients surgery has succeeded in abolishing transient ischemic attacks when anticoagulant therapy has failed. The final answer is certainly in the future. We shall have to learn of the results of follow-up of patients and the results of additional groups. We know that our group has had a much higher morbidity and mortality in the performance of angiography,14 which is an essential part of the diagnostic workup, and that some of the patients so treated at The New York Hospital and Bellevue Hospital to date have not done well. While there is no doubt that surgery has a place in the therapy of strokes, it may well be a more limited role than some workers at present suggest. Here again a controlled study would be of great value. A word of warning: a patient experiencing transient ischemic attacks need not have vascular disease. In the younger individual multiple sclerosis may certainly present in this fashion, and we have seen brain tumors cause just such a symptom complex.15

Phase 2. The Acute Phase

A. Carbon Dioxide Inhalation

Carbon dioxide is a most potent cerebral vasodilator. It is questionable, however, whether it can add any further vasodilator effect to an infarcted area. Two careful studies of the effects of carbon dioxide inhalation during the acute phase of a stroke have failed to find any benefit from it.16,17 In similar fashion, vasodilator drugs have not been found to be of value.18-20

B. Stellate Ganglion Block

There are numerous case reports in the literature describing spectacular results in individual patients following stellate block.
Incidence of hemorrhagic complications in untreated and treated patients.

De Takats reports that in a series of 55 patients, 55 per cent demonstrated improvement in their clinical status following single or multiple injections of the stellate ganglion.\textsuperscript{21} It is difficult to see a physiologic basis for this, and in two controlled studies, no value of the procedure could be demonstrated.\textsuperscript{17,22} We find it even more difficult to ignore these controlled studies because of the variability of the picture of stroke.

\textbf{C. Anticoagulant Therapy}

There are several questions that must be asked as one contemplates the use of anticoagulant therapy in strokes:

1. What are the risks of misdiagnosis?\textsuperscript{1}
2. What is the rationale of such therapy?\textsuperscript{1}
3. What has been the risk of complications as experienced to date?\textsuperscript{1}
4. What has been the gain to date?\textsuperscript{1}

\textbf{Answers.} 1. There is a 10 per cent chance of diagnosing a small intracerebral hemorrhage as a cerebral thrombosis. The likelihood of overlooking some other type of cerebral lesion, such as subdural hematoma or brain tumor, is approximately 5 per cent.

2. Anticoagulants are used in the hope of preventing an extension of an intraluminal thrombosis and thus of limiting the area of infarction.\textsuperscript{10} It is also hoped that, as in animals, anticoagulant therapy will hasten recanalization of the obstructed vessel.\textsuperscript{23,24} In addition, the work of Meyer\textsuperscript{25} has demonstrated the prevention of sludging of blood in small cortical vessels with the use of anticoagulants. Finally, 14 per cent of the deaths in patients with cerebral thrombosis are due to pulmonary emboli and 37 per cent of all patients with a stroke have extracerebral thromboembolic complications with a mortality of 30 to 38 per cent.\textsuperscript{1} Anticoagulant therapy may well prevent the occurrence of these complications or lessen their frequency.

3. If one should misdiagnose a small intracerebral hemorrhage as a cerebral thrombosis and initiate anticoagulant therapy, one obviously will worsen the situation. This would seem inevitable if a large enough group of patients is treated.

In addition, the raising of a prothrombin time above normal has risks inherent in the procedure itself. Several authors have now reported fatal cerebral hemorrhages in the course of anticoagulant therapy in the acute phase of cerebral thrombosis.\textsuperscript{26-28} The protocols of these patients reveal that many of these complications have occurred in association with a prothrombin time well beyond the accepted therapeutic range. This does not absolve anticoagulant therapy, however, for this may occur with the best of laboratory control. The thromboplastin used by the authors reporting severe hemorrhagic complications has been a brain thromboplastin. Our group believes that this type of thromboplastin is not sufficiently sensitive for this type of work. In addition, our group believes that a dilution of plasma to 12.5 per cent is most helpful in detecting early excess in action on prothrombin activity before the undilute specimen rises into the dangerous area.\textsuperscript{29}

It is our opinion that every patient should have a spinal fluid examination prior to the institution of anticoagulants for a stroke. Furthermore, we believe that to use anticoagulants...
in the presence of severe hypertension is to court disaster.

In our controlled study we have not as yet had the ill fortune of a hemorrhagic complication resulting in death either in the acute phase or on long-term therapy. We hope that we can continue to avoid such a tragedy.

4. It is generally agreed that anticoagulant therapy is of no definite value if used after a complete lesion has occurred. In a slowly advancing stroke both Fisher and Carter report a definite benefit gained by the use of anticoagulants and this also has been our experience. On the other hand, others have reported anticoagulants to be of no benefit even in this type of stroke. Here again it is hoped that the results of the Cooperative Study may be enlightening.

Anticoagulants have definitely been shown to reduce the incidence of extracerebral thrombosis if used during the acute phase of a stroke. In one large series the incidence has been reduced from 37 to 3 per cent. It has also been the experience of our study group that this is true although at present the number of patients is not large enough to make definite statements.

Thus, one must balance the dangers of the use of anticoagulants against the benefits one hopes to gain. It would seem that at this point the answer is not available and one should avoid advocating the routine use of anticoagulants in the acute phase of a cerebral thrombosis. If the individual physician does use anticoagulants, he must carefully select his patients, realizing that this therapy is still in the early stages of development and that far more must be learned before all of the indications and contraindications are universally accepted.

D. Surgery

To date the good results claimed for surgery have occurred only if surgery has been undertaken for the treatment of transient ischemic attacks or very shortly (minutes) after a complete occlusion has taken place. The use of this procedure late in the development of a complete lesion has usually resulted in failure. The successful areas approached have been the carotid arteries, especially at the bifurcation, and the vertebral arteries. Well-controlled long-term studies of the value of surgery for these conditions are needed.

E. Fibrinolytic Agents

There are no large studies of the use of these agents in patients with strokes. It may well be that these agents will prove most efficacious in treatment of transient attacks or a slowly progressive stroke, the logic of such thinking being self-evident. It is hoped that a group that is planning to apply its resources to testing these agents will perform a controlled study of the effects of these drugs.

Phase 3. Recovery Phase

What are the facts known at present that support a study of long-term anticoagulant therapy following a complete or incomplete stroke? In a recent paper the recurrence rate of strokes in a large number of patients was described. At the end of 1 year one third of the survivors of the acute phase had had another stroke. By the end of 4 years, two thirds of the initial surviving patients had experienced a second stroke. Eighty-two per cent of all the deaths in the group surviving the initial stroke were due to cerebral or coronary artery disease. These figures are shocking in their indictment of atherosclerosis with resulting thromboembolism as the cause of repetitive disability and death in this particular group of patients.
Mortality rate in untreated and treated patients.

In another study, the greatest cause of death was again disease of the vessels of the brain and heart. In yet another study of 65 patients with thrombosis of the carotid-middle cerebral tree, 34 per cent were dead of recurrent stroke in 2 years.

Thus, one would use anticoagulants in an attempt to reduce the incidence of recurrent thrombosis.

Is there a risk to long-term anticoagulant therapy. In our study there has been a 20 per cent incidence of nonfatal hemorrhagic complications, some of which were definitely serious, with one patient experiencing a subarachnoid hemorrhage (fig. 1).

In other studies of the long-term use of anticoagulant drugs in the therapy of coronary artery disease bleeding complications have occurred with a similar incidence. In addition, fatal intracerebral hemorrhage has occurred in 3 per cent of patients treated.

What has been the gain reported? McDevitt and associates recently described their experience with a small group of patients who were allowed to serve as their own controls during periods when anticoagulant therapy was discontinued. Of 28 patients, 21 patients experienced a recurrence while off anticoagulant therapy, whereas 8 experienced a recurrence while on anticoagulant therapy.

In our controlled study the number of patients is not large enough to attain any degree of significance (146 patients followed for a maximum period of 33 months). However, there has been a reduction in the incidence of thromboembolism (20 versus 8 per cent) and in the number of deaths attributable to recurrent thromboembolism (38 versus 9 per cent). In addition some of the complications in the "anticoagulant group" occurred after therapy had been discontinued (figs. 2 and 3). Thus, the results are suggestive of benefit to be derived from long-term therapy.

A last word about one of the problems of long-term anticoagulant therapy. The charts of a group of patients who had received anticoagulant therapy for 12 months or more were reviewed (fig. 4). They demonstrated the difficulty of maintaining a patient within therapeutic range for any prolonged period of time. One cannot therefore assume that adequate protection against recurrent thromboembolism exists at all times. This emphasizes the desirability of close supervision by the physician.

Cerebral Embolism

The value of long-term anticoagulant therapy in the prevention of recurrent cerebral and peripheral embolism appears to be well established. However, the early use of anticoagulants in patients with a clinical diagnosis of cerebral embolus has been questioned. Blumgart and associates have demonstrated that with the early use of anticoagulants in acute myocardial infarction there is no increase in myocardial hemorrhage.
experiments performed by two groups of researchers indicate, however, that the early use of anticoagulants in cerebral vascular disease tends to increase the degree of hemorrhage in hemorrhagic infarcts.41,42

Since more than a majority of infarcts produced by cerebral emboli are hemorrhagic, one must wonder how early one may use anticoagulants with impunity.43,44 There are two studies of the use of anticoagulants in the acute phase of a cerebral embolus in man. Wells45 in a review of a series of records from The New York Hospital, found a mortality rate of 25 per cent of 53 patients who did not receive anticoagulant therapy. Contrasted with this result is a 6 per cent mortality of 34 patients who did receive anticoagulant therapy. Although these numbers are small, they do indicate that anticoagulants did not worsen the prognosis in this group of patients. It should be pointed out, however, that although the patients who did not receive anticoagulants had clear and colorless cerebrospinal fluids, five patients who received anticoagulants shortly after the acute stroke or who were receiving anticoagulants at the time of the stroke, had an appreciable number of red blood cells in the cerebrospinal fluid. These patients either died or survived with a severe disability.

Carter46 has reported a small number of patients who received anticoagulant therapy shortly after a diagnosis of cerebral embolism. In this study there also was a difference of mortality rates, 24 per cent in the treated group and 54 per cent in the control group. In addition, autopsies were performed on seven patients who died after receiving anticoagulants. In none did he observe any increase in cerebral hemorrhage.

How then does one balance the therapy of early recurrent embolus with the above observations? Probably it is best to compromise. We usually withhold anticoagulants for a period of 24 to 36 hours after an acute cerebral embolus. In addition, anticoagulants are not administered in the presence of a xanthochromic cerebral spinal fluid.

Cerebral Hemorrhage

Unfortunately, there is little that we can do or discuss concerning intracerebral hemorrhage. The prognosis is poor for the massive hemorrhage with the exception of those few patients in whom neurosurgical evacuation of an intracerebral hematoma produces spectacular improvement. We have not reached a point where we can prevent an intracerebral hemorrhage and we can do little for the acute phase. All one can say is that for prophylaxis, severe hypertension with recurrent headache should be treated vigorously.

Subarachnoid hemorrhage has a better prognosis when treated by suitable surgical procedures.

Summary

The various measures available for the therapy of a patient with a stroke have been discussed. The value of vigorous conservative therapy has been emphasized. The role of anticoagulant drugs has been detailed. This mode of therapy seems most efficacious in treatment of recurrent transient ischemic attacks and the slowly progressive stroke. The value of anticoagulants in the acute phase of cerebral thrombosis and in long-term postinfarction therapy is not clear as yet. The role of anticoagulant drugs in treatment of cerebral embolism seems well established. It may be wise to delay institution of these drugs for 24 to 36 hours after the acute stroke. Surgical procedures give promise of value in certain well-defined syndromes. The patient with cerebral hemorrhage remains a formidable therapeutic problem.

References

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I believe there shall never be an Anarchy in Heaven; but, as there are Hierarchies amongst the Angels, so shall there be degrees of priority amongst the Saints. Yet is it (I protest) beyond my ambition to aspire unto the first ranks; my desires only are (and I shall be happy therein) to be but the last man, and bring up the Rere in Heaven.
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