The Challenge of cerebral vascular diseases*)

From the Department of Medicine, Cornell University Medical College and the New York Hospital

Irving S. Wright

For many years the problems of cerebral vascular diseases have been neglected. The rather fatalistic approach of the medical profession too often resulted in lack of intensive study, and positive thinking on the part of the physician, which was reflected by depression and poor attempts at rehabilitation by the patient. That this is a major problem to the stricken individual and his family there can be no doubt (1). That it is a major problem to all communities is made clear by the fact that in 1952 more than 170,000 persons died of strokes in the United States alone. This is over three times the number who died of diabetes and tuberculosis combined. It is estimated that there are over 1,800,000 victims of strokes in the United States today. These patients are not all old. Twenty seven percent or 44,000 deaths occurred in patients between 23 and 65 years of age, the most highly productive period in life.

A critical analysis of knowledge of these conditions sharply emphasizes the great ignorance regarding their pathogenesis as well as the limits of therapeutic efforts. Some of the gaps are in areas of basic science, others more specifically apply to this clinical field (2).

Of primary importance is the lack of knowledge regarding the development of atherosclerosis. This is the missing key.

While the ingestion of cholesterol and other fats may contribute in an important degree to the laying down of atherosclerotic plaques in the arterial walls, this is quite obviously not the sole factor. There must also be an inherent factor within the individual which renders him susceptible or resistant to this process. We have studied patients who have lived for fifty years on high cholesterol diets prescribed for peptic ulcers without developing atherosclerosis or hypercholesteremia beyond that expected for their age. Others on relatively low cholesterol intake, although not on fat starvation have developed serious complications of atherosclerosis at an early age. Whether this is due to the relative amounts of estrogens and androgens present or to a mixture of additional unknown components is still a matter for study.

Work which we carried out nearly twenty years ago (3), (4), and which has since been greatly developed by Barr (5), (6) and others strongly suggests

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that hormones may play a leading role. The role of the blood clotting factors must be of great importance but we do not understand how most of them function or by what mechanism they are increased or decreased. The knowledge in this area remains very limited despite concentrated efforts by many workers. Even the nomenclature is so confused that the International Committee for the Standardization of Blood Clotting Factors (7) is confronted with some years of work in order to make communication possible. These factors are none the less doubtless of great significance, as they play a role in both the thrombotic and hemorrhagic episodes which make up between them the great majority of acute lesions of cerebral vascular disease. We know little about the development of congenital aneurysms and nothing about how to prevent them. We understand very little about the metabolic processes of brain tissue or why it is so slow to return to normal function as compared with muscle tissue. The chemical changes which take place in the tissues of the brain after a cerebral infarction represent an unknown territory.

At times the differential diagnosis between thrombosis, hemorrhage, and tumor is difficult and prognostication is at best a guess. Therapy is distinctly limited at this time. Thus we have a field which challenges the young investigators of all countries, one which should absorb the services of many for the next several decades.

On the positive side we are able to make more satisfactory diagnoses than in the past (1). The following facts are helpful in deciding the correct diagnosis, the first step in therapy.

In a large group of patients with regular cardiac rhythm and normal blood pressure, from 60 to 85% of strokes will be found to be on the basis of thrombosis of a cerebral artery.

If the rhythm is irregular, especially on the basis of atrial fibrillation, the incidence of cerebral embolism increases relatively, and thrombosis becomes correspondingly less common. This is especially true of patients with late rheumatic heart disease under the age of 55 years.

When the blood pressure is elevated the relative incidence of hemorrhage increase and thrombosis assumes a correspondingly lesser role. It still, however, remains more common than hemorrhage according to most studies.

The history of past thromboembolic episodes or evidence of generalized atherosclerosis with occlusive phenomena occuring in any segments of the arterial system increases the likelihood of cerebral thrombosis.

Evidence of increased intracranial pressure such as choked disc, a feeling of fullness with severe headache, or rapidly spreading neurological involvement with increased manometric readings suggests a space-occupying lesion such as hemorrhage with or without tumor.

Within the past few years the fear of the lumbar tap for the study of the spinal fluid has been largely overcome and it is now much more widely used. A small bore needle should be used and small amounts of fluid (5—10 cc) should be withdrawn slowly. The critical questions for these cases are, a) the presence or absence of increased pressure and b) the presence of blood cells in quantity or xanthochromic fluid. These constitute contraindications for anticoagulant therapy.

Electroencephalographic studies are only of value if they show abnormalities. They may be normal in the presence of large infarctions. If abnormalities are present serial studies may show reversion toward normal after a thrombosis, embolism or hemorrhage, but this is unlikely in the presence of a tumor.

Angiography is of value in the study of aneurysms, A-V anastomoses, and vascular tumors. It is still to be regarded as in the experimental phase of study for use in the presence of thrombosis, embolism or hemorrhage and indeed serious accidents have followed its use.

Intermittant Premonitory Episodes

There are several types of circumstances under which transient, intermittent, mild episodes of neurological weakness may occur. These frequently presage serious, major paralysis and they are therefore not to be considered lightly.

The mechanism producing these "little strokes" is frequently not clear. It may vary between cases and even within a single case. Indeed more than one mechanism may participate at a given time.

The concept of vasospasm as a factor in such episodes is still a matter of debate in some areas. Yet vasospasm of the cerebral vessels has been repeatedly demonstrated under direct vision experimentally and at neurosurgical operations. It has been stated that in certain cases the presence of atherosclerotic plaques in the affected vessels at autopsy has ruled out the possibility of spasm having been a factor during life. This is not logical in view of similar situations elsewhere in the arterial tree. For example, the major vessels of a leg may be heavily involved and even occluded with atherosclerotic plaques, yet spasm with blanching can be produced in the collateral vessels by means of cold, pain and anger. No one has proven that this mechanism cannot operate in the brain.

D e n n y - B r o w n (8) has emphasized the possible role of stenosis of the basilar or carotid arteries in this type of picture, but this has not been a

universal finding at autopsy and it does not satisfactorily explain the intermittent phases with complete clearing.

Millikan and Siekert (9), (10), (11) have recently presented studies of intermittent insufficiency of the Basilar Arterial System and of the Carotid Arterial System. The symptoms and signs of these conditions have been recognized for many years but the significance of the premonitory symptoms and signs have only recently been emphasized by these workers and others (12), (13), (14). The syndrome produced by basilar artery disease finally terminating with thrombosis is a very complex one. It is characterized by transitory episodes occurring months or even years before the final illness. These episodes may appear minor or moderately severe lasting from a few moments to many hours. The manifestations vary greatly depending on the centers involved. They may include-diplopia, blurred vision, vertigo, weakness of the extremities, thickened speech, numbness, suboccipital headache, vertigo with or without vomiting, ataxia, mental confusion, faintness, hemiparesis with paresthesis which may develop into quadripegia, twitching of the extremities and even convulsions; coma is common. The visual symptoms may include dimness, or focal blindness. Portions of the visual fields are commonly affected, but in some patients this involves the lower halves, and in others hemianopsia may occur. One patient we studied could not read the last few words of each line in a newspaper column for two weeks, after which normal vision returned.

One of the most characteristic features of intermittent insufficiency of the Basilar arteries is the shifting of the signs from one side of the body to the other and often back to the original side. This is in contradistinction to involvement of the middle cerebral artery when the signs and symptoms are largely confined to the contralateral side. During terminal attacks these patients usually develop a fever which may rise to above 105°F.

This condition may be divided into two phases (15). The first phase may be termed "intermittent insufficiency of the basilar artery" during which periodic episodes of neurologic dysfunction occur, with the patient returning to a state of well being between episodes. This may recur over a period of weeks, months or years. The mechanism of this is not understood. It may be due to vasospasm of the Basilar arteries or their collateral branches or it may be on the basis of sludge formation of blood passing very slowly or even stopping temporarily in narrowed areas of atherosclerotic vessels. Temporary stenosis and aneurysmal dilatation have also been suggested (8).

The second phase may be termed "impending (or actual) thrombosis within the Basilar arterial system" consists of a progression of neurologic abnormalities over a period of days or weeks. This results in permanent involvement

frequently terminating in paralysis, blindness, coma, and death. Occlusion of the Basilar artery is very serious and few patients survive this development

Intermittent insufficiency and thrombosis of the Carotid arterial system has also recently been subjected to more careful investigation. While the fixed syndrome of unilateral weakness with contralateral blindness has come to be considered typical of Carotid artery thrombosis (12), (13), (14) the premonitory syndrome which warns of impending tragedy has only recently been emphasized by Millikan and Siekert (11). The first branch of the Internal Carotid artery is the ophthalmic artery. The Internal Carotid then gives off the posterior communicating artery and the anterior choroidal artery and finally divides into the anterior and middle cerebral arteries. These vessels thus supply the homolateral retina, frontal lobe, portions of the temporal and parietal lobes as well as the corpus striatum and the posterior limb of the internal capsule. Interference with the blood flow in these branches can produce a wide variety of symptoms depending on the site of maximum ischemia.

The typical premonitory syndrome consists of intermittent attacks of unilateral impairment of motor or sensory function, or both, frequently associated with difficulty with speech and homolateral visual disturbance. There is no evidence of impaired consciousness or convulsions. The patient returns to normal after each premonitory episode. Later the complete occlusion by thrombosis may be demonstrated by arteriography, surgical exploration, or autopsy.

This syndrome does not produce the signs of intracranial pressure seen with space occupying lesions such as neoplasms. It may be confused with a Basilar artery occlusion but does not produce symptoms which shift from side to side. In some instances both the carotid and the basilar arterial segments may be involved producing a very confused picture.

The mechanism of the intermittant episodes with recovery is not clear and the reader is referred to the previous comments regarding the pathogenesis of Basilar artery insufficiency which are equally pertinent to this condition.

Treatment

Until recently the treatment for all cerebral vascular diseases was futile, and the outcome was rarely affected by any steps the physician could take. We are now entering an era of positive therapy. We do not consider our present treatment entirely satisfactory, but progress has been made both in the prevention and treatment of these conditions. This report will be concerned only with the treatment of thrombosis, embolism and to a lesser degree with hemorrhage.

Preventive treatment. The most clearly demonstrated step in the prevention of strokes relates to those due to embolism. Since we (16), (17), (18), (19) first reported the prevention of emboli, including cerebral emboli, arising from hearts in atrial fibrillation, as well as those suffering from recent myocardial infarction, other workers have confirmed these observations. We have reported a series of 57 cardiac patients who were observed for 795 patient months without anticoagulants, during which time they suffered 205 thromboembolic episodes, of which 81 were cerebral vascular. These same 57 patients acting as their own controls then placed on anticoagulant therapy, were followed for 1162 months, during which time they suffered only 23 thromboembolic complications, of which 6 were cerebral vascular. A larger series is now being subjected to analysis and will be reported shortly. Similar series of patients studied by Askey (20) and Cosgriff (21) have been confirmatory.

At first it was widely held that mitral commissurotomy would prevent further emboli, but unfortunately this has not proven to be true. It probably does reduce the incidence, but if the patient has suffered embolization before operation, and if the heart continues in a state of fibrillation, the chances of recurrent emboli after the operation are high enough to justify continued anticoagulant therapy. We now prepare all patients for commissurotomy by giving a course of anticogulant therapy for from two to four weeks prior to surgery. The prothrombin time is then reduced to a few seconds above normal or to normal levels. Within a day or two after the operation is performed, therapeutic levels are resumed. If the rhythm is regular and no emboli have occurred we discontinue the anticoagulants from three to four weeks after operation: if irregular, we continue them depending on the personal situation of the patient. Astrup* and his coworkers in Copenhagen carry their patients at therapeutic levels of anticoagulant therapy throughout the surgical period and we are beginning to recommend this. The basis for this approach rests in the suggestion that many thrombi which are later troublesome start immediately after operation if the patient is not under anticoagulants. This does, of course, compel the surgeon to be more meticulous with his hemostats.

Since the majority of hemorrhagic episodes occur in patients with hypertension, it is logical to attempt to prevent them by reducing the blood pressure. The new antihypertensive drugs appear to help in this regard. However, since with the use of these drugs it appears that fewer hypertensive patients are dying of other complications of their disease, a larger percentage are living long enough to finally succumb to cerebral vascular disease. It should be pointed out that sudden drops in blood pressure may produce or accentuate

*) Personal communication and visit to the Copenhagen Medical School, October 5, 1956.

both renal and cerebral complications.

In patients with polycythemia the risk of both thrombosis and hemorrhage appears to be lessened by reducing the blood count by phlebotomy or isotopes.

Anticoagulant therapy treatment of an acute episode. It has proved easier to demonstrate the favorable effect of anticoagulants on the incidence of later episodes than to establish beyond doubt a favorable effect on the course of an acute episode (22). It appears logical to use these substances where the diagnosis of thrombosis or embolism is reasonably established in an effort to (a) encourage disintegration of a soft clot as rapidly as possible, (b) prevent the propagation of the existing clot which might otherwise block off additional branches of the vessel, thus increasing the size of the infarction, (c) prevent additional new thrombi from forming in other cerebral vessels or elsewhere while the blood is in a hypercoagulable state, which is common after an initial thrombus, (d) prevent new emboli from arising from the heart by interrupting the propagation of the mother mural thrombus. There has been some concern that the hemorrhage encountered in cerebral infarcts may be aggravated by anticoagulants, but preliminary studies seem to indicate that as with myocardial, renal and pulmonary infarcts this is not of significance. However, we do not accept this as proven as yet, and are initiating a ten year comprehensive study under the joint auspices of Cornell and New York University Medical Schools and Bellevue Hospital, to attempt to obtain definitive information regarding this and many other facets of the problem. We have used this treatment for thromboembolism whenever it has occurred within the cerebral vascular tree since 1946, but our studies are still incomplete. Millikan and Siekert have studied in some detail the use of anticoagulants in the treatment of intermittent insufficiency of the carotid arterial system (11) and of thrombosis of the basilar artery (15). In the later condition, 14% of the patients receiving anticoagulants died, while 43% of a control group (not receiving such therapy) died. It can be concluded that this form of therapy is promising, but it needs further study, especially in the technique for the selection of suitable patients.

Stellate sympathetic ganglion block. This is presently a highly controversial form of therapy. De Takats (23) and others have reported favorably on its use. The proponents of this form of therapy claim that cerebral ischemia secondary to vasoconstriction in the zones surrounding the infarction is benefited by the increase in vascularity and collateral circulation. In favor of this is the fact that improvement in neurological signs has been reported in some patients. This has frequently been temporary. Other observers (24) have concluded that the procedure is not worth the risk, and our general impression is that it is used less than it was several years ago. Measurements have failed to indicate any increase in cerebral blood flow as a result of this procedure. In

evaluating improvement during the early days after an acute episode, it should be remembered that without any treatment, remarkable and rapid improvement is not unusual.

Inhalation of CO_2. The work of K e t y (25) and others has demonstrated that increased CO_2 in the blood does increase the blood flow to the brain. The inhalation of this gas would therefore appear to be a sound approach. This can be accomplished by using a mixture of 5% CO_2 and 95% O_2, or by rebreathing into a paper or plastic bag. The effect is short and the treatment must be repeated many times a day. Its value in the treatment of cerebral infarction is yet to be finally established.

Other therapy. No other forms of therapy have been generally accepted to be of value. Among those which have been advocated are the following:

a) Intravenous procaine (500 mg) in 500 cc of Normal Saline infusion (25);
b) Histamine phosphate 5.5 mg with 50 grms of dextrose in 1000 cc of saline as an infusion (26);
c) Nicotinic Acid 100 mg, three times daily;
d) Alcohol;
e) Cortisone;
f) Surgical procedures.

S k i l l i c o r n and A i r d have recently reviewed available therapy (27).

Summary

Cerebral vascular diseases are of major importance but unfortunately their study has been greatly neglected until recent years.

There are serious gaps in our basic knowledge regarding their pathogenesis and therapy. The differential diagnoses of thrombosis, embolism, hemorrhage and tumor have been outlined. Intermittent neurological signs due to cerebral vascular diseases have been discussed. The distinctions between intermittent and permanent occlusion of the basilar artery, carotid artery and cerebral artery have been elaborated.

Long term anticoagulant therapy is of value in the prevention of recurrent thromboses and emboli wherever they may occur in the carotid, basilar or cerebral arterial tree.

Anticoagulants are indicated as a prophylactic measure before mitral commisurotomy when the patient has had previous emboli or when his heart is in atrial fibrillation. They should also be continued after this surgery. The question whether the patient should be carried through the operation at therapeutic levels of anticoagulant therapy is at present under study in several clinics, but the evidence suggests that this is feasible and improves the chances of avoiding emboli.

It appears logical to use anticoagulants in the treatment of acute episodes of thrombosis and embolism but this is under further study at present.

Other forms of therapy including the stellate sympathetic ganglion block, and the inhalation of CO_2 have been evaluated. Thus far the evidence suggests that while the inhalation of CO_2 may be helpful theoretically the others are of doubtful value.

This is a challenging field which should attract the attention of many workers during the next several decades.

Résumé

Les maladies vasculaires cérébrales sont d'une grande importance mais n'ont, malheureusement, pas retenu l'attention des chercheurs jusqu'il y a quelques années.

Il y a des lacunes évidentes en ce qui concerne nos notions fondamentales sur leur pathogenèse et thérapeutique. Nous avons discuté le diagnostic différentiel entre la thrombose, l'embloie, l'hémorragie et les tumeurs cérébrales ainsi que les symptômes neurologiques passagers ou intermittents dus à ces états. Une distinction est faite entre l'occlusion temporaire ou permanente de l'artère basale, la carotide et l'artère cérébrale.

L'emploi prolongé des anticoagulants est indiqué pour prévenir les récidives de thromboses et d'embolies dans la carotide, l'artère basilaire ou dans les vaisseaux cérébraux.

Les anticoagulants sont également conseillés comme agent prophylactique chez les malades atteints de sténose mitrale qui sont en fibrillation ou ont fait une thrombose. Ce traitement sera institué avant la commissurotomie et continué après l'intervention. Plusieurs centres étudient actuellement la possibilité de maintenir les malades en état d'hypocoagulabilité pendant l'opération et il semble que ce procédé de travail serait techniquement possible et diminuerait le danger d'embolies.

Autres possibilités thérapeutiques telles que l'infiltration des ganglions sympathiques et l'inhalation de CO_2 ont été étudiées. Notre impression actuelle est que si l'inhalation de CO_2 peut être intéressante sur le plan théorique, la valeur pratique des autres procédés est très discutable.

Zusammenfassung

Die zerebralen Gefäßerkrankungen sind von großer Bedeutung; ihr Studium wurde jedoch bis vor kurzem sehr vernachlässigt. Unser Wissen über ihre Pathogenese und Therapie weist große Lücken auf. Es wird die Differentialdiagnose zwischen Thrombose, Embolie, Blutung und Tumor besprochen sowie die intermittierenden neurologischen Symptome als Folge zerebraler Gefäßerkrankungen

diskutiert. Die Unterschiede zwischen vorübergehendem und dauerndem Verschluß der A. basilaris, carotis und cerebralis werden herausgearbeitet.

Die Antikoagulantien-Dauerbehandlung ist zur Verhütung rezidivierender Thrombosen und Embolien in allen zerebralen Gefäßgebieten wertvoll. Desgleichen sind Antikoagulantien zur Prophylaxe vor der Commissurotomie der Mitralklappen indiziert, wenn Vorhofflimmern besteht oder mehrfach Embolien aufgetreten waren. Die gerinnungshemmenden Maßnahmen sollen auch nach der Operation fortgesetzt werden. Die Frage, ob die Gerinnungshemmung auch während der Operation aufrecht erhalten werden soll, wird derzeit in zahlreichen Kliniken untersucht. Die bisherigen Beobachtungen sprechen nicht nur dafür, daß dies möglich ist, sondern auch daß die Aussichten, Embolien zu vermeiden, verbessert werden.

Es erscheint naheliegend, Antikoagulantien im akuten Stadium von Thrombose und Embolie der Zerebralgefäße zu verwenden, doch wird diese Frage derzeit noch untersucht.

Andere Therapieformen, wie Blockade des Ganglion stellatum und Inhalation von CO_2 werden kritisch besprochen. Während nach den bisherigen Ergebnissen die Inhalation von CO_2 wirksam sein dürfte, ist der Wert der anderen Maßnahmen zweifelhaft.

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