THE DIAGNOSIS AND TREATMENT OF CEREBROVASCULAR DISEASE

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THE considerable investment of thought and endeavour in the field of cerebrovascular disease in recent years, has not yet yielded substantial dividend. Measured purely in terms of direct benefit to the individual afflicted by this disease in its wide variety of forms, advances have not been outstanding. Nevertheless it is justifiable to hope that we are reaching a stage, identifiable in all medical progress, when increasing knowledge can be translated into terms of practical achievement in diagnosis and treatment.

Before describing in detail such clinical advances as have been made, it is perhaps worth while considering some of the past and present impediments to progress and the fields of study designed to overcome them. With growing interest in morbidity and mortality statistics it has become increasingly apparent that this group of diseases, formerly regarded as an inevitable part of the ageing process if not, indeed, its very definition, takes its toll in the younger age-groups also. While it is undoubtedly in the later decades that cerebrovascular accidents have their maximum incidence, scrutiny of the age distributions in nearly all published clinical studies reveals the extent to which the younger groups are affected. The wider recognition of this fact has in itself provided a stimulus to research.

For the purposes of this discussion we are not concerned with conditions such as spontaneous or traumatic extracerebral hæmorrhage, intracranial aneurysm or angioma, but with the various manifestations of occlusive vascular disease and intracerebral hæmorrhage. In other words with conditions which result from atherosclerotic and hypertensive vascular disease, and it has too often been assumed that any real advance in the treatment of cerebrovascular disease must await solution of these fundamental problems. The vast amount of work in a wide range of disciplines that is being directed towards this end is, of course, relevant to cerebrovascular disease; no attempt will be made here to review it but one recent piece of work may be of particular relevance because it postulates a relationship between cere-

brovascular disease and the 'causation' of hypertension. That hypertension is an important factor in atherogenesis is not disputed but Dickinson and Thomson (1959, 1960) have recently produced evidence that narrowing of the arteries to the brain may be a cause as well as a result of hypertension. In this they have revived a suggestion made by Starling (1925) that interference with the blood supply to the vasomotor centre in the medulla oblongata due to vascular narrowing may result in an elevation of blood pressure in order to maintain the needs of the centre.

Fortunately, progress is not entirely dependent on the solution of these major problems. Adams (1958), discussing cerebrovascular diseases, rightly stated that 'their ultimate solution will be accomplished by whosoever learns the secret of atherogenesis and elevated blood pressure', but he went on to consider many of the factors which determine their impact on cerebral function and ways in which these might be modified. Martin, Whisnant and Sayre (1960) have demonstrated in a precise post-mortem study of the extracranial cerebral circulation the remarkable extent to which these vessels are frequently affected by occlusive disease even in absence of any evidence of cerebral ischaemia and the question arises—why does one individual with cerebrovascular disease develop overt neurological manifestations while another, with comparable or more extensive disease, fails to do so? There must be conditioning mechanisms, some of which Adams (1958) has called 'ischaemia-modifying factors', which determine the effects of arterial disease on brain function and which may themselves be amenable to modification by medical treatment. Clearly the anastomotic systems of the cerebral vessels are relevant to this concept. Willis himself perceived not only the anatomical arrangement of the circle of vessels which bears his name but appreciated its physiological significance. He encountered the condition of carotid obstruction and recognised that the circle provided a mechanism whereby one carotid artery might assume the functional role of both.

While the circle of Willis must undoubtedly

mitigate the adverse effects of proximal occlusive disease in many cases, its reliability is not invariable as emphasized by Alpers, Berry and Paddison (1959). In a series of 350 autopsies they found that the circle of Willis conformed to what is regarded as the normal anatomical pattern in only 52.3% and there were multiple anomalies in 13.4%. A large number of individuals must have a vascular arrangement which is below optimal efficiency in maintaining blood flow under pathological conditions.

The existence of anastomotic pathways other than the circle of Willis has also been established. Vander Eecken and Adams (1953) in a series of post-mortem injection studies demonstrated the extensive leptomeningeal communications and their capacity for connecting adjacent vascular territories when required to do so. There are also the capillary anastomoses but apart from these there are no communications between neighbouring arteries once they have entered the substance of the brain.

It was probably faith in the capacity and integrity of the anastomotic arrangement of the circle of Willis combined with an unwarranted conviction that all its distal branches were end-arteries which delayed the full realisation of the importance of the four great proximal vessels in the causation of strokes. Whereas formerly the majority of fore-brain infarcts were attributed to 'middle cerebral thrombosis', in spite of the comparative rarity of this finding at post-mortem (Moossy, 1959; Blackwood, 1961), it is now generally accepted that in many instances the occlusive lesions are to be found in the extracranial arteries and that no post-mortem examination is complete unless it includes these vessels. Fisher (1951, 1954), on the basis of an extensive autopsy study, demonstrated the high incidence of occlusive disease in the internal carotid arteries and in this country Hutchinson and Yates (1956, 1957) have stressed the importance of atherosclerosis in the vertebral arteries and have shown that in a high proportion of cases of cerebrovascular disease both the carotid and vertebral arteries are affected. In 40 instances where significant stenosis or occlusion of one or more of the major neck vessels was found at post-mortem, disease was confined to the carotid arteries in 10, and to the vertebral arteries in 7, whereas in 23 both systems were involved. Studies such as these emphasize our dependence on the anastomotic pathways for the maintenance of blood supply to the brain under pathological conditions and they have obvious bearing on the problems of reconstructive surgery. They help us to understand some of the apparent anomalies encountered in clinical practice as when occlusion of a major vessel results in infarction in

a part of the brain beyond its normal territory of supply.

Most of the studies discussed so far have been based on anatomical and pathological observation. The physiological and pharmacological approaches have, on the whole, shed less light on problems in cerebrovascular disease principally because no convenient method is available for measuring regional cerebral blood flow in man. The polarographic technique employed by Meyer and Hunter (1957) has only very limited application in man. The nitrous oxide method for determination of total cerebral blood flow described by Kety and Schmidt (1945, 1948) has been of great value in the study of metabolic diseases of the brain and of physicochemical factors which affect overall cerebral circulation. However, the clinical manifestations of cerebrovascular disease are seldom related to disturbances of flow to the cerebrum as a whole: rather are they reflections of focal disorders of blood flow beyond the scope of the method, and we have no experimental evidence that procedures such as stellate ganglionectomy or drugs which cause vasodilatation increase the blood flow to ischaemic zones of the brain. The total flow methods may prove of value in connection with the use of hypothermia as a therapeutic measure following cerebrovascular accidents, an approach that has been tried by Howell and his associates (Howell, Stratford and Posnikoff, 1956), but that has not yet been fully explored. Otherwise, however, these methods are of little practical value in the problems we are concerned with.

Perhaps the greatest contribution to our understanding of the dynamic factors involved in the production of symptoms of cerebrovascular disease derives from the studies of Denny-Brown, Meyer and their co-workers. Their extensive series of experiments has recently been reviewed by Denny-Brown (1960). Their starting point was the observation that the recurrent episodes of transient hemiplegia in patients with carotid occlusion could in many instances be related to situations that lowered the systolic blood pressure or the cardiac output. Transient attacks precipitated by blood loss, syncope or the use of peripheral vasodilator drugs had been encountered and catastrophic hemiplegia determined by myocardial infarction was cited. Denny-Brown elaborated the concept of *carotid insufficiency* in which the vascular territory of a stenosed or occluded carotid artery becomes dependent on collateral supply and therefore susceptible to influences which impair that supply. He recognized a similar situation in relation to the basilar artery accounting for insufficiency of blood supply to the brain stem and posterior cerebral territory of that artery. Carotid or basilar insufficiency

was defined as 'a physiological, potential hæmodynamic state, in which reversible hæmodynamic crises could be elicited by any factor that impaired the collateral circulation. The hæmodynamic crisis resulted in symptoms that were transient, and completely or partially reversible, depending on whether the crisis was so prolonged or so severe as to produce anatomical damage in the vulnerable area'.

Inasmuch as this concept of insufficiency involves a failure of collateral blood flow it led Denny-Brown and his associates to further study of the physiological factors governing it. They carried out a beautiful series of experiments on monkeys in which they recorded *inter alia* changes under varying conditions in the oxygen saturation of cerebral cortical tissue, the blood flow in cortical vessels and latterly also the stereomicroscopic appearance of the arterioles and capillaries. By occluding a major vessel and lowering the systemic blood pressure they were able to reproduce experimentally the conditions in which the insufficiency syndromes occur in man and to study precisely the physiology of collateral blood flow.

This concept of insufficiency was offered as an alternative to the vexed question of vasospasm which has so often been invoked, *faute de mieux*, as a cause of transient and recoverable neurological deficits of one sort and another. In fact, the situations in which cerebrovascular spasm does occur were examined: these include mechanical traction on vessels, perhaps comparable to the effect produced by localised hæmorrhages from aneurysms in the region of the circle of Willis, and sudden rises in intraluminal pressure which may explain the marked narrowing of vessels not infrequently encountered in cerebral angiography. A third situation was demonstrated experimentally in hypertensive monkeys where spasm of cortical vessels was encountered similar to that observed by Byrom (1954) in rats. However, the conclusion was reached that spasm was not a mechanism which usually operated in insufficiency states. It was emphasized that the latter was a physiological and not a pathological entity and a plea was made for restriction in the use of the term to the precise situation which it was intended originally to represent.

Denny-Brown also turned his attention to the problem of embolism and observed, and in one experiment actually photographed (Denny-Brown and Meyer, 1957), a fibrin-platelet embolus from a partially damaged middle cerebral artery in a monkey, lodged in a small peripheral branch of that artery. They were able to observe its effects on the territory of the artery in question and postulate that such a mechanism may be responsible for the production of symptoms of transient

ischæmia in patients whose clinical attacks cannot be related to circumstances associated with fall in blood pressure and in whom neither an attack nor a change in the EEG can be induced by lowering the pressure. Of interest in connection with this hypothesis is the report by Fisher (1959) of a patient subject to repeated attacks of visual failure in whom a retinal embolus of similar type was observed. Denny-Brown suggests that it may be in patients whose transient ischæmic attacks are determined in this way that anticoagulant therapy may be effective rather than in those suffering from the true insufficiency syndromes as he defined them. He also draws attention to the possibility of repeated trauma to the vertebral arteries from spondylitic disease or congenital anomaly of the cervical spine resulting in the production of platelet emboli. The clinical association between cervical spondylosis and vertebral artery syndromes has recently been emphasized by Williams (1961).

Thus far we have been concerned principally with the physiological and pathological features of the blood vessels themselves and their contribution to the development of neurological disturbances. There are undoubtedly situations, however, where disturbances in the transportation of oxygen to the nerve cells must be determined by changes in the nature of the blood which flows through the cerebral vessels with or without coincidental disease of those vessels. The predisposition to major cerebrovascular accidents of patients with polycythæmia has long been recognized, but recently Millikan, Siekert and Whisnant (1960) have drawn attention to the association of this condition with intermittent carotid and vertebro-basilar ischæmic attacks. The same authors (Siekert *et al.*, 1960) have described five patients in whom they suggested that an anæmia might be related to focal, as opposed to general, cerebral ischæmic attacks. The administration of high-fat meals to experimental animals has been shown by Meyer and Waltz (1959) to increase the aggregation of erythrocytes within the pial vessels producing a tendency to clumping and slowing of blood flow. Other features of the circulating blood of possible significance in this context have been described by Swank (1959), who has reported the viscosity of the blood to be relatively high in patients with cerebrovascular disease, and by Elliott and Buckell (1961) who have demonstrated changes in blood fibrinogen level in relation to cerebrovascular accidents.

These then are some of the recent concepts which have been formulated and lines of investigation which have been followed. Many of them and others have been more fully discussed by Wells (1960) in his excellent review, but it is hoped

that they serve to show that progress in the study of cerebrovascular disease has been made which cannot be measured purely in terms of advances in diagnosis and treatment. They represent much new thought and provide a foundation on which further researches will be based. Some of them have already been assimilated into the clinical precepts that we are about to consider, whereby patients are managed, and it is reasonable to hope that others will mature into practical instruments of therapy.

Diagnosis of Cerebrovascular Disease

Clinical Considerations

Let us turn now to some of the advances which have been incorporated in the everyday management of patients suffering from cerebrovascular disease. It is probably in the field of clinical diagnosis that the most marked changes have been witnessed in recent years: many new distinctions have been made and new terms introduced. Whereas formerly 'stroke' and 'hemiplegia' were frequently accepted as clinical diagnoses, and pathological interest was largely confined to distinguishing between hæmorrhage, thrombosis and embolism, attempts are generally made nowadays at more precise definition of the clinical syndrome. In the case of brain stem disease it is true that posterior inferior cerebellar artery thrombosis, pontine hæmorrhage and one or two others have long been taught as specific vascular syndromes, but it is only during the past few years that clinicians generally have become aware of the variety of presentations of patients with occlusive disease of the vertebro-basilar system. So too with fore-brain infarcts which were usually designated middle cerebral thrombosis or embolism, while now the frequency of internal carotid occlusion is widely recognized. A major advance has been the development of the concept of the insufficiency syndromes, whose underlying mechanisms have been discussed, and which are already accepted as familiar clinical entities.

It is unnecessary to describe in detail the various patterns of neurological disturbance which result from these vascular syndromes. Many series of patients have been studied and described, the most valuable being those in which clinical features are correlated with angiographic and pathological findings. The papers of Symonds (1957) and Silverstein (1959) embody most of our knowledge about occlusive disease of the carotid arteries and Meyer, Sheehan and Bauer (1960) have recently reviewed the clinical features of vertebro-basilar disease in light of a carefully studied series of their own. In his Lumleian lectures, Elkington (1958) surveyed the whole problem of the diagnosis of

insufficiency and occlusion of the internal carotid and basilar arteries.

Other advances in diagnosis have resulted from the wider usage of cerebral angiography which has demonstrated the importance of vascular malformations in the causation of cerebral hæmorrhage and has permitted a more accurate estimate of the frequency of aneurysms. The realization of the significance of systemic diseases and of inflammatory diseases of arteries in the production of cerebrovascular symptoms has added further to the complexity of the problems of diagnosis, while the introduction of new forms of treatment has demanded an increased degree of accuracy. These and other developments have raised problems in classification and terminology which have been to some extent clarified by an *ad hoc* committee appointed by the Advisory Council for the National Institute of Neurological Diseases and Blindness, Bethesda. Its report (1958) deals with the definition, classification and general clinicopathological aspects of cerebrovascular disease.

In spite of our more precise approach to diagnosis in cerebrovascular disease and the delineation of new clinical syndromes, there is still one outstanding defect, namely our inability to distinguish with complete confidence between infarction and hæmorrhage. Aring and Merritt (1935) attempted to define the diagnostic features of each by correlating the symptoms and signs in life with the autopsy findings in a series of 245 cerebrovascular accidents. Application of their diagnostic criteria is not however infallible, and, of course, it is not justifiable to extrapolate their findings in fatal cases for non-fatal ones. Dalsgaard-Nielsen (1956) found that the diagnosis of cerebral hæmorrhage made clinically in 239 patients was confirmed at autopsy in only 155 (65%). The clinical diagnosis of cerebral arterial thrombo-embolic occlusion in 139 patients proved correct in only 81 (58%). Lumbar puncture was not performed in all these cases and this investigation undoubtedly raises considerably diagnostic accuracy. It is not an infallible test, however. Intracerebral hæmorrhages very seldom rupture through the surface of the brain, nor do they necessarily reach the ventricular system; thus contamination of the cerebrospinal fluid pathway is not invariable. Nor is the presence of red cells in the spinal fluid incompatible with the diagnosis of cerebral infarction. This inability to make so important a pathological distinction with complete certainty is unfortunate and introduces an element of uncertainty and hazard in the planning of therapy.

Radiological Diagnosis

The radiological investigation of patients with

cerebrovascular disease was reviewed by Bull (1958); he pointed out that plain radiographs and, in a limited number of cases, pneumoencephalograms could be of value, but it is, of course, on the use of opaque media that we mainly depend. The development of percutaneous cerebral angiography has brought enormous advance in the study of cerebrovascular disease, apart altogether from its use in cases of cerebral tumour, and there is no single technique of comparable diagnostic value. Its greatest application in this field is probably still in regard to aneurysms and vascular malformations, but it is also as a result of angiographic investigation that we are now aware of the high incidence of internal carotid occlusion in the causation of cerebrovascular symptoms. In other vascular occlusions and in the demonstration of intracerebral haematomas its precise use and limitations are less clearly defined; the extent to which it should be employed in patients suffering acute strokes is a matter of controversy. Bull, Marshall and Shaw (1960) studied angiographically 80 patients admitted to hospital with strokes and found the angiogram to be of positive diagnostic help in 33 cases (41%); in 17 of these the lesion demonstrated was other than that suspected clinically. They encountered 14 cases of internal carotid artery occlusion: 10 were complete and four partial. Only the vessel appropriate to the anatomical site of the lesion as judged clinically was examined and complete angiography, bilateral carotid and vertebral, might have yielded a higher number of positive findings. Dobrak, Beck, Murphy and Zoll (1960) found definite angiographic abnormality in 39% of a series of 38 patients who had had cerebrovascular accidents; they made complete examinations in some but not all of their patients.

While the diagnostic value of cerebral angiography in many situations is beyond dispute, the investigation in its present form has its limitations. It is a relatively crude procedure in that only the larger vessels can be clearly outlined and identified, and this may be the reason why quite extensive brain damage can exist on the basis of vascular disease without there necessarily being any abnormality, which we are capable of recognizing, in the angiographic pattern. Nor is it entirely without hazard. The exact complication rate is difficult to assess and varies in different series, depending on such factors as the contrast medium used and the clinical condition of the patients submitted to examination. Furthermore, in acutely ill patients it is not always possible to decide whether deterioration is attributable to the investigative procedure or to the natural course of the disease. Kuhn (1959) referred to the complete absence of morbidity and mortality associated with

angiography in over 100 patients with strokes but Bull *et al.* (1960) observed transient deterioration with no fatalities in 11% of patients examined in their series. Of the 16 deaths in the series of Dobrak *et al.* (1960) four were considered in part at least attributable to angiography. Segelov (1956) had no complications in a series of 660 angiograms, but he reviewed nine reported series comprising a total of 3,788 angiograms and listed 22 deaths and 81 other complications. It would seem therefore that we must accept that some risk attaches to the procedure, but whether or not that risk is increased in the presence of cerebrovascular disease is not definitely established; Riishede (1957), on the basis of a very wide experience, has expressed the view that the risk is not greater than in neurosurgical patients generally, but there are many who would disagree with this opinion. Vertebral angiography in particular is widely thought to carry increased hazard in patients with diseased arteries.

Reference has already been made to the fact that in a high proportion of patients there is disease of main vessels other than or in addition to the one apparently implicated by the clinical symptoms. Ideally, therefore, it is desirable to make a complete examination which necessitates bilateral carotid and vertebral angiography, a fairly formidable procedure. Furthermore, the standard method of examination does not demonstrate the origins of the vertebral arteries, the importance of which has been stressed by Hutchinson and Yates (1957). There is also the objection that the standard procedures involve puncturing diseased arteries which many regard as dangerous. For these reasons methods are now being sought which will obviate the necessity of making multiple injections, which will show the origins of the great vessels and at the same time avoid puncturing diseased arteries. It is beyond the scope of this review to describe them in detail, but recently Schramel, Creech, Llewellyn and Corales (1961) have advocated a modified technique of cardio-angiography for demonstrating the extracranial cerebral vessels. A catheter is introduced via the saphenous vein into the inferior vena cava and 90% sodium diatrizoate (Hypaque Sodium) is injected by hand. Serial exposures allow demonstration of both the aortic arch and its branches and also of the intracranial cerebral vessels. Alternatively the opaque medium can be delivered by catheterization of the right atrium as advocated by Zerbi-Ortiz and Weldon (1961) who prefer mechanical injector. These methods probably give better opacification than do the intravenous techniques described by Viallet, Sendra, Chevrot, Combe, Descuns and Aubry (1956) and by Steinberg, Finby and Evans (1959) which required

injection of large quantities of contrast material. All these methods obviously involve the passage of the bolus of contrast medium through the pulmonary vascular bed, and to avoid this, techniques have been developed whereby it is delivered intra-arterially but proximal to the orthodox sites of vertebral and carotid puncture. In this way direct puncture of affected vessels is avoided and several vessels can be outlined simultaneously. Gensini and Ecker (1960) have achieved very good results by passing a catheter into the arch of the aorta via the femoral artery, although difficulty is occasionally encountered in presence of marked tortuosity or plaque formation in the iliac artery. The main objection to direct subclavian puncture has always been the risk of inducing pneumothorax, but Baker (1960) has described an approach which has given very good filling of vessels without the occurrence of this complication in a series of over 60 consecutive cases.

It will be seen that considerable strides have been taken towards achieving our aim which must be a standardized, safe and reasonably simple method of pan-angiography, capable of demonstrating both extracranial and intracranial cerebral vessels. In concentrating on the former, the latter must not be neglected because occasional cases will always be encountered where an apparently vascular clinical presentation results from an intracranial tumour distinguishable only by a pathological circulation or displacement of intracranial vessels.

Ancillary Diagnostic Investigations

Lumbar Puncture

The importance of examination of the cerebrospinal fluid in the diagnosis of the acute cerebrovascular accident has already been mentioned. It is not an infallible method of distinguishing between infarction and hæmorrhage, but it should not be omitted. The presence of blood does usually indicate that a hæmorrhage has occurred and from time to time the unexpected positive Wassermann reaction or grossly elevated protein level will indicate that the underlying pathology is contrary to expectation.

Pulsations and Bruits

Whilst angiography remains much the most reliable investigation in the diagnosis of internal carotid occlusion, various ancillary aids have been advocated; these can undoubtedly be helpful although none is entirely reliable. Thus absence of a palpable arterial pulsation in the neck may indicate an occlusion, but Rosegay (1956) has found this sign to be of inconstant value. Palpation of the vessel in the pharynx as described by Dunning (1953) is not practised by many and

methods involving compression of the carotid artery may be dangerous to the patient. The detection and localisation of audible bruits is generally a more useful indication of occlusive disease and the importance of auscultation in this context has been emphasized by Peart and Rob (1960). Crevasse (1961) has studied in detail the interpretation of carotid artery murmurs.

Ophthalmodynamometry

A more objective assessment of flow in the internal carotid artery depends on the measurable fall in pressure in its ophthalmic branch when the internal carotid is occluded. This is the basis of ophthalmodynamometry by means of which the ophthalmic artery pressures are compared on the two sides. It is performed by applying pressure on the sclera with a dynamometer and observing the effects upon the pulsations of the central retinal artery. Wood and Toole (1957), Hurwitz, Groch, Wright and McDowell (1959), Smith (1960) and others have found this technique to be reliable in the diagnosis of internal carotid occlusion, although in long-standing cases the establishment of collateral flow via the external carotid artery may reduce the differential. It is undoubtedly a technique which requires considerable experience before consistent results are obtainable.

Electroencephalography

The value of electroencephalography in the diagnosis of cerebrovascular diseases was recently commented upon by Wells (1961). With regard to structural damage resulting from vascular lesions he conceded that it might aid in precise localization, that a normal pattern might implicate the brain stem rather than hemisphere and that a resolving pattern favoured a vascular lesion rather than a tumour; however, he concluded that the results of electroencephalography were disappointing in the routine diagnosis of patients. So too in the case of functional vascular disturbance without structural damage it is as yet an investigation of limited practical application.

Treatment of Cerebrovascular Disease

It is probably fair to say that most recent innovations in treatment have stimulated rather than derived from the various advances in knowledge that have so far been considered. When a therapeutic technique is applied in a new field it immediately demands greater precision in diagnosis, greater understanding of ætiological mechanisms and greater knowledge of the natural history of the disease in the absence of treatment. Deficiencies in these three respects have made appraisal of the new forms of treatment in cerebrovascular

disease extremely difficult. Patterns of the disease are so variable and unpredictable that unless a new therapeutic approach is conspicuously successful, its value is very hard to measure. Spontaneous recovery may bestow on a treatment a reputation that it never deserved. This has undoubtedly been the case with some of the measures advocated in the past in cerebrovascular disease and nowadays there is increasing awareness of the necessity for controlled experiment in the trial of new forms of treatment.

Before considering any specialized medical or surgical methods of treatment it is worth recalling the extent to which the general supportive management can modify the mortality and morbidity in patients with cerebrovascular disease. This applies both to the acute and chronic phases. In the former, the standard of nursing care and physiotherapy, for both lungs and limbs, probably has greater influence on the outcome than any of the more sophisticated forms of treatment. In the chronic stage, too, the quality of the life achieved is in many cases proportional to the amount of time and effort devoted to the patient's rehabilitation. Adams (1960) has outlined the principles of management of patients with acute strokes and the practical measures which are so important in the rehabilitation of those that survive.

Drug Treatment

Discussion here will be limited to the possible applications of hypotensive, anticoagulant and fibrinolytic agents; of the many others which have been tried, all have been found wanting and it is not proposed to consider them further. The most effective cerebral vasodilator substance is undoubtedly carbon dioxide and it is surely already present in abundance at the site of an acute cerebral infarct.

Hypotensive Drugs

The position regarding the use of hypotensive drugs is far from clear. There is no evidence that they reduce the mortality in acute strokes, infarctions or hæmorrhages, in severely hypertensive patients unless there are coexisting features such as left ventricular failure or Grade IV retinopathy which, in their own right, demand their application. In hypertensive patients with chronic cerebrovascular disease there is usually reluctance to use hypotensive agents because of the anticipated risk of inducing further infarcts or insufficiency attacks. Beyond doubt this risk must exist, but on the other hand, untreated hypertensive patients with cerebrovascular disease have a much shorter average survival than do those with relatively normal blood pressures (Marshall and Kaeser, 1961), and it might be that the

advantages of hypotensive therapy would outweigh the hazards.

Anticoagulant Therapy

The apparent benefits of anticoagulant drugs in coronary artery disease inspired the hope that they might prove of value in the treatment of occlusive cerebrovascular disease. Over the past few years many reports have been published of series of patients with various types of cerebrovascular disease treated with anticoagulants, but because of the variable pattern of the disease, its unpredictable natural history and its limited susceptibility to precision in diagnosis, their evaluation has been difficult. The necessity for strictly controlled trial has not always been appreciated; the factors mentioned make such control hard to achieve but mandatory for valid clinical assessment. Without it, not only do we lack a yardstick whereby we can measure the beneficial effects of the treatment but, and of equal importance, the precise magnitude and the implications of the adverse effects are easily overlooked. Barron and Fergusson (1959) have drawn attention to the large number of fatal cerebral hæmorrhages among the extensive reports on anticoagulant therapy in cerebrovascular disease.

On the whole, enthusiasm for anticoagulant therapy has waned with the passage of time and it has become clear that it does not have wide application in cerebrovascular disease. However, its restricted use in a few particular situations is generally accepted to be of benefit and the indications have become fairly clearly defined. Wright and his co-workers (McDevitt, Carter, Gatje, Foley and Wright, 1958), on the basis of a very extensive experience, have clearly established the place of long-term anticoagulants in the prophylaxis of cerebral embolism in patients known to be at risk because of conditions such as rheumatic heart disease. So too in the immediate treatment of established cerebral embolism, Carter (1957) and Wells (1959) found that anticoagulants reduced the mortality rate. In the case of non-embolic cerebral infarction, however, such benefit has not been shown (Marshall and Shaw, 1960). There are several possible explanations for this discrepancy between the results of therapy in the two types of infarction which runs contrary to what might be expected on pathological grounds. The main reason is probably that there is less likelihood of diagnostic error *qua* intracerebral hæmatoma in the embolic group in virtue of the existence of a demonstrable predisposing cause such as a fibrillating left atrium. Also there is often no intrinsic disease of the cerebral vasculature in patients who sustain embolic infarction and they are usually in a younger age-group and less likely

to be hypertensive than are those who have non-embolic infarcts. It may be that these factors modify the response to anticoagulant therapy. Although Carter (1959) also found that patients with non-embolic cerebral infarction resulting in sudden hemiplegia were not benefited by anticoagulants, he has reported that these drugs improve the outlook for patients whose infarction is of gradual onset (Carter, 1960). Fisher (1958) also reported that the downhill course of the progressively evolving stroke due to cerebral thrombosis might be arrested and reversed. With regard to immediate treatment with anticoagulants in the acute phase of the illness, Millikan, Siekert and Whisnant (1958) have recommended their use in actively advancing occlusion of the carotid system and thrombosis with infarction in the vertebro-basilar system.

Apart from their use in the prophylaxis of cerebral embolism the only real indication for long-term therapy in cerebrovascular disease is in patients suffering from frequently recurring transient ischaemic attacks where Fisher (1958) and Millikan and his co-workers (1958) have shown striking benefit. Such cases, however, are numerically few in proportion to the total number of cases of cerebrovascular disease and reference to hospital at the stage of transient ischaemia, without established neural damage, is relatively uncommon. In the broad spectrum of stroke cases commonly encountered in general medical practice Hill, Marshall and Shaw (1960) found that anticoagulants neither increased the expectation of life nor decreased the incidence of further non-fatal cerebrovascular accidents. They emphasized the hazard of inducing cerebral haemorrhage with anticoagulant treatment as did Fisher (1961) in his interim report on the national co-operative study of anticoagulant therapy in cerebral thrombosis and cerebral embolism under his chairmanship.

Initial hopes that anticoagulant therapy might represent a major advance in the treatment of cerebrovascular disease have thus not been fulfilled and, to summarize, in the present stage of knowledge their use should be limited to: (1) the prophylaxis and immediate treatment of cerebral embolism; (2) the prophylaxis of transient ischaemic attacks in carotid and vertebro-basilar insufficiency syndromes; (3) infarcts in either of these territories characterized by gradually increasing neurological deficit, although even this clinical presentation can result from haemorrhage so that treatment will not be without risk.

Thrombolytic Therapy

Interest has recently turned to the development of methods of dissolving intravascular thrombus.

Fibrin, which is the principal insoluble constituent of the clot, is susceptible to enzymatic lysis so that such methods would appear to be rational and to raise exciting therapeutic possibilities in occlusive cerebrovascular disease. Already small series of patients treated with fibrinolysin have been reported (Sussman and Fitch, 1959; Haddon, Meyer, Johnson and Landers, 1960; Clarke and Clifton, 1960) but results are inconclusive. It would seem probable that commercial preparation and standardization of thrombolytic agents of the types used in these studies, and also the methods of therapeutic control are as yet at a stage when clinical evaluation is premature. Moreover, it is unlikely on theoretical grounds that preparations purporting to contain therapeutic doses of fibrinolysin (plasmin) will prove effective. Methods involving their use are based on the assumption that because plasmin is the physiologically occurring fibrinolytic enzyme, an infusion of this substance will be effective in resolving pathological thrombus. This concept disregards the dynamics of the thrombolytic mechanism which Alkjaersig, Fletcher and Sherry (1959) have shown to depend on the diffusion of a plasminogen activator into the thrombus, with activation of the intrinsic thrombus plasminogen and consequent production of plasmin, rather than on the direct action of circulating plasmin. Furthermore, it overlooks the fact that infused plasmin will readily be inactivated by plasma inhibitors. Were doses of plasmin infused which were adequate to resist complete inhibition, then a state of excessive plasma proteolysis would ensue with resultant severe coagulation defects. Sherry and Fletcher (1960) have expressed the view that the therapeutic use of the enzyme plasmin is unlikely to prove effective in man. Other proteolytic enzymes such as trypsin are likewise rendered biochemically inactive by plasma inhibitors unless administered in such excess that a haemorrhagic state is liable to result.

The alternative approach, and the one which holds much more therapeutic promise, depends on the control of the plasminogen activator level of the plasma. Although not ideal, because of its antigenic properties, streptokinase is the only activator at present available which is capable of raising the thrombolytic activity of the plasma and which can be produced in a sufficiently pure and non-pyrogenic form to be used in man. Depending upon previous streptococcal infections, human plasma contains variable concentrations of specific streptokinase antibody which renders streptokinase inert. Thus individual dosage requirements must obviously vary and it becomes necessary before starting treatment to assay the patient's plasma for streptokinase antibody. The dosage

schedule necessary to sustain the required degree of thrombolytic activity can then be calculated to include a priming dose sufficient to neutralize all circulating antibody. A course of treatment will result in further immunization which may complicate subsequent therapy should such be required. There is thus a need for a non-antigenic plasminogen activator, and it is hoped that it may prove possible to develop a preparation of urokinase sufficiently pure for therapeutic use.

It is too early to assess the potential value of thrombolytic therapy in cerebrovascular disease, but it undoubtedly warrants exploration and may hold promise for the future. Should it prove to be effective, the same problem of differentiating between infarction and hæmorrhage encountered in anticoagulant therapy will arise, and its use will probably be limited to cases in which vascular occlusions have been demonstrated angiographically.

Surgical Treatment

Reference was made in an earlier section to studies which showed that cerebral blood flow was not increased by methods designed to interfere with its very limited neurogenic regulation. There is thus no rational basis for surgical procedures such as stellate ganglion block or cervical sympathectomy in the treatment of cerebrovascular disease. Surgical treatment along other lines has, however, established its place, although precise indications and limitations have yet to be defined. Apart from its contribution to the management of aneurysms and arteriovenous malformations, which are beyond our present scope, there are two main situations in which surgery may be indicated.

The first is in internal carotid artery occlusion where the scope of surgical treatment has been considerably expanded by advances in operative technique and the introduction of hypothermia. Edwards, Gordon and Rob (1960) have reviewed their experience of the surgical treatment of internal carotid artery occlusion in light of follow-up over periods extending from one month to three and a half years. Forty patients were included in the study of whom thirty-two had operations. In eighteen of these it was found possible to remove the obstruction, whereas in the remaining fourteen patients blood flow could not be re-established. Nearly all of those in whom the operation was technically successful had partial as opposed to complete occlusions, and the latter are considered to be operable only if the occlusion is very recent and as yet unorganized clot can be removed by gentle suction. This report has the great merit of discussing operative detail and the authors provisionally express the view that in carotid surgery the best results follow a direct end-to-end

anastomosis, although this operation is seldom technically possible. Otherwise they have preference for thromboendarterectomy, finding the procedure generally more satisfactory than arterial transplant or venous graft.

This study thus sheds considerable light upon the surgical aspects of restoring blood flow in the carotid arteries and on the selection of patients in whom surgical treatment is most likely to be technically successful. However, what has yet to be established is the precise influence of such successful operative treatment on the course of the disease. The subsequent follow-up of the total series of forty patients, after a maximum interval of three and a half years, showed that nine had died, the condition of twenty had not significantly altered and that of the remaining eleven was thought to have improved. Unfortunately we do not possess sufficient knowledge of the natural history of the disease to judge from these figures what has been the exact influence of the surgical treatment. The authors expressed the view that the patients most likely to benefit from surgery were those in whom partial obstruction of the artery was manifest by 'stuttering' onset of symptoms, i.e. patients with transient ischaemic attacks before the development of severe and permanent neurological disability. They felt that the operation should be regarded as primarily prophylactic to prevent transient symptoms from becoming permanent and already permanent symptoms from becoming worse.

An aggressive surgical approach to extracranial arterial occlusive lesions is recommended by Crawford, De Bakey, Fields, Cooley, and Morrison (1959). They report highly successful results of reconstructive surgery not only in internal carotid artery disease but also in occlusions of vertebral arteries and great vessels arising from the aortic arch. Although the selection of their patients has been different Riishede, Ottosen and Søndergaard (1960) are much more cautious in the interpretation of their results of surgical treatment in internal carotid occlusion.

The other situation in which surgery may be indicated is in the treatment of patients with primary intracerebral hæmorrhage. McKissock, Richardson and Walsh (1959) have reported the results of surgical treatment in a consecutive series of 244 such patients. Hæmatoma was evacuated by burr-hole aspiration or by craniotomy and in some patients both procedures were undertaken. The operative mortality was 51% and the overall mortality, after an average follow-up period of two years, was 74%. It was found that the mortality was influenced by the site rather than the size of the lesion, capsular hæmorrhages carrying the

worst prognosis. The existence of hypertension adversely affected the prognosis and the greater the impairment of consciousness at the time of operation, the higher was the mortality. Again we have no satisfactory data on untreated patients against which these results can be measured and, as the authors emphasize, a controlled trial will be necessary before a proper assessment of the

value of this form of therapy can be made.

These then are some of the advances in diagnosis and treatment that have been made in recent years. Their contribution to the alleviation of suffering occasioned by cerebrovascular disease is small, but they do reflect a very considerable growth in knowledge from which it can be hoped that greater benefits will derive.

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