THE REGULATION OF THE CEREBRAL CIRCULATION*

SIR RUSSELL BRAIN, BT., D.M., LL.D., D.C.L., F.R.C.P.

London

The cerebral circulation is peculiarly dependent upon the systemic blood pressure, since it normally tends to follow passively upon changes in arterial pressure to a greater extent than is the case in most other organs. There is little evidence that either vasoconstrictor or vasodilator drugs in pharmacopoeial doses have any effect upon the cerebral blood vessels in man, which are, however, dilated by all the usual products of metabolism (decreased oxygen, increased carbon dioxide, increased acidity and increased temperature) as well as a number of other agents which have recently come to be associated with cellular activity, and are constricted by some of the reverse changes, especially by increased oxygen and decreased carbon dioxide. It would seem that carbon-dioxide tension is the dominant influence in regulating both the tone of the cerebral blood vessels and the activity of the respiratory centre over the ordinary physiological range. This means that, given the requisite head of pressure, the blood flow through the brain is controlled by its metabolic needs of the moment. How closely the blood flow through the brain is regulated, even in some pathological conditions, is illustrated by what happens in hypertension. Kety *et al.* (1948) have shown that in patients with simple hypertension the cerebral blood flow, the oxygen consumption of the brain, and the arteriovenous oxygen difference are all normal. This is brought about by a concomitant increase in cerebral vascular resistance equal to the elevation in the mean blood pressure. Conversely, Dewar *et al.* (1953) found that hexamethonium given to hypertensives did not lower the cerebral blood flow, but this may not be true of patients with premalignant or malignant hypertension (Crumpton *et al.*, 1955).

The peculiarities of the regulation of the cerebral circulation must be to some extent dictated by the fact that the brain is contained within the skull, which functions for all practical purposes as a rigid box. Since the contents of the cranial cavity must remain virtually constant, this must materially limit the range of both expansion and contraction of the cerebral vessels. It seems likely that the histological structure of the cerebral arteries is related to the regulation

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of the cerebral circulation. They have a prominent internal elastic lamina, in which they resemble the coronary arteries, and few elastic fibrils in the media and adventitia. It has been argued by Wolff (1938) that the effect of the well-developed elastic internal lamina is to damp down the pulsation of the vessels. One may suppose that in the circular muscle fibres of the media, which is so poor in elastic tissue, resides the tonic function of contracting in response to internal stress, for example a rise of blood pressure.

THE ROLE OF THE CIRCLE OF WILLIS

Ever since its discovery in the 17th century the circle of Willis has attracted attention. The fact that the 4 arteries which supply the brain, the 2 internal carotids and the 2 vertebrals, should be thus linked together would seem likely to fulfil some biological function. Macdonald and Potter (1951) have made an experimental study of the cerebral circulation in the rabbit, in which the arrangement of the cerebral arteries is similar to that seen in man. Their observations show that the internal carotid artery and the basilar artery share the blood supply to each cerebral hemisphere in such a way that there is normally no interchange of blood between them. The opposing streams of the two arteries meet in the posterior communicating artery at a 'dead point' at which the pressure of the two is equal. Consequently they do not mix there. Similarly the territories of the two internal carotid arteries meet at a 'dead point' in the middle of the anterior communicating artery. If, however, both internal carotids or both vertebral arteries are occluded, blood passes forwards or backwards respectively from the pair which are still patent. There is then a functioning antero-posterior anastomosis in each posterior communicating artery. Similarly, occlusion of one internal carotid artery leads to its territory being invaded by the basilar supply through the posterior communicating artery and by the opposite internal carotid through the anterior communicating artery. The latter can readily be demonstrated in the course of angiography, for when the opaque medium is injected into one carotid, and the opposite one is compressed, the medium normally crosses the middle line through the anterior communicating artery, but this does not occur if the normal flow through the uninjected carotid is allowed to continue.

The clinician is apt to look upon the circle of Willis in the light of the way in which it reacts to occlusion by disease of one of its contributory arteries, but it can hardly have been evolved to provide a compensation for a pathological state. It seems more probable that, speaking teleologically, its purpose is to guarantee that whatever may be the position of the head in relation to gravity and to the trunk, and however, from one moment to another, this may influence the relative flow through either carotid or vertebral artery, these variations are always compensated for at a point distal to these vessels and within the cranial cavity by the freest possible anastomoses before the brain is reached. Hence, the schema which partitions the circle of Willis symmetrically between the areas of supply of the various vessels with 'dead points' between them is an abstract conception, true only when the head is maintained in a certain position of rest, and perhaps not always even then.

There are also other anastomotic channels distal to the circle of Willis, namely, the anastomoses described by Beevor (1909), Shellshear (1927) and Abbie (1934) at the periphery of the cortical fields of supply of the anterior, middle and posterior cerebral arteries. As Abbie writes: 'There is no such thing as a non-anastomotic artery on the surface of the brain although the anastomoses are not always sufficiently large to compensate for occlusion of some of them. Every vessel joins another and the primitive network whence they have all arisen remains intact. No cerebral artery becomes an end-artery until it has entered the brain substance, but once within the brain no artery appears ever to join another'.

There is yet another anastomosis which is much less important in man than in some other mammals, namely, that between the external and internal carotid artery supplies through the orbit. I shall have more to say about this later.

THE CEREBRAL BLOOD SUPPLY IN HYPERTENSION

As I have already said, in benign hypertension the cerebral blood flow remains the same in spite of the rise of blood pressure, a fact which can be explained only if there is a diminution in the calibre of the cerebral vessels proportional to the rise in blood pressure. As Dewar *et al.* have shown, hexamethonium in such cases does not lower the cerebral blood flow. This must be because the cerebral vascular resistance falls parallel with the blood pressure. This, however, takes time and, if the blood pressure is lowered too rapidly, the fall in the cerebral vascular resistance may not keep pace with it, and cerebral symptoms may occur. Crumpton *et al.* in their careful study of the effect of hexamethonium on the cerebral blood flow showed that 13 patients with malignant and premalignant hypertension had an increase of cerebral vascular resistance of 119%. After hexamethonium the blood pressure fell 39% and the cerebral vascular resistance 29%. The cerebral blood flow fell 16%.

The pathogenesis of malignant hypertension remains obscure in the sense that we do not know why it should occur in some patients with hypertension and not in others with an equally high blood pressure. The experimental work of Byrom (1954) suggests that hypertensive encephalopathy is related to a spasm of the cerebral arterioles. Pathologically there is a necrotizing arteriolitis associated with gross oedema of the brain and multiple foci of ischaemic necrosis 150–300μ in diameter, but local examination of the arterioles may fail to reveal the cause of these lesions. The cerebrospinal fluid commonly shows both a raised pressure and a raised protein content. The raised intracranial pressure may be so great that the patient dies of a cerebellar pressure cone. It seems probable that the essential feature of hypertensive encephalopathy is the reaction of the vessel to a sudden rise of blood pressure. The necrotizing arteriolitis and the oedema of the brain are doubtless changes secondary to the functional disturbance. In the early stages the disorder is reversible, and encephalopathy and acute nephritis will often respond well to reduction of the blood volume by venesection. Hypotensive drugs are also effective, but two points must be remembered. First, in long-standing cases of hypertension the changes of hypertensive encephalopathy may be associated with narrowing of cerebral vessels due to atheroma. The symptoms of the two may co-exist and the possible effects of lowering the blood pressure upon a brain which is already subject to the risk of ischaemia has to be borne in mind. The second point is that even when treatment

has been effective in overcoming the encephalopathy some irreversible changes may have taken place.

CEREBRAL ISCHAEMIA DUE TO ATHEROMA

Owing to the complexity of the cerebral blood supply the effects of atheroma may be complex. The first and most obvious is local narrowing, but the effects of such narrowing depend upon its situation in relation particularly to the collateral circulation. When the collateral circulation is good, a major vessel, such as one internal carotid artery, may be completely occluded without any symptoms resulting. Recent work has shown the importance of the relationship between the carotid and vertebral supplies (Hutchinson and Yates, 1956, 1957). A patient with atheromatous narrowing of both these vessels on one side may remain free from symptoms until the internal carotid becomes completely occluded, when the combined supply becomes inadequate not only for the affected cerebral hemisphere, but also for structures in the posterior fossae so that infarction of the ipsilateral cerebellar hemisphere may also occur.

The commonest symptom of cerebral atheroma is the ischaemic cerebral attack. Such attacks may precede a stroke, or follow partial recovery from one, or occur briefly and intermittently for a long time as the sole manifestation of the impaired circulation. The most probable cause of such attacks is that a vessel has become so narrow that its calibre is normally just adequate and becomes inadequate if the systemic blood pressure falls, for example during sleep. It is possible that arterial spasm may sometimes play a part. It is, I think, less likely that such attacks are usually embolic.

A common early symptom of atheroma of the internal carotid is a transitory attack of amblyopia on the affected side. This must surely be due to a temporary fall of blood pressure in the ophthalmic artery. Why, then, does the eye so rarely become permanently blind when the internal carotid becomes completely occluded? Symonds (1955) has plausibly suggested that in most cases a collateral circulation to the orbit *via* the external carotid and internal maxillary arteries becomes established in time to maintain the blood supply to the eye and so preserve vision even though the normal supply to the ophthalmic artery from the internal carotid eventually becomes cut off.

The symptoms of transitory ischaemia of one cerebral hemisphere resulting from atheroma of the internal carotid artery are too familiar to need more than a brief mention. They include periods of mental confusion with subsequent amnesia, generalized epileptic attacks (though in my experience these are not very common), transitory numbness or tingling or weakness of one or other limb on the opposite side of the body or of a hemiplegic distribution and, when the left hemisphere is involved in a right-handed person, transitory aphasic attacks of various kinds. Attacks of myoclonic twitching of a limb are fairly common after a stroke, and usually involve the lower limb, being particularly prone to occur at night. It is tempting to explain these twitches in terms of fluctuations of the collateral circulation to the leg area of the cortex on the damaged side from the opposite internal carotid artery by the anterior communicating artery.

Headache is sometimes a prominent symptom of atheroma of the internal carotid artery. It may precede more serious disability, such as a stroke. It is common immediately after a stroke and sometimes persists for long periods. Symonds has suggested that it is frequently due to dilatation of collateral vessels, and this seems very probable. If so, at least two sources of the headache can, I think, be distinguished. The commoner type probably arises from dilatation of the vessels of the circle of Willis, but another kind of headache may occur, somewhat resembling migraine and associated with dilatation and increased pulsation of the branches of the external carotid artery.

VERTEBRO-BASILAR ISCHAEMIA

We have only recently learned to recognize in their full variety the symptoms of ischaemia within the distribution of the vertebro-basilar supply. These symptoms are sometimes difficult to distinguish from those of internal carotid atheroma, for which they may sometimes be mistaken, though the reverse is less common. Since the supply to the posterior cerebral arteries normally comes from the basilar artery, vertebro-basilar atheroma may cause ischaemic disturbances of one or both temporal and occipital lobes. The symptoms of these include attacks of confusion and disorientation, impairment of memory, which may amount to severe and persistent memory loss, defects of vision, such as teichopsic attacks reminiscent of migraine, transitory or permanent hemianopia, or even complete cortical blindness. Impairment of the blood supply to the brain-stem and cerebellum may lead to a wide variety of symptoms, such as diplopia, dizziness, unilateral, crossed or bilateral numbness or weakness, dysarthria and ataxia of the limbs (Millikan and Sieckert, 1955). Headache when present is most likely to be occipital.

I have mentioned earlier the importance of atheroma of the vertebral arteries in relation to the blood supply to the brain. Their position in their bony canals in the cervical spine and in relation to the neurocentral joints means that they may be narrowed as the result of pressure from osteophytes in cervical spondylosis. The degree of narrowing may be influenced by the position of the head. Consequently we are now beginning to recognize that transitory cerebral symptoms may be produced in this way by turning the head. Giddiness is the commonest such symptom and it is important to remember this cause of giddiness in elderly people with atheroma and with or without hypertension and to distinguish it from vertigo of aural origin.

ANCILLARY DIAGNOSTIC AIDS

The impairment of the blood supply to the eye resulting from atheroma of the internal carotid artery has recently been employed as a diagnostic test. By using a measured pressure upon the eye it may be shown that the blood pressure in the central retinal artery is lower upon the affected than upon the normal side (Milletti, 1950; Svien and Hollenhorst, 1956). Examination of the cerebrospinal fluid often gives useful information. For two or three weeks after a recent cerebral infarction the fluid is likely to have a raised protein and may be xanthochromic. There is often a moderate excess of cells, in which polymorphonuclears may be in the minority. When there is no reason to suspect infection the presence of a few polymorphonuclear cells in the cerebrospinal fluid is a useful indication of recent brain damage of vascular origin.

In cases of atheroma of the internal carotid artery electro-

encephalographic abnormalities are commonly found over some part of the affected cerebral hemisphere. Webster, Gurdjian and Martin (1955) and Gurdjian, Webster and Martin (1957) discuss the diagnostic value of carotid compression in the neck.

Palpation of the carotids should always be carried out. Sometimes it is easy to be sure that there is a difference between the two sides, but this is a test which is often difficult to interpret. Auscultation occasionally reveals a bruit which may be heard either in the neck or on listening over the eye, and is presumably due to narrowing of the internal carotid.

Cerebral angiography may give valuable information. Some hold that it is best avoided as liable to produce a cerebral vascular accident when used in cases of carotid atheroma, especially perhaps if accompanied by hypertension. Most workers who use it regularly, however, regard such risks as slight, and it would seem justifiable to use carotid angiography when it can provide information which could not be obtained in any other way, and which may be essential in order to decide what treatment to adopt. It has been suggested that surgical exploration of the vessel is less risky and can provide as much information. Only angiography, however, can tell us what is happening in the intracranial course of the vessel and its branches.

Vertebral angiography by the method of direct puncture is certainly more risky than carotid angiography in patients with vascular disease and should therefore be used with caution in such cases.

SOME PROBLEMS OF TREATMENT

In the past our attitude to cerebral infarction, threatened or actual, has been largely fatalistic. Even today the limitations of treatment are all too obvious. Nevertheless, we have a much greater understanding than before of the factors involved, and we can therefore see more clearly what should be the aim of treatment, even if the value of particular methods is often still *sub judice*.

Early diagnosis based upon the recognition of the significance of early symptoms and signs, aided when necessary by special diagnostic methods, is likely, as our methods of treatment improve, to make it increasingly possible to avert, or at any rate postpone, the more serious effects of atheroma of the cerebral vessels.

When once an ischaemic stroke has occurred, whether major or minor, it should be borne in mind that the degree of recovery will often depend upon the extent to which a collateral circulation can be established, particularly to what may be termed marginal areas. This in turn will depend upon a patency of the collateral channels, the height of the systemic blood pressure, and the adequacy of the blood itself in respect of oxygen and nutrients, particularly vitamins. Although bed rest will be essential during the stage of shock, or coma, and in the case of patients too severely disabled to sit up, the aim should always be to get the patient to move his sound limbs and to sit out of bed as soon as possible. This is particularly important with non-hypertensive patients, since immobilizing them may lead to a fall of blood pressure which will militate against the establishment of a good collateral circulation.

There is no evidence that any vasodilator drug dilates the cerebral vessels. Aminophylline is sometimes used for this purpose, but such evidence as there is suggests that it may have a vasoconstrictor action on the vessels of the brain (Kety, 1950). If we bear in mind the relationship between the cerebral circulation and the systemic blood pressure, it is clear that vasodilator drugs which do not dilate the cerebral blood vessels may indirectly impair the cerebral blood flow by lowering the systemic blood pressure.

A similar caution applies to the use of hypotensive drugs. Dewar, Owen and Jenkins (1953) have shown that hexamethonium does not lower the cerebral blood flow. This is because when the blood pressure falls as the result of giving hexamethonium there is a corresponding increase in the calibre of the cerebral vessels. These authors, however, point out that if the mean cerebral flow does not alter there will be a slowing of the linear flow rate and a prolongation of the local circulation time. If, therefore, this is already below normal owing to atheroma of a vessel, the use of such a drug as hexamethonium, although it does not diminish the cerebral blood flow as a whole, may increase the risk of local thrombosis. Before using such drugs in the treatment of hypertension, therefore, it is important to look for evidence of cerebral vascular disease in the history and clinical condition of the patient.

Cervical sympathetic block has had a certain vogue in the treatment of cerebral infarction. If the cerebral vessels in man have no important vasoconstrictor nerve supply it is difficult to see how sympathetic block could directly improve the blood flow through the brain. If, however, in any individuals the collateral circulation through the external carotid is of any magnitude, this might presumably be improved by interrupting the vasoconstrictor fibres to it through the cervical sympathetic. The prognosis of untreated cerebral ischaemia is so extremely variable that it is very difficult to assess the significance of the improvement which it has been claimed may follow cervical sympathetic block.

The value of anticoagulants, and hence the indications for their use, are also debatable. Here, again, we need more statistical evidence than is at present available. Clearly the first diagnostic essential is to be sure that the lesion with which we are dealing is ischaemic and not haemorrhagic. Even so, immediately after an ischaemic stroke has occurred, there is an area of brain in which the capillaries are damaged, and there is undoubtedly a risk that anticoagulants may lead to a haemorrhage into such an infarcted area. Since it is doubtful whether they will in other respects do good it would seem unwise to give anticoagulants within at least 3 weeks of an attack of cerebral infarction. Some would use the cerebrospinal fluid as a guide in such cases and withhold anticoagulants as long as the fluid is xanthochromic. The level of the blood pressure must also presumably be relevant to the risk of haemorrhage. The selection of an upper limit must necessarily be somewhat arbitrary, but most workers would regard a severe degree of hypertension as in itself a contra-indication to the use of anticoagulants.

The most plausible argument for the use of anticoagulants is in patients with cerebral atheroma who suffer from transitory ischaemic attacks, which are rightly regarded as a warning that a more severe occlusion lesion may occur. Several American workers have claimed that the number of ischaemic attacks suffered by patients after being put on anticoagulant therapy is very much less than the frequency with which they occurred before, though there is no adequate explanation of this fact. The clearest indication for the use of anticoagulants, subject always to the precautions I have

already mentioned, is perhaps in those patients whose ischaemic attacks indicate atheroma of the vertebro-basilar system, since the prognosis in such cases is always grave, and there is some evidence that it is considerably better in those treated with anticoagulants (Millikan, Sieckert and Schick, 1955).

Finally, a word or two about arterial surgery. Since the commonest site of narrowing by atheroma of the internal carotid artery is just above the bifurcation of the common carotid, the early recognition of this lesion may render it amenable to surgery and, even when the vessel at that site is completely occluded by a thrombus, it may be patent more distally, and the removal of the obstruction may enable the cerebral blood flow through that vessel to be re-established. Here is a promising method of treatment which will obviously be particularly valuable for patients who happen to have a localized lesion (Robb and Wheeler, 1957).

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