Do Vasomotor Nerves Significantly Regulate Cerebral Blood Flow?

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IT IS worthwhile noting at the outset that this controversy is not new, the topic having been debated with vigor for the past 100 years or so. What has changed is the way in which the question at issue has been posed. In earlier experiments, the question was whether or not vasomotor nerves existed; but once they had been demonstrated, the problem was to assign a functional role to them. By the end of the 1930’s, during which the action of vasomotor nerves and various drugs on pial vessels had been studied intensively, this question still was far from being resolved. On the one hand, it was clear that there were vasomotor nerves, and it was equally clear that section or stimulation of these nerves could markedly affect the caliber of pial vessels. On the other hand, the responses of pial vessels to such disturbances as hypoxia, hypercapnia, and hypotension were similar whether the nervous pathways were intact or not. Hence it was concluded that vasomotor nerves played little part in the regulation of cerebral vessels; the more important factors were intrinsic to the vascular bed.

In the intervening years, extensive research has, if anything, sharpened the controversy. On the one hand, morphological and histological studies have shown that, in virtually every respect, the density of the adrenergic and cholinergic plexus on cerebral blood vessels and the appearance of the terminals at the neuromuscular junction are identical to those in other vascular beds. Pharmacological studies have identified adrenergic constrictor and cholinergic dilator receptors on smooth muscle, and experiments in which cerebral blood flow has been measured quantitatively have in most cases confirmed the earlier actions of vasomotor nerves. On the other hand, a number of studies using the same methods or modifications of them have shown that these actions are either very small or nonexistent. It is not surprising, therefore, that there are contemporary echoes of the earlier bewilderment while others have, in addition, pointed out that the operation of vasomotor nerves to cerebral blood vessels could be teleologically inconvenient.

The view I wish to develop is that, although it is at present difficult to assign a precise role to cerebral vasomotor nerves, it is premature to dismiss such a role. This is because there is, in my view, sufficient evidence in their favor which is strong enough to withstand insinuations of artifact and the contrary negative evidence. In addition, it is abundantly clear that, despite a great deal of research in this field over recent years, there are still substantial areas of ignorance or uncertainty about these vasomotor pathways and about the responses of cerebral vessels. In this review, I survey these areas of uncertainty, I attempt to reconcile the discrepant physiological evidence, and I attempt a synthesis which might at least be testable. In short, I wish to sow sufficient seeds of doubt so that those who might be tempted to dismiss a functional role for cerebral vasomotor nerves should pause and reconsider their position.

Areas of Uncertainty Concerning the Neural Pathways

It is not disputed that cerebral blood vessels are innervated by adrenergic fibers which have their origin in the superior cervical and stellate ganglia. The density of this plexus is not less than in other vascular beds, but the distribution is far from homogeneous. In general, the internal carotid artery and its branches are more densely innervated than the vertebral artery and its branches, but within these two areas, there are wide variations. The density of the plexus also varies with the caliber of the vessel. Although we remain uncertain about a number of important points concerning this plexus—for example, whether the density of the
plexus represents a genuine innervation or whether a proportion of the fibers are en passant to more distant blood vessels—there does seem to be a close relation between the density of the plexus and the effects of sympathetic nerve stimulation. Thus Sercombe et al.\(^4\) have shown that with sympathetic nerve stimulation, blood flow in the caudate nucleus falls to a greater degree than in the lateral geniculate nucleus and that this difference is proportional to the density of the nerve plexus in the two areas. Similarly, both Wei et al.\(^5\) and Kuschinsky and Wahl\(^6\) have shown that stimulation of the sympathetic nerves causes a proportionately greater degree of vasoconstriction in the larger than in the smaller pial vessels. Although it is difficult at present to be certain about the effects of sympathetic stimulation upon vascular resistance in different parts of the cerebral vascular bed in quantitative terms, these observations suggest, first, that the sympathetic fibers can affect blood flow in intracerebral blood vessels, a conclusion supported also by the studies of Cross and Silver.\(^8\) Second, from a consideration of the partition of total cerebral vascular resistance determined by Shapiro et al.,\(^7\) it is clear that changes in the caliber of extracranial vessels can substantially affect cerebral vascular resistance. This means that it may be difficult to consider the cerebrovascular bed as consisting of components in series which are principally regulated by either neural or metabolic factors.\(^9\)

Nor is it in dispute that in morphological terms the adrenergic terminals are identical to those seen in other vascular beds and effector organs. They approximate to within 80–300 nm\(^6\) of the adventitial border of smooth muscle. They contain small, 50-nm electron-dense vesicles which most probably store norepinephrine,\(^12, 13\) since they are depleted by 5-hydroxydopamine. An unusual feature of the adrenergic terminals is their close apposition, that is within a distance of 25 nm, to nonadrenergic, probably cholinergic, terminals.\(^9, 15\) The electronmicroscopic appearances suggest axo-axonal junctions, and these are of considerable interest since there is evidence from in vitro experiments that the release of norepinephrine from the adrenergic terminals can be reduced or abolished by acetylcholine acting through nicotinic receptors.\(^16\) If this operates in vivo, the effectiveness of sympathetic vasoconstriction could be very largely influenced by the simultaneous operation of cholinergic fibers.

Alpha-adrenergic receptors undoubtedly exist on cerebrovascular smooth muscle, since they can be excited by a stimulation of sympathetic nerves and the close microapplication of norepinephrine, and the resulting constriction can be abolished by reversible inhibitors such as biperoxan and phentolamine or irreversible inhibitors such as phenoxybenzamine or dibenamine.\(^17-19\) However, this action is weak: a 15% reduction in pial artery caliber requires 10 times as much norepinephrine as for mesenteric vessels and 400 times as much as for cremasteric vessels. Why this is so is not clear. There is some evidence that the uptake of norepinephrine by nerves (uptake\(_1\)) is more avid than in other vascular beds,\(^20\) and the uptake by muscle, by the action of catechol-O-methyltransferase,\(^21\) is also greater. There is also evidence that, in the cerebrovascular bed, \(\alpha\)-adrenergic receptors are unusual. Thus, the specific agonist, phenylephrine, acts only as a partial agonist, has a potency less than that of isoproterenol, and has a potency ratio with norepinephrine about 10 times less than elsewhere.\(^19\) \(\alpha\)-Norepinephrine has a greater potency than \(\beta\)-norepinephrine, and the receptors have an extremely high phenolamine dissociation constant. It also seems that the \(\alpha\)-adrenergic receptors vary in sensitivity or frequency in different parts of the vascular bed and in different species. There is similar variation with respect to \(\beta\)-adrenergic receptors. They have been found in the feline middle cerebral artery, where they are of the \(\beta_1\) type;\(^22\) in the hypothalamus and caudate nucleus but not the lateral geniculate body of the rabbit;\(^23\) they do not appear to be present in the basilar artery of the rabbit,\(^24\) and their action is minimal in pial vessels of the cat.\(^24\) The cholinergic system has been studied much less extensively, partly because it is anatomically inaccessible, being encased in bone for most of its course, and partly because the technique for staining for acetylcholinesterase (AChE) is more difficult and less specific than for adrenergic fibers.

We depend heavily on two papers\(^25, 26\) which suggest that the unique origin of the cerebral dilator pathway is the 7th cranial and greater superficial petrosal nerves, the fibers then being distributed with the sympathetic fibers to the major afferent and pial vessels. More recent work has provided further evidence for such a cholinergic pathway. A dense plexus of AChE-staining nerves has been shown on the internal carotid artery, its branches, and on pial vessels but not, so far, on intracerebral vessels.\(^27\) As described above, nonadrenergic, probably cholinergic, terminals have been demonstrated on smooth muscle. Cholinergic dilator receptors have been shown on smooth muscle which can be inhibited by atropine.\(^28\) However, recent studies have shown that the AChE plexus is unaffected by unilateral or bilateral section of the petrosal nerves (Vasquez and Purves, unpublished observations), and only occasional degenerate terminals can be seen up to 4 months after nerve section. This suggests that the contribution from the petrosal nerves is very small—not zero, however, because stimulation of the peripheral cut end of the petrosal nerve causes a rise in cerebral blood flow which is blocked by atropine.

Where, then, does the cholinergic dilator pathway originate? With respect to that part which travels with the petrosal nerve, it may correspond to the projection from the petrosal nerve to the lateral...
The reticular formation in the medulla via the nervus intermedius. If this is so, then this would place the cell bodies of this particular part of the pathway among other vasomotor neurones in this area and which are known to be affected by descending activity from the cortex and hypothalamus. However, it should be recalled that the petrosal nerve is mixed, carrying efferent fibers to the lacrimal glands, 34-37 vasomotor fibers to the nasal arterioles, 38, 39 and afferent fibers from taste buds in the palatine region. This makes identification of individual pathways difficult, but it is probable that resolution of this question is of less importance than that of identifying the origin of the major source of AChE-staining fibers on cerebral vessels. This is because there is a clear sense in which dilator responses of cerebral vessels are physiologically more important than constrictor responses and, further, until this source is identified, it will be impossible to be certain whether a dilator pathway is involved even when the major extrinsic pathways, e.g., the vagus and sympathetic nerves, have been cut.

Recently, two other systems of nerve fibers associated with intracerebral vessels have been identified. The first of these is the "vasoactive intestinal polypeptide" system, visualized immunohistochemically. The axons have the same relation to blood vessels as sympathetic fibers, but they originate elsewhere, possibly from intracerebral sources. Preliminary tests in vivo suggest that these fibers are dilator, and thus they may contribute to the non-adrenergic, non-cholinergic dilation of vessels considered by Lee et al. The second system consists of noradrenergic fibers, also in association with cerebral vessels, which originate in the locus coeruleus and adjacent regions. There is at present no convincing and reproducible evidence that these fibers make synaptic contact with smooth muscle, nor that lesions of the locus coeruleus affect cerebral vascular responses. However, this pathway must remain of potential interest because of its possible regulation of the cerebral microcirculation and because it may itself be responsive to such stimuli as hypoxia.

In addition to these pathways, nonmyelinated fibers of unknown origin innervate capillary pericytes and endothelial cells in the hypothalamus. Although the function of these fibers is unknown, their presence has an added interest because of the recent findings of actin and myosin in these cells. Clearly they could be important in vasomotor control at the capillary level and could affect the permeability of the blood-brain barrier.

This review, so far, has considered only the motor aspects of possible reflex arcs, and further evidence for the existence of such arcs must come from a study of the central organization within the pons and medulla. The available evidence suggests that the majority of cell bodies of vasomotor neurones which descend to the spinal cord are to be found in the reticular formation of the medulla, that the predominant state of excitation or inhibition of these neurones is determined largely by afferent activity from baroreceptors, and that this baroreflex can be markedly modified by descending activity from the cortex and hypothalamus. The sympathetic cholinergic system to blood vessels of the hindlimb and possibly other vascular beds appears to bypass the medullary vasomotor system. That a similar system could affect cerebral blood vessels was first suggested by the experiments of Stavraky, who showed that stimulation of the ventral and posterior parts of the hypothalamus caused, respectively, bilateral dilation and constriction of pial vessels, and that these changes could be dissociated from the accompanying changes in blood pressure and, further, certainly with respect to the constrictor responses, that they could be abolished by section of the sympathetic nerves. Similar types of response have been demonstrated by Molnar and Szanto, Langfitt and Kessel, and Meyer et al., while Shalit et al. and, more recently, Scremin et al. have shown that the vascular response to CO2 can be reduced markedly by specific and discrete electrolytic lesions in the pontine area. Yet further evidence is provided by Reis and his colleagues (personal communication), who have shown that stimulation of the fastigial nucleus causes complete abolition of pressure-flow autoregulation and a profound increase in cerebral blood flow, the motor pathway being unknown but not carried in the spinal cord or sympathetic nerves. In contrast, stimulation in the pressor area in the dorsal tegmentum of the medulla elevates the upper limit of autoregulation, and if this stimulation is repeated after the cervical preganglionic sympathetic nerves are cut, the autoregulation is again abolished. These results would suggest that there are powerful dilator and constrictor pathways in the brain which may be stimulated together (in the medulla) or independently (in the fastigial nucleus).

It is not difficult to criticize certain aspects of the protocol in this group of experiments, involving as they do lengthy exposure of the brain, the possibility of current spread, damage to neighboring areas, and the possibility of vascular changes which are secondary to nonspecific neural activation. However, in most of the experiments, most of these factors can be excluded with some confidence, and there thus would be a strong case for the central representation of reflex pathways which regulate cerebral blood vessels in a fashion analogous to other vascular beds. These pathways would provide a structural basis for the responses of cerebral blood vessels to external stimuli such as cooling of the skin, electrical stimulation of the sciatic nerve, stimulation of pain receptors, 51 stimulation of the peripheral baro- and chemoreceptors, or electrical stimulation of the aortic and carotid nerves.
aspects of the neural pathways, there are still sub-
stantial areas of uncertainty that make it difficult
to interpret the significance of physiological exper-
iments. Of particular importance in this respect are
the species differences in the adrenergic pathway and
the adrenergic receptors on smooth muscle and
the origin of the cholinergic dilator pathway.

The Results of Physiological Experiments

A very large number of experiments have been
carried out to determine whether and by how much
reflex pathways affect cerebral blood vessels. The
great majority of these have been concerned with
the properties of the sympathetic fibers, and only a
few have been concerned with the dilator pathway
and the receptors and afferent limb of the reflex
arc. The experiments have involved cutting or stim-
ulating the nerves and measuring the effect on the
caliber of pial vessels or blood flow under control
conditions and, in addition, determining whether
such maneuvers affect the responses of the cerebral
vascular bed to changes in O₂, CO₂, and perfusion
pressure. A detailed criticism of all of these exper-
iments would be impossible here and, in any case,
this has been attempted elsewhere. Here, I con-
sider more recent experiments in which there has
been good control of blood gas tensions and arterial
pressure and in which the effect of cutting or stim-
ulating nervous pathways has been measured by
alterations of pial arterial caliber, the use of clear-
ance techniques and techniques involving the injec-
tion of microspheres, and the measurement of ve-
nous drainage. The results may be summarized as
follows:

1. Section of the sympathetic nerves causes a
small increase in blood flow followed by a late
decrease in flow with recovery in 14 days or
more.

2. Supramaximal stimulation of sympathetic
nerves causes a reduction in the caliber of pial
vessels and a reduction in blood flow which can
vary from 10% to 80% of control.

3. Stimulation of the peripheral cut end of the
7th cranial or petrosal nerves causes pial dilation
and an increase in cerebral blood flow, an in-
crease which does not appear to be CO₂ dependent.
Electrical stimulation of the vagus, aortic, and sinus
nerves causes pial vasodilation and an increase in
blood flow; physiological stimulation of chemore-
ceptors causes an increase in cerebral blood flow,
a response abolished by sinus nerve section.

4. The cerebral vascular response to hypotension
is affected by section of the sympathetic nerves
and by section of the 7th cranial nerves. The
response to hypertension is affected by sympathetic
section and stimulation. Typical independ-
ence of flow and pressure is virtually abolished
by section of the vasoconstrictor nerves. The
response to CO₂ is reduced by specific lesions in the
brain stem, by section of the 7th cranial nerves,
and by section of the vasoconstrictor nerves, as is the
response to hypoxia. The large increase in blood
flow which accompanies the asphyxia of birth is
abolished by bilateral vagotomy.

5. Microapplication of norepinephrine in vivo causes
constriction of pial vessels, a response which is
abolished by the local application of phentol-
amine. If phentolamine is applied to the vessel
directly, there is negligible change, suggesting that
sympathetic nerves exert a very slight tonic influ-
ence under control conditions. Similarly, the mi-
acroapplication of acetylcholine causes pial dilation,
a response abolished by atropine.

At first sight, this catalogue of responses would
suggest an impressive role for the constrictor and
dilator pathways. However, against these, a sub-
stantial number of experiments have found only a
very small change to the same stimuli or none at
all. These are: (1) section of the sympathetic nerves
causes no change in resting cerebral blood flow,
(2) stimulation of the sympathetics is without effect
on cerebral blood flow in the cat, monkey, and
dog, nor are the larger vessels affected; (3) the
relation between flow and pressure is not affected
by sympathectomy nor is flow affected by stimu-
lation of the baroreceptors or denervation of the
baroreceptors; and (4) the cerebrovascular re-
ponse to changes in O₂ or CO₂ is unaffected by
denervation of the chemoreceptors or in vivo
stimulation of the chemoreceptors.

In short, these studies suggest that the system of
extrinsic nerves, together with the reflex arcs in-
volving the baro- and chemoreceptors, play an in-
significant role in the regulation of cerebrovascular
responses, and thus they broadly confirm the con-
clusions made many years ago, namely, that the
responses to changes in perfusion pressure, O₂, and
CO₂ are due to mechanisms which are intrinsic to the
vascular bed.

There are only two ways of explaining these
discrepancious experimental results. Either there is
some fundamental flaw in one or more of the meth-
ods which have been used to measure cerebral blood
flow or in the way in which they have been applied
(and this could include species differences); or, both
sets of results are largely correct and they simply
reflect different functions of cerebral blood flow. In
connection with these possibilities, it is of interest
that there is some, but not complete, correlation
between the methods and the experimental animals
used and the results obtained. Thus, in the first
group, that in which positive results were obtained
with section or stimulation of neural pathways, the
most common method used was the clearance of inert
gases, and the most common animal used was the
baboon or monkey. In the second group, that in
which the results were mainly negative, the com-
monest method used was the injection of micro-
spheres and the commonest animal used, the dog.
The implication of this correlation is amplified as briefly as possible below.

**Methods**

**Measurement of Pial Artery Caliber**

This method is obviously the most direct and, with the introduction of the image-splitting technique, the accuracy of measurement of caliber change has been increased considerably. The method has been of particular value for estimates of the action in vivo of the close application of drugs to pial vessels or of stimulating sympathetic nerves. However, the change in caliber of pial vessels gives no reliable index of the change in pial blood flow since, without simultaneous measurements of local intravascular pressure, there is no guarantee that these changes are linearly related. Further, there is ample evidence that, because of the presence of abundant anastomoses, the responses of pial vessels are far from homogeneous. In addition, changes in the caliber of pial vessels cannot indicate with any accuracy the direction and size of changes of blood flow in intracerebral vessels, although it is of interest that these follow each other very closely in the first group of experiments outlined above.

**Indicator Clearance Curves**

**Radioactive Indicators**

$^{133}\text{Xe}$ and $^{85}\text{Kr}$ have been used as inert indicators for the measurement of cerebral blood flow for more than a decade and, in this time, much effort has been devoted to the theoretical and practical drawbacks of the method as well as its usefulness. It seems clear, first, that if it can be assumed that the resistance to diffusion of the gases between tissue and blood is negligible, the clearance curve is a good measure of a function of the product of blood flow and capillary surface area. In the great majority of tests, the curve can be resolved in two components; the problem is to assign these components to perfusion in specific parts of the brain being sampled. Although there is some evidence that the fast component represents grey matter and the slow component, white matter flow, and although there is consistency between values for blood flow measured by the clearance curve and by the fractional distribution of antipyrene, the correlation can only be approximate and under carefully defined conditions. However, this point is fairly generally appreciated, and most thoughtful workers would not press the accuracy of the method beyond the statement that it indicates the direction of flow and the magnitude of change to approximately ±15%.

A second, practical problem with this technique is the elimination of spurious, extracranial activity from the clearance curve. Again, this possibility is widely recognized, and in the majority of tests outlined above, a number of precautions have been taken, notably the use of lead shielding and removal of extracranial tissue from which activity might immediately affect the counter. As a result of these measures and a number of tests, there is every reason to believe that, in recent experiments, at least, contamination from extracranial sources has been reduced to very small proportions.

**Heat and $H_2$ Clearance**

Similar difficulties arise with the use of heat and $H_2$ as indicators, but, in addition, these require the insertion of thermocouples or electrodes into brain substance. These may be chronically implanted, in which case there is the real possibility that the blood-brain barrier is breached or that blood flow from an unrepresentative form of reactive, glial tissue is being measured. The authors of this technique have examined these possibilities in some detail, but some doubt must remain, since they have shown that the infusion of norepinephrine causes substantial reductions in blood flow in the caudate nucleus. It is generally believed, however, that norepinephrine does not cross the blood-brain barrier and therefore cannot act upon $\alpha$-adrenergic receptors on the adventitial surface of blood vessels.

**Fractionation Indicator Techniques**

The use of nondiffusible indicators to define the distribution of blood flow in the brain was introduced by Sapirstein. Subsequent modifications of the technique, with iodoantipyrene, have allowed blood flow to most structures in the brain to be measured quantitatively under control and a number of experimental conditions. The advantage of the method is that surgery is minimal, measurements can be made in awake, unanesthetized animals, and the possibility of extracranial contamination is virtually eliminated. The disadvantage is that only one measurement can be made. It also has been possible to show a consistency between values obtained by this technique, using a bimodal Gaussian model and values obtained from the two-phase exponential clearance of $^{133}\text{Xe}$.

Recently, the technique has been modified further by using nuclide-labeled microspheres of 15 µm average diameter, and it has been possible to show that the lodging of microspheres in brain capillaries does not significantly affect their sensitivity, that the vast majority of microspheres are removed after one circulation, and that there is adequate mixing with blood despite the significantly different specific gravity of the microsphere suspension. The results in large measure confirm those with antipyrene, although, in two studies, the observation that blood flow in all areas was low and the difference between grey and white matter blood flow was very small must remain a matter for concern.
measurements of blood flow using the $^{133}$Xe clearance and microsphere techniques be carried out in parallel. From previous evidence, but with the qualifications outlined below, I would predict that, certainly over the physiological range, the results should agree closely.

**Venous Drainage Techniques**

These techniques are clearly the most direct; equally clearly, they require high expertise, and much patient surgery to ensure that blood from only the brain is being measured and that a substantial proportion of cerebral venous blood does not escape the measuring devices by draining elsewhere. A further difficulty is to estimate the volume of blood from which blood drains; this is usually estimated by injecting acrylate or other similar substance retrogradely, and the possibility of artifact must be high. Nevertheless, the method has been investigated exhaustively and further tests have been carried out which suggest that the modification introduced by D'Alecy and Fieg1 may have allowed substantial contamination from extracranial sources.

This very brief review suggests to me that, despite the drawbacks involved in every method used, none is likely to be substantially in error, although quantitative estimates of cerebrovascular responses probably will differ. The question of extracranial contamination has been discussed. A further possible source of error is that the sensitivity of cerebral vessels may be affected by surgery which affects the major afferent vessels and veins. This is the most likely explanation of the linear relation between perfusion pressure and flow found in the experiments of Sagawa and Guyton, in which the complete isolation of the cerebral circulation was attempted. It is also a possible explanation of some but not all of the results obtained by Ponte and Purves, who perfused the brain artificially, although it should be added that these workers were mindful of this possible artifact and took some trouble at each stage of the experiment to ensure that the sensitivity of vessels, in particular to CO$_2$, was not impaired. Apart from these examples, I find it difficult to conclude that all of the discrepant results outlined above were due to artifact on the part of one group of experimenters or the other.

What explanation then can be offered if, as I believe, differences in method or in their application cannot be incriminated? I propose two for consideration:

First, although species differences are often proposed by the despairing to explain experimental discrepancies, there is a very real possibility that the organization of cerebral vascular control and, in particular, the neural contribution, may differ between species. I have in mind, for example, the very different effects on brain function which are found when afferent vessels are ligated in different species which reflect the consequences of having a rete mirabile or a circle of Willis and the very different magnitude of anastomoses between carotid and vertebral circulations. Add to these differences those in the distribution and nature of $\alpha$-adrenergic receptors briefly mentioned above and the possibility of quite different responses to the same stimuli becomes clear. It is of some interest in this connection that, in the lists of experiments given above, cerebral blood vessels in the dog and cat have generally been insensitive to neural stimulation; those in the baboon have been sensitive. This topic requires very much more study.

Second, when the sympathetic nerve is stimulated, the pial vessels constrict with a time constant of approximately 1–2 minutes. In contrast, there is an initial fall in intracerebral blood flow which recovers within 2–3 minutes to control levels, although sympathetic stimulation is continued. This “escape” could be due to exhaustion of the transmitter or it could be due to a response of vessels downstream of the pial vasculature to maintain perfusion and intracerebral blood flow constant. The response which is measured will then depend very much on whether blood flow in intra- or extracerebral blood vessels is being measured. I wish to suggest that in the $^{133}$Xe and, possibly even more so, in the $^{86}$Kr clearance method, the so called fast component is predominantly affected by activity from pial vessels because (1) after a bolus injection of the indicator, full equilibration between blood and tissue is unlikely, whereas activity in the pial vessels will be maximal, (2) the pial vessels being closest to the counter will, because of the limited penetration distance, affect the NaI crystal by a corresponding amount and, (3) clearance of the indicator from pial vessels will be most rapid. If this possibility is accepted, it follows that the fast component, which has generally been found to be more sensitive to a variety of stimuli than has the slow component, will reflect changes to an unknown but possibly large extent in pial vessels. In contrast, the microsphere and venous drainage techniques will reflect changes in regional or total intracerebral blood flow. It is therefore quite possible that blood flow estimated in particular from the fast component of the $^{133}$Xe or the $^{86}$Kr clearance curve might be reduced during sympathetic stimulation, whereas the microsphere technique that gives information about instantaneous blood flow could reflect the responses of intracerebral blood vessels. However, if a stimulus such as CO$_2$ is applied, which is thought to affect cerebral blood vessels indiscriminately, the changes in blood flow measured by the clearance or microsphere techniques should agree closely.

The mechanism whereby intracerebral blood vessels might compensate for changes in pial vasculature is quite unknown. Possibly the more important and immediate question to be answered is whether and at what speed such compensation occurs. The technique introduced by Shapiro et al. in which
the pressure drop over successive segments of the cerebral vascular bed is measured would be ideal because it has already been shown, for example, that in response to hypertension, the extra- and intracerebral vessels respond in different proportions. The results from such a series of experiments would be likely not only to clarify whether the neural pathways affect components of the cerebral vascular bed in different amounts but they would also increase our understanding more generally of the compensatory responses of cerebral blood vessels.

In summary, I suggest that the discrepant experimental results which are and have been the immediate cause of this continuing controversy are not due to fundamental flaws in the methods used; that although failure to control some experimental variables may contribute to the confusion, they are unlikely to explain all the discrepancies; that the controversy is due in part to an imperfect understanding of the neural pathways themselves, a point particularly relevant to the dilator pathway whose origin and course is obscure; that species differences may be very important; that the principal methods used, the results of which are at issue, may in fact be measuring different aspects of cerebral blood flow in space and time; that the components of the cerebral circulation may be responding quite differently to nerve stimulation; and that, until these questions are resolved, it would be premature to dismiss a functional role for the extrinsic neural pathways.

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