PHARMACOLOGICAL REVIEWS
Vol. 28, No. 4

Printed in U.S.A.

Amine Mechanisms in the Cerebral Circulation[1]

LARS EDVINSSON AND ERIC T. MACKENZIE

Department of Histology, University of Lund, Lund, Sweden, and Wellcome Surgical Research Institute, University of Glasgow, Glasgow, Scotland

[1] This study was supported by the Swedish Medical Research Council (Grant No. 04X-732), and by Tenovus (Scotland).

I. Introduction

RECENT histochemical and electronmicroscopic investigations have, with a high degree of precision and selectivity, demonstrated the existence of neural elements in cerebral vessels. A regional distribution of sympathetic (adrenergic) and parasympathetic (cholinergic) nerves has also been shown: *e.g.*, the vessels of the rostral part of the circle of Willis have a more dense network of autonomic fibres than those of the caudal part. Intracerebral vessels (those vessels found within the cerebral parenchyma proper) have so far been found to receive only an adrenergic innervation. These morphological findings, along with the discoveries of endogenous aminergic pathways, have reinforced the considerable interest in the relationship between amines and the cerebral circulation.

The earlier studies in this field were reviewed by Sokoloff in 1959 (641). However, since then a great variety of more sophisticated techniques have been developed to measure cerebral blood flow. Some techniques, such as the inert gas clearance methods, are noninvasive and are not considered to disturb the cerebral circulation during the measurement; other techniques are less reliable. Nevertheless, despite the greatly improved technology, there are many conflicting opinions about the possible neurogenic influence on the cerebral circulation. Such discrepancies can, in a large part, be traced to the methodological differences although other factors are also involved. There is a general lack of awareness about the fundamental principles necessary for the interpretation of the cerebrovascular effects of amines such as the existence of aminergic blood-brain barrier mechanisms, the possible effects of amines on neuronal structures, and the pharmacological characteristics of the cerebrovascular receptors.

This review was undertaken to present and to discuss the available information about aminergic mechanisms and the cerebral circulation in an attempt to obtain a relatively cohesive view of the field. Some avenues of research that might lead to a greater understanding of the physiological role of amines in the cerebral circulation are also mentioned—a most desirable understanding, as amines are being implicated increasingly in cerebrovascular pathologies such as vasospasm, cerebral ischaemia, and migraine.

II. Methods of Assessing Cerebrovascular Reactivity

Before any appreciation of the physiology and pharmacology of the cerebral circulation can be achieved there must be an assessment of the available methods for measuring blood flow through the brain. Probably more than any other factor, methodology accounts for the major discrepancies in interpretation within the literature. The number of techniques that measure, or are claimed to measure, blood flow through the brain are almost legion and the details of these techniques have been reviewed fairly comprehensively within recent years (382, 384, 387, 509, 536, 539). This section of the literature review does not attempt to cover every method that putatively measures cerebral blood flow or the responsiveness of cerebrovascular smooth muscle; rather the validity, the advantages, and the disadvantages of more commonly used techniques are discussed.

A. In Vitro Models

A large number of investigations have been performed with simple *in vitro* systems from various vascular beds to estab-

lish the receptor mechanisms involved in the vascular response. It is therefore surprising that the receptor mechanisms in such a complex and controversial system as the cerebral circulation have not previously been examined in depth. Investigations that have used isolated brain vessels have gained renewed interest and several papers have appeared during the last 5 years. However, many of these studies either do not contain sufficient quantitative information or they have not taken into consideration certain experimental precautions necessary for a detailed characterisation of the receptor mechanisms (137, 212). For instance, knowledge about the interaction between drugs and receptors requires certain assumptions to be made in order to characterise the various amine receptor mechanisms. A drug-receptor system is composed of, firstly, the tissue component which interacts with the agonist; and secondly, the complete sequence of events which connects the receptor with the response mechanism. The pial arteries contain a variety of pharmacological receptors. The way to identify the presence of these receptors is either to obtain responses to various agonists and compare their potencies, or to show that the response can be antagonised by specific receptor blocking agents. Until the receptors have been isolated biochemically and ultrastructurally, one has to depend on the assumption that similarities or differences in response reflect similarities or differences in the receptors that mediate these responses. In this way numerous receptor types have been discovered in smooth muscle tissue.

Schild (600) has demonstrated that responses to agonists which interact with the same receptor are blocked to a similar degree by a given reversible competitive agonist. From this observation it must follow that the action of an agonist on various tissues will be antagonised to the same extent by a competitive blocking agent if the receptors for the antagonist in those tissues are identical. Schild introduced the concept of the pA_2 (log concentration of the agonist necessary to increase the ED50 by a factor of 2) to quantify this relationship. A similar measure of antagonism can be represented by the dissociation constant (K_b) of the receptor-antagonist complex which is the relation between the concentration of antagonist and dose ratio minus 1 (211). Another quantitative way of defining the receptors is to use the dissociation constant (K_a) for the receptor-agonist interaction (212). This requires the use of an irreversible inhibitor (*e.g.*, dibenamine or phenoxybenzamine) which can block a fraction of the receptors. The doses producing equal responses before and after this reaction can be used to calculate K_a. Further, at equilibrium there exists a relation between the fraction of receptors occupied and the response which makes it possible to achieve further information about this receptor-agonist interaction (149, 212).

During any analysis of the receptors certain precautions have to be taken into consideration: a fundamental problem which has been particularly stressed by Furchgott (212). Factors, such as the exact knowledge of the concentration at the receptor of agonist and antagonist and the allowance of adequate exposure time, are often neglected. In addition, the response to the agonist should be the result of the activation of only one receptor type. Therefore, any additional receptors that are activated by the agonist under study must be blocked.

When a response is measured, the concentration of agonist must be in equilibrium with the receptor. This is easily achieved in preparations *in vitro* in which the neuronal and/or extraneuronal uptake of the agents can be inhibited by denervation and the use of uptake blockers. Such precautions are, however, sometimes overlooked in certain *in vivo* models in which, for example, too short administration times are used and thus the full agonist response is not achieved.

B. Pial Calibre Techniques

This technique, perhaps the method that has withstood the advance of time and scientific sophistication better than any other, uses changes in pial arterial calibre as an index of cerebral tissue perfusion. It does *not* measure cerebral tissue perfusion—the amount of blood supplying a known amount of brain tissue during a given time interval—because Poiseuille's law, relating direct flow to the fourth power of the radius is only valid when dealing with straight tubes, laminar flow, and a Newtonian fluid. The cerebral circulation does not possess any of these features.

Perhaps an even more telling criticism of the interpretation of the pial calibre experiments involves the phenomenon of autoregulation within the cerebral circulation. Since Fog's careful studies in 1939 (196) it has been known that the pial vessels will constrict in response to increased blood pressure and, after systemic hypotension, will dilate. Later investigations, in which cerebral tissue perfusion was directly measured, have confirmed the fact that relative constancy of cerebral blood flow is maintained in the face of moderate variations of systemic arterial pressure; a phenomenon which, for the moment, will be termed autoregulation (170, 257, 269, 382, 654).

Now, should a systemic hypotensive or pressor agent be administered, then it would be difficult to tell whether that agent had any direct effect on cerebral blood flow from the variations in pial arterial diameter. Adrenaline, when given intravenously, will constrict pial vessels; but is this constriction due to the adrenaline *per se*, or is it due to the increase in systemic arterial pressure (195)? Autoregulatory adaptations of the cerebrovascular bed can occur without any changes in systemic arterial pressure; *e.g.*, intracranial pressure is increased (414, 469) after carotid ligation (612) and during the infusion of an agent, such as serotonin, which selectively constricts the larger arteries supplying the brain (123, 551). In all such experimental instances the use of pial artery calibre variations to predict cerebral tissue perfusion would be suspect.

One further factor should be taken into consideration in pial calibre studies. If pharmacological investigations are being undertaken then, should the entire cortex be flushed with the agent being studied, any observed changes could be due to either the direct cerebrovascular actions of that agent, or to vascular actions that would be secondary to metabolic alterations of the cortical tissue.

A recent refinement to pial vessel studies has been the adoption of the image-splitting television technique of Baez (21) which allows the accurate and rapid measurement of vascular calibre to be made *in situ*. When the image-splitting technique and micropuncture administration of various solutions into the subarachnoid space have been used together, many profitable and meaningful studies have resulted. The reactions of pial arterioles to ionic changes in their local milieu (42, 370, 685, 689) and of a number of autonomic agonists and blocking agents (369, 371, 683, 687) are examples of pial calibre studies that have yielded much useful information. However, as was discussed in the section on *in vitro* techniques, a number of important criteria are not under control in these studies. Firstly, the concentration at the receptors of the agents being studied is not known. This is due to limitations such as neuronal and non-neuronal uptake of the agonists that are being tested (212). These mechanisms would tend to reduce the exposure of the test organ to the agent and thereby reduce the recorded effect. Secondly, from pharmacological studies it is well known that the response of an agent will sometimes take more than 1 min, and in some extreme cases up to 30 min before the maximum is reached (212). With the pial micropuncture technique the response may well have disappeared in 30 to 40 sec and only a fraction of the effect might have been recorded. Furthermore, in the case of antagonists, a period of 20 to 30 min is

commonly considered necessary for equilibration with the receptors (212). Accordingly, care must be taken in the interpretation of pharmacological experiments with the pial calibre technique.

C. Isolated Perfused Brain Techniques

There are obvious niceties about the measurement of blood flow from isolated perfused brains. Systemic influences are removed, so allowing the determination of direct effects of various agents and procedures on the cerebrovascular bed.

Geiger and Magnes (220) isolated the cerebral circulation of cats and measured cerebral perfusion from the total venous outflow from their preparation. Extensive surgery was found necessary to separate the cerebral from the extracranial circulation in this species; a great number of venous, sinus, and arterial ligations were involved. The absolute values found by Geiger and Magnes for cerebral blood flow are very high in comparison to other techniques, being of the order of 100 to 150 ml/100 g per min. This is approximately 100% greater than the values quoted normally. In a similar preparation, but in dogs, Sagawa and Guyton (590) argued that the pressure-flow relationship within the cerebral circulation was passive. The authors went on even to doubt whether autoregulation existed in any species.

These two examples of the isolated perfused brain technique highlight the greatest pitfalls with the method. The high flows found by Geiger and Magnes (220) and the absence of autoregulation noted by Sagawa and Guyton (590) are, in all probability, explained by ischaemic or hypoxic insult to the preparation then resulting in abolished autoregulation and cerebral hyper-perfusion at normotension (189, 207). When great care is taken in isolating canine brains then autoregulation is noted (376), although reactive hyperaemia is observed after periods of complete ischaemia as short as 1 min (375, 724). Further, it has been shown that the stimulation of the internal carotid artery with a pair of surgical forceps (which caused the vessel to go into spasm) could greatly affect the physiological reactivity of the cerebral circulation (273). This observation emphasises the undesirability of surgically interfering with the large arteries feeding the brain, as is necessary with the isolated perfused brain technique.

Other problems with the technique include cerebral microembolisation due to platelet aggregation, although when adequate steps are taken to filter the blood this artifact can be minimised (226). The low values obtained from these preparations for oxygen consumption (725) and for glucose consumption (39) lead one to suspect that either the functional activity of the brain is pathologically depressed, or that there is still contamination (due to incomplete surgical "isolation") from extra-cerebral tissues in these animals. In either instance the studies of adrenergic agents, supposedly on the cerebral circulation, must be treated with caution.

D. Venous Outflow Techniques

Some of the disadvantages raised in the section on isolated perfused brain techniques also apply to the measurement of cerebral blood flow by venous outflow. One would mention especially the effects of trauma (in this instance the trauma is intracranial) and the impossibility of completely obliterating the anastomoses between the intracranial and extracranial circulations in species such as the dog and cat. The venous outflow technique should really only be used in the dog and cat, if it has to be used, because in primates there are superior methods for assessing cerebral tissue perfusion. Notwithstanding the methodological criticisms of the venous outflow technique, it has been used in Rhesus monkeys and baboons (453).

Green and Denison (243) investigated a number of different surgical preparations in the dog before they felt reasonably confident that blood flow, as measured by venous outflow, was uncomplicated by alterations in vasomotor tone within the extracranial tissues. Their method, later refined by Rapela and Green (549) and Ra-

pela *et al.* (550), involved collecting and measuring the cerebral venous outflow at the confluence of the sagittal, straight, and lateral sinuses, with the lateral sinuses occluded. This procedure, it was felt, removed the majority of anastomotic channels between the venous drainage of the face and scalp and the brain proper, although then only some 50 to 70% of venous outflow from the brain is estimated (673). A somewhat similar technique has been used in cerebral circulatory studies in the cat (303). In dogs it is a matter of crucial importance to obstruct the lateral sinuses if cerebral blood flow is to be measured by venous outflow. Should they remain patent (116, 117), then errors of interpretation could result due to the presence of extracerebral venous blood flowing through the confluence of the sinuses, otherwise known as the torcular Herophili (673).

E. Electromagnetic Flowmetry Techniques

Electromagnetic flowmeters, when placed around an artery or vein, measure the velocity of blood flow through that vessel. The theories and applications of electromagnetic flowmetry have been extensively covered (82, 238, 275). It should be remembered that the values obtained from flowmetry are considerably affected by variations in haematocrit (573).

This technique measures velocity in an individual vessel, and not cerebral tissue perfusion. Nevertheless, as such it does have some value in neurosurgical practice, an example being the operation of carotid endarterectomy. The limitations and values of electromagnetic flowmetry in the operating theatre have been discussed (315).

For research applications in the cerebral circulation the limitations of electromagnetic flowmetry would tend to outweigh any advantages in most situations. Extensive surgery is required if flow probes are to be placed around both carotid and both vertebral arteries; more usually the vertebral arteries would simply be ligated (133). An alternative would be to place flow probes around both internal jugular veins, after ligation of the facial, external jugular, and vertebral veins (456, 460, 462). In these experiments, in primates, flow probes were additionally placed around the vertebral arteries and the common carotid arteries, after ligation of the external carotid arteries. Although one must admire the dedication and patience this amount of surgery requires, considerable methodological errors still exist. As a result of the extensive ligations, the extracranial tissues will be supplied by the internal carotid arterial system *via* anastomotic channels such as the ophthalmic artery and its branches and the occipital diploic vessels.

In the dog and cat the inability to identify a vessel that will supply solely the cerebral circulation precludes the use of electromagnetic flowmetry. The "equivalent" of the internal carotid artery in the goat (the internal maxillary artery) likewise supplies extracranial tissues as well as the cerebral circulation (136).

However, in conjunction with a measurement of cerebral tissue perfusion with a diffusible isotope, electromagnetic flowmetry can yield more information than the former would by itself (123).

F. Microsphere Techniques

The calculation of cerebral blood flow from labeled microspheres is based upon the bolus fractionation principle, developed by Sapirstein (595). In brief, a known amount of radioactive tracer is injected and then the concentration of tracer in various regions of the brain are measured *post mortem*. However, accurate measurement of unbound tracer has proved difficult, and it has been found advantageous to bind the tracer to microspheres injected into the heart that then lodge in the capillaries of the cerebral parenchyma.

Advantages of the microsphere technique are that it avoids any extracerebral contamination, it allows the measurement of blood flow in well-circumscribed regions

of the brain, and surgical trauma to the preparation is minimised. Nevertheless, there are considerable pitfalls in, and drawbacks with, the method. The tracer must reach all areas being investigated at the same time, which should also be the time of sacrifice. The optimal time of death is the instant the microspheres lodge in the capillaries. There is the major disadvantage that only a limited number of measurements of blood flow can be made in one experimental animal. Furthermore, the microsphere technique can be greatly affected by rheological factors (389) such as axial streaming and plasma skimming; problems which might well occur within the cerebrum where penetrating arterioles come off at right angles from pial arterioles and, in turn, these penetrating arterioles give off vessels at right angles which then run parallel to the cortex.

The size of the microsphere is also crucial: larger (>15 μm diameter) microspheres will tend to be trapped in the pial arterioles and the blood flow will be overestimated (9). This methodological factor could lead to systematic errors: should pial arterioles dilate and cerebral blood flow increase, then this increase will be underestimated; should pial arterioles constrict and cerebral blood flow decrease, then this decrease will be likewise underestimated.

Another crucial point is the number of measurements (*i.e.*, the number of microsphere injections) performed in each animal, since the trapping of microspheres in the capillary bed should in itself tend to disturb the normal flow. If such flow disturbances are not possible to reveal in repeated injections, then one might question the validity of the method to discriminate small flow changes. It has yet to be demonstrated that the microspheres do not result in pathological changes, such as ischaemic cell damage, within the brain.

In some instances the microsphere technique has yielded values in close agreement with inert gas methods (191, 464), whereas in other studies there are disturbing discrepancies (10, 463). The microsphere technique can be, and has been, used to compare responses to procedures, such as catecholamine infusions and CO_2 administration, in brain with responses in peripheral tissues (311).

G. Autoradiography Techniques

This method, based upon the intra-arterial injection of freely diffusible isotopes and subsequent decapitation, involves measuring the brain tissue concentration of the labeled tracer by placing sections of the brain on to x-ray plates. After a period of times has elapsed for adequate exposure the degree of darkening of the plate is proportional to blood flow through the tissue. For quantification, the arterial concentration at the time of death must also be known.

For accuracy, the time of sacrifice must be as close after the injection as possible and yet allow homogenous saturation of the tissue. A practical time would seem to be about 30 sec (165, 465).

The first tracer to be used in cerebral circulation studies, utilising autoradiography, was ^{14}C-antipyrine (565, 566). There is now considerable doubt that ^{14}C-antipyrine is a freely diffusible tracer (135, 165, 505) and that either ^{14}C-nicotine or ^{14}C-ethanol would be more acceptable. Antipyrine is barrier limited and, accordingly, its use to study conditions with greatly altered flow is suspect (718).

Although autoradiography only allows one flow measurement in one animal, close correlation can be made between alternate histological and autoradiographical sections through an area of brain tissue, as measurements can be made in microscopic regions of the brain.

H. Blood Volume Techniques

Cerebral blood flow (tissue perfusion), cerebral blood volume, and the mean transit time of the cerebral circulation are related by the following equation:

$$F = \frac{V}{\bar{t}}$$

in which F = volume flow per unit time, V = brain blood volume, and $\bar{t}$ = mean transit time (449).

Because cerebral blood volume can be simply measured by the intravenous injection of a nondiffusible radioactive tracer and then continuously monitored by external detectors, the measurement of cerebral blood volume as an index of perfusion of the brain has a considerable attraction, especially within the clinical situation. The most common tracer for blood volume studies is RISA (^{131}I labeled serum albumin). A linear relationship has been shown to exist between changes in cerebral blood volume and cerebral blood flow, the latter measured by the intra-arterial ^{133}Xe clearance technique in cats (570). Were this validated then the measurement of cerebral blood flow could become a simple routine laboratory test.

Unfortunately, there are a number of reasons to believe that blood volume measurements do not adequately reflect cerebral tissue perfusion. In the study by Risberg *et al.* (570), the measurement of blood flow in cats by intracarotid ^{133}Xe and external counting is questionable due to the numerous anastomoses between the cerebral and extracranial circulations in this species. Further, mean transit time does not vary linearly with cerebral blood flow; the relationship between these two parameters approximates a parabola (216, 316, 586). In the clinical situation mean transit time has been shown to be a most unreliable indicator of the adequacy of tissue perfusion (585). If one examines a limited portion of the flow to transit time relationship then the mean transit time, determined angiographically, bears a near-linear relationship with the reciprocal of cerebral blood flow (216). Therefore, should the relationship between mean transit time and blood flow be nonlinear, then so too will be the relationship between cerebral blood volume and flow.

Intracranial blood volume could vary greatly without any flow alteration in situations such as hydrocephalus or cerebral tumours where the increase in volume due to such conditions would displace the blood out of the capacitance vessels of the cerebrovascular tree.

Notwithstanding these criticisms of the technique, blood volume measurement could result in much useful information, especially the latest x-ray fluorescence studies that permit measurement of blood volume in small, localised regions of the brain (249).

I. Oxygen Electrodes, AV Oxygen Techniques

Implanted O_2-sensitive electrodes (366, 709) and cerebral arteriovenous oxygen content difference (655) have both been employed as indices of cerebral tissue perfusion. Implanted O_2-sensitive electrodes are not possible to quantitate, but the reciprocal of the AV oxygen content difference is linearly related to cerebral blood flow if the assumption that cerebral oxygen consumption does not change is tenable. This relationship was demonstrated by Lennox and Gibbs (395) and is shown mathematically below:

$$CMRO_2 = CBF \times (A - V)O_2$$

where $CMRO_2$ = oxygen consumption by the brain, CBF = cerebral tissue perfusion (both in ml/100 g per min), and $(A - V)O_2$ = arteriovenous oxygen content difference. These measurements have some prognostic and diagnostic value in clinical practice (221), but their use in the experimental field depends upon (a) the constancy of $CMRO_2$, and (b) how representative the venous sample is of cerebral venous blood.

Even in man, considerable variations in cerebral metabolism have been reported. Kety (345) described a subject whose cerebral oxygen consumption increased from 3.7 to 5.0 ml O_2/100 g per min during extreme apprehension. This was confirmed by King *et al.* (348). Other states that would affect cerebral metabolism include insulin coma, diabetic coma, anaesthesia, cerebral trauma, severe hypotension, and hypoxic hypoxia, as reviewed by Purves (539). The variations in cerebral metabo-

lism during most forms of anaesthesia in experimental animals and in man would virtually preclude the use of arteriovenous oxygen content difference as an index of tissue perfusion (603).

The second difficulty with this method is obtaining blood samples that drain the cerebral tissues and are not contaminated by blood from extracranial sources. In man, normally thought of as having the most complete separation between the cerebral and extracranial circulations, internal jugular venous blood is considered by some workers not to be representative of mixed cerebral venous blood and that, therefore, it is of limited value in the study of cerebral blood flow or metabolism (186). This situation would be compounded in experimental animals, leaving one with no choice but to obtain cerebral venous blood from the intracranial sinuses, even though these may be contaminated in a number of species.

J. Thermal Techniques

The qualitative estimation of blood flow through the brain is possible with various thermal techniques. As enunciated by Betz (41), the principle is that the temperature of a heated probe within tissue is dependent upon two factors: the conduction of heat through the tissue, and the convection of heat by the circulation through that tissue. A probe with two thermocouple junctions is inserted into the tissue. One junction is heated, the other not. The difference between the two junctions, if recorded continuously, gives the rate of heat clearance from that tissue. From the rate of heat clearance an estimate of blood flow through that tissue can be derived.

Techniques similar to that described by Betz have been developed in a number of other laboratories (63, 338, 435). The greatest disadvantage in research applications of these techniques is that they necessitate the introduction of a foreign body (the heat probe) into the cerebral parenchyma. This could result in an altered blood-brain barrier permeability; effects recorded in conjunction with pharmacological testings might therefore reflect effects on neuronal metabolism rather than direct motor responses of the vascular smooth musculature. However, provided the small probe is chronically implanted, the resulting oedema and change in blood-brain barrier permeability can be minimised and reliable effects can be recorded (615, 618, 619). Other criticisms of this technique revolve around the conduction of heat through the tissue (not convection by the blood). Were cerebral metabolism to increase in the area around the heat probe, then there would be an accompanying rise in tissue temperature which, in turn, would affect the conduction. Conduction could also be affected by factors such as focal cerebral oedema around the heat probe.

However, several advantages of this technique in basic research have emerged as changes in heat clearance are directly related to changes in blood flow with some methods. When chronically (at least 2 weeks) implanted probes are used, the damaged blood-brain barrier has fully regenerated and the introduction of a feedback principle in the recordings ensures a constant temperature in the measuring probe. Any rise in tissue temperature is fully controlled by the use of contralateral probes measuring brain temperature in regions similar to that under study. Continuous atraumatic measurements can be achieved as can very rapid changes in flow in well-defined regions of nonanaesthetised animals (615, 618, 619).

A number of modifications of the thermal method exist, including thermistors in the jugular veins (713), cold-sensitive thermistors over the exposed cortex (79), and the use of infra-red microscopes (15). All of these refinements require further evaluation before they can become generally acceptable.

K. Freely Diffusible Tracer Techniques

It was realised by Kety (344) that the Fick principle could be adopted to measure blood flow through the brain, as he said:

"Unfortunately, the brain, unlike the kidney,

does not specifically and selectively remove foreign substances from the blood and excrete them for accurate measurement. Furthermore, although it does consume large quantities of oxygen, that consumption cannot independently be measured or even assumed to be constant since it would be expected to vary with activity and disease. The brain does, however, absorb by physical solution an inert gas such as nitrous oxide, which reaches it by way of the arterial blood. It was hoped that the quantity of this gas absorbed by the brain would be independent of the state of mental activity and susceptible of measurement on the basis of physical solution alone. If this were found to be the case, then the numerator of the Fick equation applied to the brain could be derived."

The first method that was introduced to measure the average blood flow of the human brain by using an inert, freely diffusible tracer is now known as the Kety-Schmidt technique (346). Their method, which used inhaled nitrous oxide as the tracer substance, is based directly upon the Fick principle which asserts that the quantity of a substance taken up by an organ per unit time is equal to the product of the blood flow through that organ and the arteriovenous concentration difference for that substance. This can be expressed as:

$$Q_t = F_t \times (C_a - C_v)$$

where Q_t = quantity of substance taken up per unit time, F_t = blood flow per unit time, and C_a and C_v = the arterial and venous concentrations of that substance respectively.

The Kety-Schmidt technique has a number of limitations. It measures *average* blood flow throughout the brain, in contradistinction to the *gamma*-emitting isotope techniques that have superseded it and measure regional cerebral blood flow. As the Kety-Schmidt technique measures global cerebral perfusion, flow variations in small areas are overlooked (for example, tumours and focal contusion) as well as being incapable of detecting the localised blood flow changes that occur, *e.g.*, during intellectual effort (572).

The necessity of having to obtain cerebral venous blood introduces the problem, already discussed, of what is and what is not unsullied cerebral venous blood. Although Ferris *et al.* (186) felt that, in man, representative cerebral venous blood could not be obtained from the internal jugular vein, Lassen and Lane (388) found gross contamination in only 8% of the patients they studied. In dogs (467, 518) and cats (231) this problem can be overcome partially by inserting a catheter into the superior sagittal sinus.

Additional limitations of the Kety-Schmidt nitrous oxide technique are that the measurement of nitrous oxide is not very accurate and large blood samples are required to improve the accuracy. There is evidence that, in conditions of cerebral hypoperfusion (*e.g.*, during anaesthesia and in severe cerebrovascular disease), the blood flow is underestimated because saturation between blood and cerebral tissue has not occurred during the period of the measurement (6, 452). Complete saturation is an absolute necessity for the justified calculation of blood flow with inert gas techniques.

These errors can be minimised by using tracers that are more readily estimated in blood, and by extrapolating the arteriovenous difference to infinity rather than the 10 min as was used with the classical Kety-Schmidt technique. Examples of such tracers, which have been used for cerebral circulatory investigations in both man and animals, are ^{85}Kr (5, 446) and hydrogen (240, 627).

A recent advance of Eklöf *et al.* (164) has been the development of a ^{133}Xe Kety-Schmidt technique in order to measure cerebral blood flow in rats; this method must certainly be superior to the tissue sampling (165) or hydrogen electrode techniques (259, 260). However, care must be taken to avoid extracranial contamination during the collection of cerebral venous blood. While this problem seems to have been overcome with some developments of the rat cerebral blood flow (CBF) technique (493, 494, 496), extracranial contam-

ination remains a distinct criticism with other modifications of this technique (229).

A major development of the Kety-Schmidt technique was the introduction of the radioactive inert gases, ^{133}Xe and ^{85}Kr (230, 302, 386) after intra-arterial injection rather than inhalation. These gases obviated the necessity for arterial and venous cannulation, as the clearance of the isotope from an organ could be measured by means of external detectors. Like nitrous oxide, their entry into and exit from tissue from blood, and *vice versa,* is dependent solely upon their physical attributes of solubility and diffusion. If introduced into the brain by either arterial or tissue injection then there will be no problem of arterial recirculation because both ^{85}Kr and ^{133}Xe have a much higher affinity for air than for blood and will tend to leave the circulation on the first passage through the lungs.

However, there are grave problems in applying the inert gas techniques to laboratory animals. Most species (except the primates) have an enormous number of anastomoses between the cerebral circulation and the extracranial tissues. These anastomoses exist on both the arterial and the venous sides. The presence of such anastomoses invalidates the measurement of blood flow by inert gas techniques in animals such as dogs and cats (276). Even in primates the extracranial tissues should be removed. It must be emphasized that the measurement of cerebral blood flow in the rat by an external scintillation detector, placed over the animal's head (91), would be subject to gross contamination – even after selective injection of the tracer into the internal carotid artery.

There is an exciting future for a reliable technique for whole-brain blood flow in the rat due to the inexpensiveness of the animal, and the large number of supplementary investigations, such as measurements of energy metabolites or barrier function, that can be carried out in this species.

Two modifications of the intra-arterial ^{133}Xe technique should be considered: the intracerebral ^{133}Xe injection technique and the ^{133}Xe inhalation technique. Both are pertinent to the literature concerning the influence of the autonomic nervous system upon the cerebral circulation.

Cerebral blood flow can be measured after the introduction of ^{133}Xe into the cerebral parenchyma by injection. The attraction of this technique is that it would be theoretically possible to measure blood flow from very well defined regions of the brain. Unfortunately, that would seem not to be the case. When Espagno and Lazorthes (173) injected ^{133}Xe into cortical tissue, and then resected that cortical tissue, clearance of the isotope could be still detected. This finding indicates that either the tracer can diffuse some distance away from the injection site or the tracer clears from outside the field of view of the detector. In this latter situation the measurement of blood flow would be erroneous. Another serious objection with the tissue injection technique is that, certainly in some hands, the peak-to-background ratio is very low which makes satisfactory resolution of the clearance difficult, if not invalid (582). One further criticism is that it is, of course, necessary to insert a foreign body into the cerebral parenchyma and thus run the undesirable risk of cerebral trauma. The main advantage of the direct injection technique is that relatively large amounts of tracer can be delivered to an ischaemic region thus making it possible to measure low blood flows with a reasonable number of detected photons.

In an attempt to avoid puncture of the internal carotid artery, methods that involved the inhalation and subsequent clearance of ^{133}Xe have been investigated (352, 433, 680) in order to measure blood flow with ^{133}Xe. There are two fundamental problems to be overcome: the effects of arterial recirculation of ^{133}Xe and the complex computer analyses required to correct for radiations detected from extracranial

tissues (500). This latter factor would make the use of ^{133}Xe techniques, involving inhalation, in experimental animals most undesirable (322). One comparative study between intracarotid and inhalation ^{133}Xe cerebral blood flow techniques came to the conclusion that a quantitative evaluation of cerebral perfusion was not possible with the inhalation method (317). However, modifications of the ^{133}Xe inhalation technique have been devised recently that would minimise the problems of arterial recirculation and extracranial contamination (715, 716). These modifications involve a very short inhalation period (2 min) and correlate well with cerebral blood flow calculated by the intracarotid injection method. Nevertheless, the precision of the method as it stands at the moment is unlikely to detect the more subtle effects of amines on the cerebral circulation.

III. Innervation of Brain Vessels

A. Sympathetic (Adrenergic) Innervation

Nerve fibres were first demonstrated on the anterior and posterior cerebral arteries by Willis in 1664 (712). This observation has since been verified by many workers who have also noted that the nerves emanated, at least in part, from the superior cervical ganglion (for reviews, see 137 and 539). These early studies were performed in silver-impregnated tissue sections and, therefore, it could not be determined whether the fibres were motor or sensory, sympathetic or parasympathetic, or even nervous in origin (as with silver-impregnation techniques no differentiation can be made between reticular elements and nerve fibres in the vessel wall), and such techniques lacked considerably in specificity and precision. It was not until the advent of modern histochemical techniques (47, 356) that the basic characteristics of the nerves in the cerebral vessels could be described adequately.

A well-developed plexus of sympathetic adrenergic nerves has been observed in the pial vessels of man (fig. 1) (154) and a variety of laboratory animals: mouse (145); rat (36–41, 109, 130, 145, 309, 310, 332, 333); hamster (145); guinea-pig (145, 332); rabbit (145, 178, 526, 615); cat (130, 145, 332, 333, 439, 645); dog (59, 501); and monkey (24, 285). The histofluorescence technique has shown that the organisation of the sympathetic innervation in the pial system resembles closely that found in other parts of the circulation.

Fluorescence microscopy has revealed an adrenergic nerve plexus, located in the adventitia and at the outer border of the medial layer. Usually, the arteries are seen to receive a richer supply than the veins. Small vessels (down to 15 μ) are sometimes accompanied only by one nerve fibre. Since few muscle cells are present in the wall this innervation could be considered "satisfactory" for functional purposes. Furthermore, these single nerve fibres have been characterised by the presence of typical, intensely fluorescent enlargements on the nerve fibres, the varicosities. Extensive studies (497) have shown that the transmitter is stored in special granules (or vesicles) within the adrenergic neurons. These granules occur in all parts of the sympathetic adrenergic neuron, including the cell bodies, the nonterminal axons and the terminals, although only the latter contain high concentrations of noradrenaline. The reason for this widespread amine distribution is that the transmitter granules are formed in the cell bodies and transported down the axon (by axoplasmic flow), and eventually pile up in the varicosities of the terminals. Noradrenaline is released from the terminals into the synaptic cleft to act on specific receptor sites.

The sympathetic adrenergic nerves of the pial vessels originate from the superior cervical ganglia, as revealed by denervation experiments which have demonstrated the total disappearance of specific fluorescence (138, 145, 309, 489, 615) and of chemically measured noradrenaline (152) within 3 days. The pial innervation has been found to be strictly unilateral. The

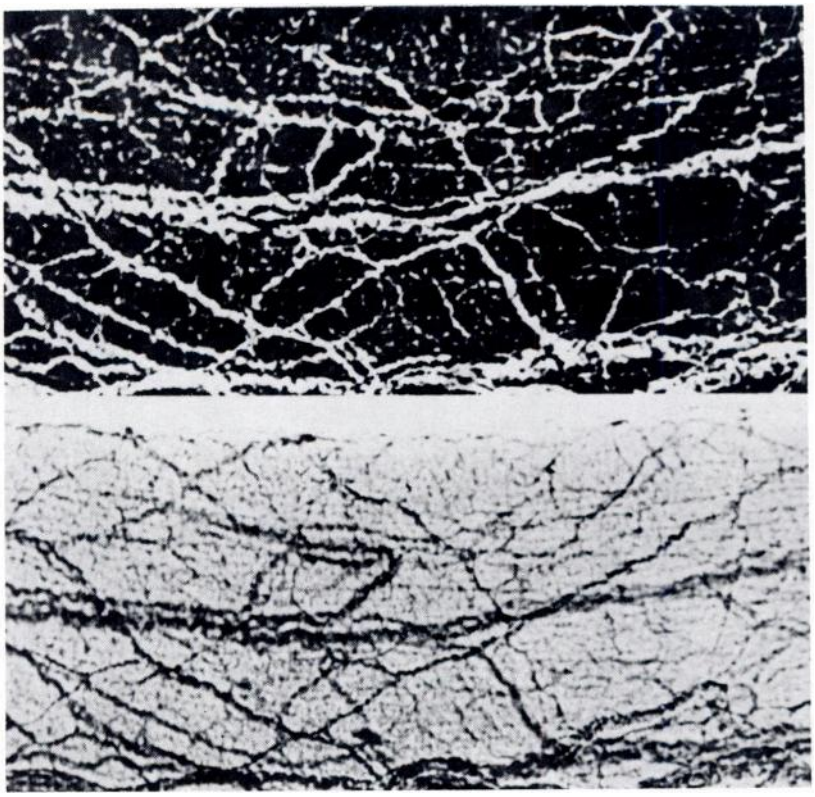


FIG. 1. Middle cerebral artery from a human foetus, cut open longitudinally and mounted flat. Magnification × 155. Upper half: The vessel was exposed first to gaseous formaldehyde for 30 min in order to visualise the adrenergic nerves. Lower half: The vessel was then incubated with acetylthiocholine for 6 hr; pseudocholinesterase was inhibited with Mipafox. Note that the plexus of acetylcholinesterase-containing nerves resembles closely the adrenergic plexus, although some minor discrepancies can be found.

ascending nerves accompany the internal carotid artery and have a characteristic distribution in the vessels of the circle of Willis. The innervation of the caudal part of the vertebral arteries and the spinal cord arteries has not been well described, but these vessels are probably supplied with nerves from sources other than the superior cervical ganglia.

The anterior and middle cerebral, internal carotid, and posterior communicating arteries have been shown to have a more dense network of adrenergic nerves than that found in the posterior cerebral, cerebellar, basilar, and vertebral arteries. This observation was based on a count of the number of nerve fibres to the diameter of the vessel. In the cat, *e.g.*, the vessels supplied by the carotid artery have roughly 40 to 50 fibres while the posterior part of the circle of Willis (the basilar and vertebral vessels) has 12 to 22 fibres, thus revealing a heterogeneity in the pattern of innervation (137). This difference seems to reflect the fact that the phylogenetically older regions (the posterior part of the brain and the brain stem) are influenced less well by sympathetic mechanisms than the neocortex. It has been shown by electronmicroscopy that nerve fibres, associated with Schwann cells, run in the adventitial layer and that some of these fibres closely approach the outermost smooth muscle layer (525). Furthermore, the nerve endings contain both granular and agranular synaptic vesicles, indicating the presence of both adrenergic and nonadrenergic axons. The shortest distance between the axon terminals and the surface of the outermost smooth muscle cells in

the media is 80 nm (113, 145, 255, 487, 488, 492, 596). The further identification of the perivascular nerve fibres has been studied by three types of approach: (a) sympathectomy, which eliminates all terminals with small (50 nm) granular vesicles concomitant with the disappearance of all the fluorescent nerves, (b) injection of the false adrenergic transmitters, 6-hydroxydopamine or 5-hydroxydopamine (to the nondenervated animal), after which the vesicles of adrenergic axons can be distinguished by degenerative phenomena or the presence of highly electron-dense cores in the synaptic vesicles, and (c) permanganate fixation, by which the catecholamine content in the synaptic vessel can be selectively visualised (145, 309, 310, 492). Taken together, the studies show that both adrenergic and nonadrenergic fibres, present in approximately equal numbers, supply the pial arterial system. The ultrastructural organisation of the pial innervation resembles closely that of other beds in which the innervation has been shown to be fully functional. On the basis of cholinesterase histochemistry it is conceivable that the nonadrenergic nerves are, partly at least, cholinergic (see below). The varicosities of the adrenergic and cholinergic fibres approach each other within a fairly wide contact area by 25 nm (145, 492). This arrangement offers a distinct possibility for a functional interaction between the two systems of nerve terminals. However, no particular membrane specialisations have been described which might indicate the direction and nature of such a functional relationship. It should be noted that close appositions are also found between those varicosities which, at the same time, form contacts with the smooth musculature of the tunica media. Evidence has been presented to support a function arising from this special anatomical arrangement (139).

The adrenergic nerve plexuses that enclose the pial arteries accompany several of the arterial branches which subsequently enter the brain parenchyma (142, 615). The intraparenchymal arteries have a small calibre and accordingly the network of axons is fairly sparse. Many of the intracerebral arterioles are accompanied by one or two varicosed, fluorescent fibres, and all these intraparenchymal nerve fibres, like those supplying the pial circulation, disappear after bilateral removal of the superior cervical ganglia (615). It should be emphasised again that the density of innervation of the vessels is not necessarily related just to the number of nerve terminals present, but obviously also to the amount of smooth musculature supplied locally by the nerves. The intracerebral arterioles are very thin-walled, the media being composed only of a single layer of smooth muscle cells (114, 525). The small number of fluorescent nerves and small volume of smooth musculature may thus represent an adrenergic innervation of intracerebral arterioles as rich as that seen in other parts of the circulatory system. A direct comparison has yet to be done that would investigate the number of sympathetic terminals related to the amount of underlying, innervated smooth musculature between pial vessels and those elsewhere in the body. There is fluorescence microscopic evidence that the number of sympathetic nerves to intracerebral vessels is related to the density of adrenergic innervation of the pial artery supplying those intracerebral vessels. For example, in the caudate nucleus which receives blood primarily from the richly innervated middle cerebral artery, at least half of the arterioles have sympathetic nerves; whereas in the lateral geniculate body, which is supplied from the poorly innervated posterior cerebral artery, few of the arterioles are accompanied by sympathetic fibres (615).

Surprisingly little has been presented on the ultrastructural appearance of the intracerebral vascular innervation. According to Cervós-Navarro and Matakas (90), the axons are located in the adventitial space and are separated from the muscle cells by a distance of at least 80 nm.

The terminals are characterised by numerous granular synaptic vesicles which vary in size from 25 to 160 nm. Approximately 66% of the arterioles studied in the cortex of the cat were found to be innervated. The existence of a vascular innervation of the intracerebral vessels has been denied by some authors on ultrastructural grounds (114, 592, 596). However, a negative finding is of little value in any electronmicroscopic investigation because it could take a decade to analyse adequately 1 mm^3 of brain tissue.

There is some controversy as to (a) whether the intracerebral arterioles are innervated only by adrenergic nerves, or (b) whether they also receive cholinergic fibres like the pial vessels, and (c) whether the adrenergic nerves are entirely sympathetic or also of intracerebral origin. Electronmicroscopic studies have demonstrated that removal of the superior cervical ganglia abolishes all adrenergic sympathetic nerves in the brain vasculature (407). Twenty-four hours after cervical sympathectomy, several perivascular axons show degenerative signs, whereas at a later stage no axons could be found in any of the intraparenchymal arterioles. These experiments have confirmed that intracerebral arterioles are devoid of cholinergic nerves, and have shown that the sympathetic nervous system innervates the intracerebral arterioles in a conventional manner. This, of course, does not rule out the possibility that transmitter substances and other vasoactive molecules, released from the brain parenchyma, may influence the cerebral microcirculation. However, such influences must then be mediated by routes other than that of the conventional neuromuscular relation.

B. Parasympathetic (Cholinergic) Innervation

The histochemical cholinesterase method, in combination with appropriate enzyme inhibitors, is at present the only usuable method for the demonstration of cholinergic nerves at the level of optical microscopy (295, 356), though non-neural tissues commonly stain for cholinesterase. This method has been used to localise and study the distribution of acetylcholinesterase-containing nerves.

The extent and distribution of the cholinergic nerves are essentially similar to the arrangement of the adrenergic nerves (137, 145). Thus, a greater number of nerves per vessel diameter was consistently observed in the anterior, when compared to the posterior, part of the pial circulation. The plexus of cholinergic nerve fibres has been demonstrated in vessels with diameters as small as 15 μ. The veins are less well supplied with cholinergic nerves than the arteries. This pattern of innervation is seen in all the laboratory animals that have been studied (mouse, rat, rabbit, hamster, guinea-pig, cat, dog, cow, pig, and monkey) (137, 145, 306, 391, 477, 478) as well as in man (fig. 1) (154). No cholinergic fibres have been found in the intracerebral vessels by either histochemistry (516) or by electronmicroscopy (407). When taken together, the findings would suggest that there is a cholinergic innervation of the extracerebral pial vessels only.

The origin of the cholinergic nerves is still unknown. It has been claimed that the major supply of parasympathetic nerves to the intracranial vessels run in the facial nerve, course off in the region of the geniculate ganglion, and continue in the greater superficial petrosal nerve to the plexus of the internal carotid artery where they form ganglia (96). Transection of the intracranial parts of the facial nerves does not affect the acetylcholinesterase activity in the pial arteries up to 2 weeks after the operation (137). Thus, there is reason to believe that cholinergic ganglia may be located very close to the effector system. Cholinergic ganglion cell formations have been identified in the adventitia of the intracranial part of the internal carotid artery and in the carotid sinus (59). Excision of the superior cervical ganglia does not overtly affect the

number and distribution of the cholinergic nerves (145).

The regional distribution of the cholinesterase-containing nerve plexuses resembles closely that of the adrenergic plexuses and the arrangement has been analysed in some detail (145). This analysis has shown that the two systems – adrenergic and cholinergic fibres – run side by side in the strands of the autonomic nerve plexuses (fig. 1) (9).

Electronmicroscopy has shown that the cholinergic nerves and terminals occur in the adventitia and advential-medial border. The cholinergic terminals are located 80 to 100 nm from the vascular smooth muscle cells and 25 nm from the adrenergic terminals (145, 492). The neuromuscular contacts have an arrangement that indicates a true innervation with fused axonal and smooth muscle membranes, and the nerve terminals lie occasionally in a shallow indentation of the plasma membrane of the muscle cell.

C. Central Amine Neuron Systems

The organisation of the central amine neuron systems will be described briefly only, as this field of research, in itself, deserves an extensive review. It was felt of great importance, however, to include in the present discussion the rough outlines of these central neuronal systems because cerebral blood flow is, of course, closely linked with the metabolism and activity of the underlying neuropil.

The mammalian brain is known to contain several amines such as dopamine, noradrenaline, adrenaline, 5-hydroxytryptamine, histamine, and acetylcholine. These amine stores have a characteristic regional distribution and are linked closely with typical neural responses.

It was suggested in 1972 by Hartman *et al.* (277) that the central noradrenergic system might directly innervate the brain vessels and thereby intrinsically control and modulate cerebral blood flow. The close association of intracerebral adrenergic nerve fibres to the wall of the arterioles in the brain parenchyma has been shown with the formaldehyde, glyoxylic acid, and immunohistochemical techniques (109, 142, 277, 407, 431, 615). A series of electronmicroscopic studies has been performed (407) on animals treated by sympathectomy in order to evaluate the possibility that there is a central neurogenic innervation in a true functional sense (as opposed to close association) of the cerebral vessels. During such circumstances it was sometimes noted that the cerebral neuropil, containing axons with electron-dense vesicles, extended very close to arteriolar walls. However, there was always a thick intervening basement membrane. These findings might well correspond with the close vascular association of parenchymal nerves, observed at the level of optical microscopy. Should such fibres influence the cerebral microcirculation then one either has to accept an unconventional kind of neurovascular relationship that would involve long diffusion distances; or the fibres might change the metabolism in neuronal and glial components in the brain and thus indirectly influence the cerebral circulation.

The possibility has arisen that capillaries in the central nervous system, or at least the anterior hypothalamus of the cat, are directly innervated by central neurones (567). Such a possibility is alien to the classic nerve to arteriolar smooth muscle relationship but deserves further, intensive investigation.

The catecholamine neuron systems are the best described due to the sensitive histofluorescence technique of Falck and Hillarp, described in detail by Björklund *et al.* (47). The location of the cell bodies was first noted in the mesencephalon, pons, and medulla oblongata, although some of the ascending axons were also visualised (115). However, the finer elements of the system contain only small amounts of the amines and were not seen in conventional formaldehyde-treated specimens.

The introduction of a new technique, the glyoxylic acid method (409), allowed the clear visualisation of all parts of the neuron system.

Noradrenaline neurons. The ascending fibres from the mesencephalic, pontine, and medullary nerve cell groups are associated with four major conducting pathways: the periventricular fibre system; the central tegmental tract; the medial forebrain bundle system; and the nigrostriatal pathway, according to the description of Lindvall and Björklund (410) with further details being given elsewhere (213, 531, 662).

The dorsal tegmental bundle emerges from the locus coeruleus and then projects rostroventrally. These fibres ascend through the mesencephalon and the middle hypothalamus; two branches project into the anterior and posterior colliculi. The dorsal tegmental bundle contributes also to the adrenergic innervation of the thalamus. At the level of the subthalamic nucleus some dorsal tegmental bundle fibres run, intermingled with fibres of the nigrostriatal dopaminergic system, into the internal capsule to course towards the catecholamine fibre system in the supraaortic decussations and the ansa lenticularis, while others reach the cortex through the neostriatum.

The central tegmental tract comprises both ascending and descending fibres. The descending axons emanate from the caudal part of the locus coeruleus. The ascending medullary catecholamine axons originate from the catecholamine cell group in the lateral reticular nucleus (A1) and in A2 cell group [according to the terminology of Dahlström and Fuxe (115)] with the lesser vagal and the commissural nuclei. Inflow of catecholamine axons comes from the pontine cell groups (with caudal inflow from A5, a massive inflow from A7, the subcoeruleus group, and from the principal locus coeruleus) and they considerably increase the density of fibres in the central tegmental tract. The fibres from the locus coeruleus project principally into the cerebral cortex, the thalamus, the hippocampal formation, the superior and inferior colliculi, and the medial and lateral geniculate bodies. The nonlocus system terminates primarily in the hypothalamic region.

The dorsal periventricular system extends to the periventricular and periaqueductal regions of the medulla oblongata, pons, mesencephalon, and diencephalon. The fibres originate from numerous cell bodies located in its course and possibly also from A1 and A2. The fibres terminate in and around many regions in the anterior and posterior colliculi, thalamus, epithalamus, pretectum, and hypothalamus.

The system of ventral periventricular fibres is found caudally in the rostral region of the mesencephalon, and then they ascend through the supramammillary region to terminate in the medial and periventricular hypothalamus and in the caudal septal area.

The medial forebrain bundle catecholamine fibres ascend from the brain stem reticular formation towards the diencephalon and telencephalon. These fibres assemble at the mesodiencephalic junction and are composed of fibres from the tegmental catecholamine radiations, mesencephalic catecholamine cell groups and, to a minor extent, from the dorsal tegmental bundle, the dorsal periventricular system, and the mammillary peduncle. The medial forebrain bundle fibres project into hypothalamic nuclei, the supraoptic decussations, the ansa lenticularis, the stria terminalis, and in the preoptic region. Although the description of the central noradrenergic pathways is based on work done primarily in rats, the topography is essentially the same in man, as revealed in foetuses (95, 495).

Dopamine neurons. The nigrostriatal dopamine pathway is known to originate from cell bodies that are located in the pars compacts of substantia nigra (A9) and also possibly in the more caudally situated A8

group (12). The fibres ascend in the internal capsule and terminate in the neostriatum. Recent evidence has suggested that the dopaminergic neurons of the substantia nigra additionally project to the rostral limbic cortex.

Other ascending dopamine-containing fibres (sited in the medial forebrain bundle) are formed by the mesolimbic system, which emanates from the mesencephalic A10 cell group. The major terminations are in the septal area (408), the olfactory tubercle, and the nucleus accumbens (675) as well as in the frontal cortex (12, 411).

Adrenaline neurons. The storage and synthesis of adrenaline have been demonstrated in the rat brain (293). Despite the fact that adrenaline can be visualised with the formaldehyde fluorescence technique (47), no histochemical evidence has so far been presented to suggest the existence of adrenaline neurons within the mammalian brain. This negative finding might be due to the difficulties in separating noradrenaline and adrenaline with the fluorescence method. However, the introduction of an immunohistochemical technique, utilising antibodies against phenylethanolamine-N-methyltransferase (the enzymes converting noradrenaline to adrenaline), has demonstrated two groups of cell bodies that satisfy the criteria for an endogenous neuronal pathway in the medulla oblongata. These cell bodies have been called C1 and C2 (293). The first one (C1) was localised in the ventrolateral reticular formation and the second one (C2) rostrally in the medulla, surrounding the medial part of the ventral surface of the fourth ventricle. These neurons give rise to both ascending and descending axon terminal plexuses in the pons, mesencephalon, diencephalon, and spinal cord, but the exact distribution has not yet been demonstrated.

Indolamine neurons. The formaldehyde histofluorescence technique has been used to visualise 5-hydroxytryptamine, which emits a weak yellow fluorescence (47). The sensitivity of the fluorescence method to identify 5-hydroxytryptamine stores can be improved greatly by selective chemical lesions with the neurotoxic dihydroxytryptamines, thus permitting a more detailed anatomical analysis of the control indolamine neuron systems. The 5-hydroxytryptamine cell bodies are located in the pons and mesencephalon and ascend *via* two bundles, a dorsal and a ventral (48). The dorsal indolamine bundle emanates from the pontine indolamine cell groups (B5 and B6) (215) which comprise only a minor portion of the ascending 5-hydroxytryptamine fibres. The dorsal indolamine bundle intermingles with the ventral bundle at the level of the fasciculus retroflexus. The ventral indolamine fibre bundle is formed from components that originate in the B7 and B9 cell groups. The fibres ascend in the medial forebrain bundle and terminate in the mammillary region, the subcommissural organ, the habenula, the suprachiasmatic nucleus, the globus pallidus, the septum, and the pretectal area. Destruction of the ventromedial tegmentum removes fibres from all the above mentioned regions except the pretectal area.

Histamine neurons. Histamine has an uneven distribution with about 0.5 to 3.0 ng/mg of protein in most brain areas, although several hypothalamic nuclei have relatively high concentrations (between 15 and 25 ng/mg of protein) (244, 640). Subcellular fractionisation studies have established that a substantial portion of the amine, as well as of its specific synthesising enzyme (L-histidine decarboxylase), is located in the nerve terminal fraction (608). Unilateral lesions of the medial forebrain bundle have resulted in an ipsilateral decrease in L-histidine decarboxylase by 25% in the hypothalamus and 50% in the cortex. A simultaneous decrease in cortical histamine content by 30% was noted. This evidence would suggest an ascending neuronal fibre system containing histamine (218). However, the existence of a large non-neuronal pool of histamine has been suggested (577), a hypothesis that is

based on the distribution of brain mast cells in a pattern resembling that of the measured histamine levels.

Cholinergic neurons. The neuroanatomical techniques at present available for the mapping of the central cholinergic systems have a sensitivity and a specificity that is not comparable to that of the above mentioned techniques. It is therefore difficult to offer a description of the anatomical relationship of such neurons to other central aminergic systems.

IV. Blood-Brain Barrier Mechanisms to Amines and Amine Precursors

Specific transport mechanisms to the passage of ions and metabolites across the blood-brain barrier will not be discussed here as full details of these processes can be found in Davson's review (121). However, with respect to the passage of amines and amine precursors, three features of the blood-brain barrier deserve special mention: firstly, current concepts for the structural basis of the blood-brain barrier; secondly, the blood-brain barrier as an enzymatic mechanism, with particular reference to dopa decarboxylase and monoamine oxidase; and lastly, those agents or procedures which are capable of causing changes in the permeability of the blood-brain barrier.

A. Morphology of the Blood-Brain Barrier

The original concept of a barrier between the brain and the circulation arose from the pristine studies of Ehrlich (160) and Goldmann (237). In the years before the advent of electronmicroscopy, anatomical studies on the blood-brain barrier were merely extensions of the crude dye methods, first used by Ehrlich and Goldmann, and the structural basis for the blood-brain barrier was much debated (128).

Reese and Karnovsky (564) injected horseradish peroxidase (an enzymatic tracer substance that can be visualised under the electron microscope after a sequence of reactions) into mice. Passage of horseradish peroxidase into the brain was not noted, although the tracer can freely enter the extravascular space of other tissue beds, *e.g.*, heart and skeletal muscle. This remarkably different permeability of the brain, when compared to other organs, was thought by Reese and Karnovsky to be due to a number of structural specialisations that are unique to the cerebral vascular endothelium. Firstly, the interspace between cerebral endothelial cells is closed by true tight junctions, and adhesions between the cerebral vascular endothelial cells could be said to form a morphological continuum. Another significant feature of the endothelium within the brain is the paucity of intracellular vesicles, these vesicles being noted frequently within peripheral endothelial cells. Although some of the few endothelial vesicles contained horseradish peroxidase, there is no evidence of these vessels discharging their contents on the contraluminal side of the capillary endothelium. The original observations of Reese and Karnovsky have been confirmed in a number of subsequent investigations (30, 51, 69, 559, 568, 587).

Although there is no evidence to suggest that the vesicles in the cerebral *capillary* endothelial cells transport their contents to the abluminal face of the endothelium, there is the possibility that this process occurs in segments of some *arterioles* (707). Pial and intraparenchymal arterioles have the same morphological features as the capillaries within the brain; the endothelial cells adhere together by tight junctions. Portions of arteriolar endothelium are capable of vesicular transport from the lumen to the extravascular space, these vessels being sited primarily in the depths of sulci (pial arterioles) and within the ventral diencephalon and adjacent brain stem (intraparenchymal arterioles). Based on electronmicroscopic investigations, it has been claimed that this vesicular transport can be enhanced by 5-hydroxytryptamine (705) and by noradrenaline and cyclic-3′,5′-adenosine monophosphate (cAMP) (328, 329, 706). From the available

evidence, it is not clear whether histamine affects the permeability of the blood-brain barrier (64, 714). In peripheral vessels, considerable evidence would suggest that histamine can increase vascular permeability (7, 432). A further suggestion is that the function of the endothelial vesicles is the ability to transfer foreign proteins *from* the brain *to* the blood (684).

Few ultrastructural investigations have examined the intima of cerebral vessels other than the capillaries. However, both intraparenchymal and pial arterioles seem to be protected by the continuous sheet of endothelial cells, joined together by tight junctions, which is a singular property of the cerebral circulation (182, 564, 707). It would be of interest to know whether larger arteries, such as the middle cerebral and internal carotid arteries, have a morphological barrier. The presence, or absence, of endothelial tight junctions might well influence the physiological and pathological responses of the different types of vessels within the cerebral circulation.

The available evidence would suggest that the ependyma, lining the cerebral ventricles, does not have the same structural barrier features as the cerebral capillary endothelium. Intraventricular injection of horseradish peroxidase results in electron-dense particles being detected microscopically within the parenchyma of the brain (66). Channels about 200 Å wide are detected between the plasmalemmae of adjacent cell processes within the brain (67). Thus even large molecules could diffuse fairly readily through cerebral tissue were these molecules to be introduced into a ventricle. Such an exchange of materials across the ventricular ependymal barrier has been demonstrated for inulin (547), for urea and creatinine (534), and for some chemotherapeutic agents (49). The ependymal cells are ciliated and are said to have unmyelinated nerve fibres running across their ventricular surface (528, 569, 610, 704). It has been suggested that the function of these fibres is concerned with either secreting into, or registering the composition of, the cerebrospinal fluid (704). The various factors concerning the transport and passage of materials across the ependyma have been reviewed in 1974 (184).

In passing, it is of interest to note that the retina, which is embryologically an extension of the central nervous system, possesses a barrier (the blood-retinal barrier) that is structurally identical with that found within the brain (89, 110, 622).

Before the use of electronmicroscopy, it was widely postulated that the neuroglia were the cells responsible for the barrier. However, in a review of the function of glial cells, Lasansky (381) pointed out that within the central nervous system of higher vertebrates the neuroglia do not form continuous perivascular barriers. The capillary endothelium is the sole continuous barrier between the blood and the cerebral interstitial fluid.

B. Enzymatic Barrier Mechanisms to Amines and Amine Precursors

With fluorimetric assay (696, 697) and fluorescence microscopic (37, 38, 517) techniques, it has been shown that amines are not able to penetrate the brain in significant amounts. The histochemical investigations have revealed that there is a specific trapping mechanism—an enzymatic blood-brain barrier—located within the capillary endothelium for the amine precursors, L-dopa and L-5-hydroxytryptophan (25, 37, 102, 103, 516, 670). This trapping mechanism for amine precursors has essentially three phases: the active transport of the precursor into the endothelial cell; the decarboxylation of the precursor by the anabolic enzyme, dopa decarboxylase; and finally, the amines so formed are metabolised by the catabolic enzyme, monoamine oxidase.

The uptake of amine precursors into the brain is primarily by an active transport mechanism (502, 504, 683, 722), passive diffusion accounting for a small fraction of the total transfer of L-dopa from blood to brain (683). The transport mechanism is

the same for all neutral amino acids, including phenylalanine, tryptophan, and histidine, and has the characteristics of stereospecificity and competitive inhibition (252, 504, 506, 722). It is functionally distinct from the transport mechanisms for other amino acids, sugars, and monocarboxylic acids (40, 503, 504, 506, 721). The transport mechanism for L-dopa can be inhibited by 3-O-methyldopa, the major metabolite of L-dopa (682), as both substances share the same neutral amino acid uptake mechanism.

Amphetamine passes rapidly into the brain by a separate carrier-mediated process which can be inhibited by a structural analogue of amphetamine, β-phenylethylamine (521), whereas a second structural analogue, parahydroxyamphetamine, is unable to penetrate the barrier (403).

When the amine precursor has been transported into the capillary endothelial cells and pericytes, it is decarboxylated and the precursors and the resulting amines can be detected by fluorescence microscopy (37, 103, 377, 517, 670). The capillary decarboxylation is noted particularly well after the administration of a monoamine oxidase inhibitor, to prevent the catabolism of the amines formed by dopa decarboxylase (37, 103). However, if a peripherally-acting dopa decarboxylase inhibitor is administered then the capillary fluorescence is diminished, while neurons in the parenchyma are markedly fluorescent (37, 102, 103, 377, 670). These findings indicate that the enzymatic barrier to monoamines is dependent on, firstly, a rapid decarboxylation of amine precursors; and secondly, oxidation of the amines. The decarboxylase activity of cerebral capillaries differs from that found in cerebral neurons in that the two processes can be selectively affected by differing dopa decarboxylase inhibitors (25). This information, gained from fluorescence histochemistry, regarding barrier mechanisms to monoamine precursors has been confirmed by a number of functional studies (13, 438). The rate of capillary decarboxylation is approximately the same in all regions of the brain studied (267, 683). It has been suggested that there are species differences in capillary decarboxylase capacity (267, 377).

The existence of blood-brain barrier mechanisms to noradrenaline is in keeping with the findings of Oldendorf (502). He compared the penetration of a number of ^{14}C-amines, including noradrenaline, into the brain with a "freely diffusible" test substance (^{3}HOH). The brain uptake index of noradrenaline was about 4%, which was just above the lower limit of measurability of Oldendorf's technique. However, it is now known that even water is not freely diffusible at normal values for cerebral blood flow (55, 228, 534, 543, 544), and therefore the actual penetration of noradrenaline will be less than the value obtained by Oldendorf (502). The finding raises the possibility that the passage of other substances, including amines and their precursors, is dependent upon blood flow and, indeed, the blood-brain passage of tritiated water is determined almost solely by blood flow and exchangeable brain space (62). There is a considerable heterogeneity of blood flow within the brain, and an attempt should be made to correlate these regional variations with the barrier passage of amine precursors. Marked regional variations of noradrenaline and adrenaline uptake have been described (122, 307, 593, 594, 696, 697).

The classical opinion is that 5-hydroxytryptamine is incapable of crossing the blood-brain barrier. As would be expected, 5-hydroxytryptamine can cross the blood-brain barrier in neonates (264, 415); and can be taken up by central monoaminergic neurons after intraventricular injection (214). However, some studies have indicated that 5-hydroxytryptamine can cross the blood-brain barrier in mature animals after intravenous injection (74, 75); although this finding is at variance with another study (502). The discrepancies as to whether 5-hydroxytryptamine crosses the blood-brain barrier might be explained if 5-hydroxytryptamine *per se* was able to increase the permeability of the blood-

brain barrier, a phenomenon that is known to occur under certain conditions (705) but not under others (643). There is now considerable correlative (but not causal) evidence that associates elevated brain 5-hydroxytryptamine levels with various types of cerebrovascular injury, these in turn being associated with lesions of the blood-brain barrier (107, 461, 471, 515). More research is needed to clarify the relationships between circulating 5-hydroxytryptamine and the blood-brain barrier.

After gross structural damage to the blood-brain barrier, systemic noradrenaline can enter the cerebral parenchyma where it then can be localised by histofluorescence techniques (190, 262). In these studies the barrier lesions were induced by intracarotid infusion of mercuric chloride, a procedure which results in ultrastructural damage to the blood-brain barrier (693). A disadvantage of using mercury-induced barrier lesions in the experimental situation is that the transport into the brain of essential nutrients (sugars and amino acids) is inhibited in addition to the endothelial damage *per se* (646–648). Similar heavy metals, lead and nickel, induce ultrastructural changes in the cerebral capillary endothelium (327, 588).

The intraperitoneal administration of morphine has been said to decrease the permeability of the blood-brain barrier to noradrenaline (542). A wide variety of analeptic and sympatholytic agents have been reported to change (increase and decrease) the barrier passage of a variety of labeled substances (541). Nortryptyline and chlorpromazine greatly enhance the barrier passage of dopamine, but this feature is believed to be due to a non-specific, toxic effect (membrane lysis at the ultrastructural level) rather than due to blockade of the monoamine uptake mechanism (523). This question of possible drug influences on the barrier mechanisms to amines is interesting, and these influences would have considerable experimental and clinical applications. It is, accordingly, important that future research in this topic should use reliable and quantitative techniques for assessing barrier passage, and that cerebral blood flow should be measured concomitantly.

Dopa decarboxylase and monoamine oxidase are not the only enzymes present in high concentrations with the cerebral capillary endothelial cells. Both acetyl- and butyrylcholinesterases have been noted by histochemical and electronmicroscopic techniques (192, 267, 330, 373) and these enzymes are believed to be involved in the barrier mechanisms to circulating acetylcholine. The acetylcholine precursor, choline, is rapidly taken up by the brain by an active transport system (604, 605). Thus, the brain has a capillary trapping mechanism for acetylcholine analogous to that for the catecholamines. Many cholinomimetics are quaternary ammonium salts and, as markedly polar molecules, are unable to cross the blood-brain barrier (52). The existence of high concentrations of alkaline phosphatase in the capillary and arteriolar endothelial cells within the nervous system (22, 283) indicates that these cells are a highly active transport site, similar to the intestinal and renal epithelia.

Stimulation of the locus coeruleus has been reported to increase the brain vascular permeability of water (545) and, based on these findings, it has been suggested that the central noradrenergic system has the singular function of regulating cerebrovascular permeability. However, much further research remains to be done before such a hypothesis can be considered tenable: the increased permeability could be due simply to a reduction in blood flow. For example, changes in barrier permeability have been associated with a decreased function of the visual pathways, quite unconnected with the central noradrenergic system (57).

C. Factors Affecting Barrier Function

The many factors and agents that can effect permeability changes in the blood-brain barrier have been discussed lucidly

and comprehensively in a review published in 1975 (522). The function of this section is to present the factors that might complicate an experimental study concerned with the relationship between amines and the cerebral circulation.

Hypertension. Acute hypertension, induced by either metaraminol infusion or clamping of the thoracic aorta, results in multiple blood-brain barrier lesions as evidenced by the extravasation of a protein-bound tracer (180, 320, 321, 429). The sudden elevation of blood pressure results in more frequent barrier lesions than a gradual, incremental rise in blood pressure (258). Transient intracranial hypertension, produced by the rapid injection of cerebrospinal fluid into the epidural space, leads also to focal barrier lesions (278), as do other mechanical stresses such as repeated brain concussion (512) or the unilateral carotid injection of saline or blood at high pressure (258, 560).

In chronic hypertension both blood-brain barrier lesions (223, 513) and oedema development are known to occur (2, 3). The pathogenesis of these lesions is thought to be similar in both chronic and acute hypertension; the greatly increased intraluminal pressure within the cerebral arterioles overdistends the vascular wall. This pathological stretch results in the increased cerebrovascular permeability, which has been clearly demonstrated in a recent ultrastructural investigation (266).

Hypercapnia. Hypercapnia can greatly increase the penetration of various barrier-limited substances into the brain (64, 80, 98, 112, 235, 394). However, in most of these experimental studies the inspired CO_2 content was exceedingly high (10–25%) and it would be more relevant to discuss blood-brain barrier penetration in carbon dioxide narcosis. In man, where the arterial CO_2 tension was raised to between 50 and 60 mm Hg, there is an increase in permeability-surface area coefficient (54), but this is thought to be due to the increase in blood flow and not a hypercapnic effect as such.

Contrast media. It has long been recognised that the contrast media used for cerebral angiography have a marked neurotoxicity, and that lesions of the blood-brain barrier frequently occur after the intracarotid administration of these agents (70–72, 318, 481, 710). It is probable that the contrast media disrupt the blood-brain barrier because of the necessary hypertonicity of their solutions, but their neurotoxicity is related also to the lipid solubility of these agents (555, 558, 561). The iodinated contrast agents increase cerebral blood flow (248, 286) and impair the autoregulatory responses of the cerebral circulation (248). Whenever possible, angiography should be avoided in cerebral circulatory investigations for the reasons outlined above.

Hypertonicity. Hyperosmotic solutions (administered into the internal carotid artery) of many lipid insoluble electrolytes are able to disrupt the blood-brain barrier transiently and reversibly (554, 557). This action is believed to be due to the ability of hypertonic solutions to shrink the cerebral capillary endothelial cells and so open the tight junctions between these cells (564).

The intracarotid infusion of hypertonic solutions opens the barrier to molecules of widely varying size, such as horseradish peroxidase (68, 649), penicillin G (521), sugars (533, 644), noradrenaline (268, 427), and sodium (656). There is a high incidence of brain necrosis with neurological sequelae after the intracarotid infusion of hypertonic urea, but only when the common carotid artery is ligated before the infusion (556). If the vascular supply to the brain is not compromised, then osmotic opening of the barrier is not associated with neurological deficits (559). However, intracarotid hypertonic urea seems to stimulate the facilitated uptake of glucose into the brain as well as increase the simple diffusion of sugars across the blood brain barrier (533, 644). In anaesthetised baboons, intracarotid hypertonic urea does not affect cerebral blood flow, cerebral oxygen consumption, and cerebral glucose uptake, measured 5 min after the infusion

(529). The physiological responsiveness of the cerebral circulation – assessed by autoregulatory and hypercapnia tests – was likewise unaffected. Thus, the intracarotid hypertonic urea should prove useful in studies on the cerebral circulatory effects of barrier-limited agents, such as the monoamines. Certainly, the hypertonic technique is likely to prove superior to an acute hypertensive insult to open the barrier (519).

Miscellaneous agents and procedures. Electrocautery (unipolar diathermy immediately above the calvarium), simple atmospheric exposure of the cerebral cortex, and retraction of brain tissue have all been shown to increase the permeability of the blood-brain barrier (204, 298). As all these techniques are common in experimental studies on the cerebral circulation, the findings of Hudgins and Garcia (298) have some relevance. Experimentally-induced seizures transiently disrupt the barrier (416) as dose electroshock treatment (578).

V. Amines and Cerebral Metabolism

Catecholamines can influence the rate of carbohydrate metabolism in most body tissues. These influences, however, are dependent on a number of variables: the catecholamine concerned, the route of administration, the species being studied, and the organ involved. In this field, reviews published in 1966 and 1967 have pointed out (287, 423) that no universal statement can be made about the metabolic actions of the catecholamines: their effect must be determined for each individual case. Nevertheless, there are two fairly general principles: the effects of catecholamines in stimulating intermediary metabolism are mediated through *beta* adrenoceptors in the majority of cases; and the phosphorylase-activating effects of the catecholamines are closely linked to intracellular levels of cyclic-3′,5′-adenosine monophosphate (cAMP) (548).

The enzyme phosphorylase catalyses the first stage in glycogenolysis, the breakdown of glycogen to glucose- 1-phosphate. Thus modulation of phosphorylase activity can significantly affect the state of intermediary metabolism. Phosphorylase exists in two forms; phosphorylase "a" (the active state) and phosphorylase "b" (the inactive state). cAMP greatly accelerates the formation of phosphorylase a. In turn, cAMP is formed from adenosine triphosphate under the influence of another enzyme, adenyl cyclase. Robison *et al.* (574) were the first to suggest that adenyl cyclase and the *beta* adrenoceptor were the same thing, and since then considerable evidence has accumulated to support this hypothesis, as emphasised by Lefkowitz (393) in 1974.

A. In Vitro Studies

Adrenaline and noradrenaline have been shown to stimulate the production of cAMP from *in vitro* adenyl cyclase preparations, obtained from various regions of cat, sheep, and ox brain (351). Histamine and noradrenaline result in the accumulation of cAMP in rabbit cerebral cortical slices (335). The effects of noradrenaline on rabbit cerebellar slices could be abolished by *beta*-adrenergic blockade (336). However, a few studies would suggest that the response of guinea-pig brain homogenates to adrenaline is mediated *via alpha*-adrenoceptors: noradrenaline was more potent than adrenaline, and the production of cAMP could be abolished by phenoxybenzamine and phetolamine but not by propranolol (94, 598, 607). Opposite findings have been presented by McIlwain (447). In his guinea-pig neocortical preparation noradrenaline stimulated the production of cAMP, and markedly so during electrical stimulation of the neocortical slice. Propranolol blocked the cAMP-stimulating properties of the catecholamines (447). In rat cerebral cortex, noradrenaline would seem to interact with two receptors (analogous to *alpha* and *beta*), while isoprenaline will interact with a single type (analogous to *beta*) in the production of cAMP (527, 606, 639). cAMP production, induced by noradrenaline, would seem to be similarly

antagonised by both *alpha*- and *beta*-sympatholytic agents in the bovine superior cervical ganglion (575). On the other hand, the catecholamines seem to be able to elicit an accumulation of cAMP primarily *via* an interaction with a *beta* adrenoceptor in mouse cerebral cortical slices (606).

In rats pretreated with 6-hydroxydopamine (an agent which destroys the central, ascending catecholamine fibres) the cortical slices displayed an enhanced production of cAMP in response to noradrenaline administration (127). This observation could best be explained by the development of a central, adrenoceptor hypersensitivity after the administration of 6-hydroxydopamine, analogous to the hypersensitivity noted after a postganglionic sympathectomy in the periphery (*vide infra*). In contrast, chronic treatment with *d*-amphetamine results in a reduced noradrenaline-stimulated accumulation of cAMP in mouse brain slices, perhaps due to a subsensitivity of the adrenergic receptor (439).

Histamine is a potent stimulant of adenosine 3′,5′-monophosphate production in cerebral cortical slices (336, 626); histamine also markedly potentiates the ability of adenosine (297, 597, 638) and electrical stimulation (336) to produce cAMP in brain tissue. There are apparently considerable species differences in the histamine-induced accumulation of cAMP, based on experiments that have utilised histamine H_1 and H_2 antagonists (27, 404, 484, 576). An adequate pharmacological characterisation of the histaminergic effects on cerebral metabolism is still wanting.

McIlwain (448) has advanced the hypothesis that adenosine, or possibly adenosine triphosphate, may play a major neurohumoral and regulatory role in the brain production of cAMP. Adenosine augments cAMP and does so in synergistic relation with noradrenaline, 5-hydroxytryptamine, and histamine. Such studies demonstrating the metabolic effects of adenyl compounds should be remembered in light of the current interest in the cerebral circulatory effects of adenine derivatives (36, 203, 499, 589, 686).

A large fraction of brain glycogen is stored with glial, and *not* neuronal cells, and it is possible that the locus of metabolic action of biogenic amines is on the brain glial tissue (73, 97, 159, 227, 514). Such a possibility might be supported by the observation that histamine and noradrenaline have no effect on nerve endings, selectively isolated from cerebral cortical tissue (34).

B. In Vivo Studies

Intravenous noradrenaline was found not to affect the cerebral concentration of cAMP in rats (708), an understandable finding since noradrenaline should not cross the blood-brain barrier. On the other hand, intraventricular noradrenaline has been shown to increase the cerebral concentration of cAMP by approximately 100% (76). In this latter study it is interesting to note that noradrenaline was as effective as isoprenaline, although weaker than adrenaline, in stimulating cAMP. The systemic injection of various biogenic amines into neonate chicks (which lack a mature blood-brain barrier to catecholamines) results in the rapid conversion of phosphorylase b to phosphorylase a, and a marked decrease in brain glycogen concentration (159).

The intraventricular injection of noradrenaline increases cerebral oxygen and glucose consumption in anaesthetised baboons, this increase in metabolism being accompanied by a rise in cerebral blood flow. Likewise, intracarotid noradrenaline after osmotic disruption of the blood-brain barrier increases cerebral oxygen and glucose consumption and cerebral blood flow (427). In a proportion of patients with head injury (those who had an impairment of cerebral autoregulation and, possibly, increased permeability of the blood-brain barrier), the intravenous infusion of noradrenaline increased cerebral blood flow

and oxygen consumption by approximately 60% (246). It is not clear whether the increase in blood flow resulted in the increased oxygen consumption, or whether there was a primary noradrenaline-induced stimulation of cerebral metabolism in these patients. The intracarotid infusion of reserpine, an agent that can cross the blood-brain barrier and has some properties of an indirect sympathomimetic (359, 657), increases cerebral blood flow and oxygen consumption (426). Such studies are supported by the fact that amphetamine (a centrally-acting indirect sympathomimetic) increases blood flow and oxygen consumption in the rat brain (84) as was earlier noted in man (1). The effect of amphetamine on cerebral energy metabolism is to increase energy flux *in vivo* (349, 482, 483).

The intravenous infusion of adrenaline increases cerebral oxygen consumption slightly but significantly in conscious man (348). Equivalent pressor doses of noradrenaline had no effect upon the oxygen uptake by the brain. It is highly probable that the metabolic action of adrenaline seen in the study of King *et al.* (348) was not related to the brain adenyl cyclase phosphorylase systems, but rather to peripheral factors. *A priori,* adrenaline should not cross the blood-brain barrier. Secondly, intravenous adrenaline infusions can lead to alerting, tremulousness, and manifest anxiety, as noted by King *et al.* (348). The amount of afferent activity reaching the reticular activity system from the baroreceptors is considerably augmented by adrenaline (466). Cortical arousal, secondary to the reticular drive, could possibly account for the increase in cerebral oxygen consumption noted with adrenaline. Intramuscular adrenaline, resulting in a mild hypotensive response, does not affect the cerebral metabolic rate for oxygen in conscious man (613). In isolated perfused canine brains (with no intact baroreceptors) the systemic administration of adrenaline does not affect cerebral oxygen consumption (725).

Although the administration of adrenaline did not affect the concentrations of lactate and pyruvate, Hunter and Stefanik (299) have suggested that either the administration of noradrenaline, or the stimulation of the superior cervical ganglion increased cerebral lactate (but not pyruvate) concentrations. The implication of their study is that the release of noradrenaline around cerebral vessels increases brain anaerobic metabolism, and it would be interesting to see this study confirmed elsewhere.

The effects of the systemic administration of isoprenaline on cerebral blood flow have been studied on a number of occasions (313, 390, 717, 725). In every instance cerebral blood flow rose, and, with one exception (725), this rise in cerebral blood flow was accompanied by increases in cerebral oxygen consumption and glucose uptake.

In mice, the intravenous administration of propranolol (300 μg/g) increases cerebral glycogen levels as well as decreasing the amount of spontaneous motor activity in these animals (176). Earlier studies have shown that 200 μg/g of propranolol decreased lactate and pyruvate levels within mouse brain in addition to elevating the glycogen levels (177). The authors interpreted their findings as evidence of a reduced cerebral glycolytic carbohydrate metabolism. These studies have been confirmed elsewhere, as has the fact that *alpha*-adrenergic blocking agents have little effect on intermediary metabolism within the mouse brain (396, 397). Glycolysis within the rat brain *in vivo* is suppressed (that is, the concentrations of some phosphorylated intermediates of the glycolytic pathway are decreased) after reduction of central monoamine levels with reserpine (222). In anaesthetised dogs, the intracarotid infusion of 2 μg/kg per min of propranolol resulted in significant decreases in cerebral blood flow, oxygen consumption, and glucose uptake by the brain (209). A *beta*-adrenergic stimulating agent (bamethan) induced an increase in adenyl

cyclase activity and the cAMP concentration in the motor cortex of the dog, while opposite results were obtained with the *beta*-sympatholytic, dichloroisoprenaline (35). Because cerebral blood flow was measured by the Kety-Schmidt nitrous oxide technique (meaningless in dogs due to the inability to obtain cerebral venous blood that would not be contaminated by the extracranial tissues) the findings of Fujishima *et al.* (209) must be treated with caution. Cortical glucose and oxygen utilisation was reduced by propranolol (11 μg/kg per min) in a further series of experiments in anaesthetised dogs (313). Another group found that intracarotid propranolol infusions (1.45 μg/kg per min) slightly reduced hemispheric blood flow, oxygen consuption, and glucose uptake in a large series of patients with severe neurological disorders (457). In anaesthetized baboons, the intracarotid infusion of propranolol reduces markedly cerebral oxygen consumption and glucose uptake, as well as effecting a considerable attenuation of the cerebral CO_2 reactivity (426).

VI. Cerebrovascular Actions of Amines

A. Sympathetic Nerve Stimulation and Denervation Experiments

The abundant sympathetic innervation of the cerebral circulation has prompted many investigators to use the classical physiological approaches of denervation and stimulation. To quote Lassen (384), "Despite almost staggering experimental assaults, they (the nerves) remain enigmatic."

The relationship between the autonomic nerves and the smooth musculature has been analysed by three main approaches *in vitro*: firstly, studies that have involved transmural electrical stimulation under conditions that would selectively activate the perivascular nerves without influencing the smooth musculature directly; secondly, a study of the effects of indirectly acting sympathomimetics, such as tyramine, which release endogenous noradrenaline from the sympathetic nerves; and finally, the investigation of denervation experiments, designed to elucidate the changes in sensitivity of the receptors to noradrenaline that occur when the transmitter inactivation system of the sympathetic nerves is abolished.

Electrical field stimulation increases the release of tritium after the preincubation of extracerebral (pial) vessels with ^{3}H-noradrenaline (139). This result would indicate that functional perivascular nerve terminals exist, as the effect of stimulation was abolished by sympathetic denervation and treatment with guanethidine or bretylium. Quantitative measurements have shown that pial vessels contain high concentrations of noradrenaline (152) and that the transmitter level is high enough to produce vasoconstriction since electrical field stimulation constricts isolated human, cat, and rabbit pial arteries (44, 137, 154).

Tyramine is an indirectly acting agent that requires the presence of adrenergic nerves for its effect. It is taken up into the nerve terminals and then displaces the transmitter, noradrenaline. Increasing concentrations of tyramine contract the pial vessels *in vitro* (138, 491, 676). This effect is abolished either by sympathectomy or by reserpine treatment and, furthermore, the contraction is inhibited by blockade of the *alpha*-receptors with phentolamine (138, 491, 676). Pretreatment with cocaine (10^{-6} M) increases the sensitivity of the isolated vessel preparation to tyramine (138), probably due to a combination of a pronounced prejunctional receptor supersensitivity and to a reduced uptake of tyramine (673a). Higher concentrations of cocaine (10^{-4} M) have been reported to reduce the sensitivity of the test system to tyramine (676). Under such latter conditions the dominant response is the inhibited neuronal uptake of tyramine and not the increased receptor sensitivity to noradrenaline (673a).

Sympathetic denervation produces a 3-fold increase in the sensitivity of isolated cerebral vessels to noradrenaline (138). A full supersensitivity coincides with the disappearance of the perivascular fluorescent nerves. The supersensitivity can be reproduced by cocaine administration (to non-denervated vessels), and it is specific in the sense that the response to acetylcholine is unaffected. Clearly, the supersensitivity reaction is of the prejunctional type and it is due to the loss of the major inactivation mechanism for the noradrenaline transmitter in the region of the receptor. [The neuronal uptake is responsible for the re-uptake of about 70% of the noradrenaline transmitter released (681).]

Stimulation studies. The effect of sympathetic nerve stimulation on pial vessel diameter *in vivo* has also been studied intensively. The early studies by Forbes *et al*. (201), Chorobski and Penfield (96), and Fog (195) showed that pial arteries constricted when the superior cervical ganglia were stimulated. This observaion has been confirmed and extended by Kuschinsky and Wahl (369) who observed a 15% reduction in vessel diameter during stimulation, the effect being inhibited by phentolamine.

Many studies have been performed to assess cerebral perfusion (as opposed to measurements of pial vessel calibre) in conjunction with the stimulation of the cervical sympathetic trunk. These have been performed on various species, with various techniques, direct as well as indirect. The response has been fairly uniform and, of the papers listed in table 1, most have demonstrated a reduction in, and only a few observed no effect on, cerebral blood flow. Several of the reports have shown the specificity of the effect since it could be inhibited by *alpha*-antagonists. Accordingly, there can be little doubt about the cerebral vasoconstrictor ability of the adrenergic sympathetic fibres (147). However, considerable quantitative variation has been noted, this variation being primarily dependent on the specificity and reliability of the technique used to measure cerebral blood flow. The reduction in cerebral blood flow that has been noted ranges between 10% (272) and 80% (116, 117).

The venous outflow technique, where the drainage from the torcular Herophili is used as an index of brain perfusion, depends upon satisfactorily isolating the cerebral from the extracranial circulation. D'Alecy and Feigl (117) have reported that stimulation of the stellate ganglion reduced cerebral boood flow to 20% of resting values, the most pronounced effect of the autonomic nervous system upon the cerebral circulation to be found in the literature, were it justified. Furthermore, this vasoconstriction after stellate ganglion stimulation could be abolished by the administration of the *alpha*-receptor antagonists, phentolamine and dibozane (116).

The effects of stellate ganglion stimulation on cerebral venous outflow were repeated by Traystman and Rapela (673) with and without occlusion of the lateral sinuses, which drain into the torcular Herophili. As was found by D'Alecy and Feigl (117), stimulation caused decrease in venous outflow when the lateral sinuses were patent. With the lateral sinuses occluded, stellate ganglion stimulation did not affect cerebral venous outflow. Traystman and Rapela (673) concluded that "measured" cerebral blood flow was decreased significantly by sympathetic stimulation only when communications between intracranial and extracranial venous vasculatures were patent.

It has been shown that sympathetic stimulation effects a marked reduction in cerebral blood flow during hypercapnia and a lesser effect during normocapnia in anaesthetised baboons (272). Cerebral blood flow was measured by the intracarotid ^{133}Xe clearance technique. Stimulation resulted in non-uniform and minor, although significant, reductions in blood flow, almost exclusively in cortical tissue

when measuring the cerebral blood flow with ^{14}C-antipyrine (719).

There are some studies available where the effects of cervical sympathetic nerve stimulation on cerebral perfusion have been examined by the labeled microsphere method (10, 46, 463). All were unable to demonstrate any changes in blood flow during nerve stimulation. On examination of their data it will be seen that blood flow did decrease by 15 to 20% and that significant changes could well have been noted had the number of experiments been increased for adequate statistical analysis. (For further criticism of this technique, see section II.)

Denervation studies. The effects of superior cervical sympathetic ganglionectomy were demonstrated earlier to cause increased brain temperature and increase in the visually observable capillary bed (641). Blockade of the preganglionic sympathetic trunk with lidocaine, saturated potassium chloride, and nerve section also increase local cerebral blood flow (614, 615). Shackleford and Hegedus (621) showed, with the Kety-Schmidt nitrous oxide method, a 15% reduction in cerebral blood flow in chronically denervated dogs. This has in fact also been confirmed by Eklöf *et al.* (163). In these latter experiments on monkeys designed to test autoregulation, the normal flow was found to be 71 ml/100 g per min; whereas it decreased 2 weeks later to 50 ml/100 g per min. On the other hand, Hernández-Pérez *et al.* (284) observed a 34% increase in cerebral blood flow. What is the explanation of these various effects? From knowledge of denervation effects in aminergic systems in other parts of the body, as well as in the cerebral vasculature, the effects of sympathetic denervation can be described reasonably accurately. Shortly after ganglionectomy there is a reduction in the cerebral blood volume (147). This observation implies vasoconstriction, probably as a consequence of noradrenaline leakage from the degenerating postganglionic sympathetic fibres (421, 434, 679), which is known to be accompanied by an activation of the effector structures (378). The subsequent increase in cerebral blood volume (147) above control levels (reflecting vasodilatation) is due conceivably to a reduced vascular tone which occurs when a sufficient amount of noradrenaline has disappeared from the degenerating nerves (152). This vascular response coincides with the disappearance of the fluorescent nerves and of the noradrenaline concentration, determined chemically, in the pial vessels (152). The cerebral blood volume returns to control values a week postoperatively (147) probably because the vascular tone is reestablished when the denervated, adrenergic vascular receptors develop sufficient supersensitivity (378) to circulating catecholamines. At this postdenervation stage the sensitivity of the smooth musculature in pial arteries has been found to have increased about 3-fold (138). However, decentralisation of the superior cervical ganglia produced a slight increase (20–40%) of the noradrenaline concentration 1 to 2 weeks postoperatively (152), which may be due to lowered activity in the postganglionic neurons after depriving them of their afferent innervation. These decentralisation effects are followed by an increased cerebral blood volume, reflecting vasodilatation consequent to reduced activation of the nerve terminals in the vasculature (156).

These findings on the changes in cerebral blood volume after denervation or decentralisation emphasise the importance of clearly stating the time after sympathectomy when any cerebrovascular parameters are to be evaluated. Such information is often lacking in the literature, thus making the results from this type of experiment on cerebrovascular reactions difficult to evaluate.

Having these facts in mind, several authors found increased cerebral blood flow or volume after acute sympathectomy (146, 147, 272, 314, 614), while others obtained a reduced cerebral blood flow, or volume, after chronic sympathectomy

(147, 163, 621, 691) although there are some exceptions to these findings (189, 284). All such denervation experiments might possibly be explained either on the basis of vasodilatation due to a sudden deprivation of the central inflow of impulses, or as the consequence of increased sensitivity of the adrenergic receptors to circulating catecholamines in the chronic situation.

B. Sympathetic and Sympatholytic Agents

Overall, the evidence listed in the preceding section strongly suggests a cerebral vasoconstrictor nature for the sympathetic adrenergic nerve system. However, the results obtained in experiments with vasoactive amines are highly conflicting. The data from recent studies are compiled in tables 1 to 3 for both *in vitro* and *in vivo* techniques. Since the *in vivo* model is very complex, the *in vitro* effects of amines and their blockers will be considered before turning to the *in situ* response of the cerebral circulation to the drugs (fig. 2).

Alpha-adrenergic agents. It has been shown that the adrenergic agonists (adrenaline, noradrenaline, isoprenaline, and phenylephrine) contract isolated pial arteries in a dose-dependent manner and in the above order of potency (149). This order and the degree of relative potency obtained are in accord with those reported for *alpha*-receptor responses in other tissues (212) with the exception of a high ED50 and a low maximum contraction for phenylephrine. The latter compound is recognised as a partial agonist on *alpha*-receptors in feline and human cerebral arteries, showing that these vessels have distinct pharmacological features (149, 154).

Blockade experiments have been undertaken with both reversible and irreversible competitive antagonists. The reversible *alpha*-receptor antagonists, piperoxan and phentolamine, have been observed to

TABLE 1

Effects of sympathetic nerve stimulation and noradrenaline on cerebral blood flow

The numbers in last three columns are reference numbers.

Agents	Species	Decrease	No Effect	Increase
A. Sympathetic nerve stimulation:				
Direct techniques	Cat, dog, goat, monkey	116, 117, 294, 412, 413, 462	673	
Invasive techniques	Dog, duck, gull, man, rabbit	367, 419,* 420, 614, 615	419*	419*
Inert gas studies	Baboon, cat	272, 314, 353	272	
Non-invasive techniques	Cat, monkey, mouse	129, 147, 719	10,† 463,† 719	
B. Noradrenaline:				
Direct techniques	Dog, goat	413, 417, 498	136, 243	206,‡ 455§
Invasive techniques	Dog, cat, rabbit	367, 582, 615	615	45,§ 582‖
Inert gas studies	Baboon, dog, man, newborn lamb	167, 256, 272, 313, 348, 479, 613	426, 507	181,‡ 313‡ 426,‖ 442, 442,‡ 540¶
Noninvasive techniques	Mouse, rat	146, 151	146, 292	

* The response is related to the stimulus strength.

† Reduction but not statistically significant.

‡ Above or below the limits of autoregulation.

§ The preparation was not autoregulating.

‖ Opening or circumventing the blood-brain barrier.

¶ Performed on animals where the blood-brain barrier is not yet closed (or matured).

TABLE 2

Direct cerebrovascular smooth muscle effects of various agonists

The numbers in last two columns are reference numbers.

	Agonist	Species	Constriction	Dilatation
Sympathomimetics	Noradrenaline	Cat, cow, dog, goat, man, monkey, rabbit	8, 44, 118, 131, 138, 144, 145, 149, 154, 369, 392, 490, 532, 668, 677	149
	Adrenaline	Cat, dog, man	8, 149, 154, 490	149, 154
	Phenylephrine	Cat, man	144, 149, 154	
	Tyramine	Cat, goat	138, 491, 676	
	Isoprenaline	Cat, dog, man	144, 149, 154, 490, 687	149, 154, 616, 666, 687
	Terbutaline	Cat, man		149, 154
Parasympathomimetics	Acetylcholine	Cat, dog, man	138, 139, 144, 145, 490	139, 154, 666
	Carbacholine	Cat, dog	139	139
	Nicotine	Cat, dog		139, 667
Other amines	Histamine	Cat, dog, goat, man, rabbit	8, 150, 154, 392, 490, 532, 660	150, 154, 694
	5-Hydroxytryptamine	Cat, dog, goat, man, rabbit	8, 53, 131, 141, 392, 490, 532, 660, 668, 677, 720	141
	Dopamine	Dog, man	711, 723	234

cause a parallel shift in the dose-response curves obtained with adrenaline, noradrenaline, and phenylephrine, but not with isoprenaline (149). Phentolamine has been demonstrated to antagonise the contraction of noradrenaline in a typical way (158).

Irreversible *alpha*-antagonists such as phenoxybenzamine and dibenamine block the constriction induced by adrenaline, noradrenaline, and phenylephrine (149). The effect consists usually of a parallel shift in the dose-response curve in addition to a decrease in the maximum contraction. These facts emphasise the existence of a contractile *alpha*-adrenergic receptor in brain vessels. Furthermore, it has been observed that the noradrenaline response on this *alpha*-receptor is not directly proportional to the fraction of receptors occupied: half maximum contraction with noradrenaline occurred with only 11% receptor occupation and the maximum response is achieved already when 75% of the receptors are occupied by the adrenergic transmitter (149). An interesting study in 1976 (392a) has demonstrated that the basilar artery constriction, caused by adrenergic nerve stimulation, cannot be blocked by phentolamine, phenoxybenzamine, and tolazoline although it can be blocked by tetrodotoxin, guanethidine, and bretylium. This deserves to be confirmed.

The influence of amines on cerebral blood flow has been controversial for a considerable length of time. Their intravenous and intra-arterial administration have given rise to a multitude of equivocal results: noradrenaline and adrenaline have variously increased, not affected, or decreased blood flow to the brain (tables 1 and 3). The diversity of results cannot be explained readily. The most frequent response was a decrease in cerebral blood flow after the administration of noradrenaline (table 1). This noradrenaline-in-

TABLE 3

Action of amines on cerebral blood flow

The numbers in the last three columns are reference numbers.

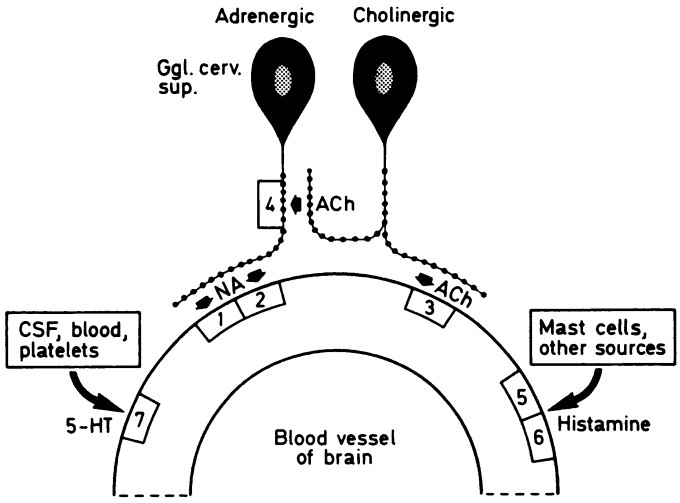
Agents	Species	Decrease	No Effect	Increase
Adrenaline	Dog, man, monkey, rabbit, rat	151, 348, 367, 417, 455, 498, 615	243, 289, 507, 613	151
Phenylephrine	Dog	417	289	
Tyramine	Dog, goat, mouse, rabbit	146, 292, 412, 413, 472	265	472
Isoprenaline	Dog, goat, man, rabbit, rat		289, 305, 510	88, 136, 141, 151, 390, 417, 498, 615, 717
Amphetamine	Man, monkey, rat	133	603	84
Acetylcholine	Dog, monkey, rat	263	263	124, 367, 418, 611
Nicotine	Man			634, 695
Histamine	Dog, man, monkey		224, 511	11, 16, 133, 225, 340, 665, 699
5-Hydroxytryptamine	Dog, man, monkey, rabbit, rat	123, 169, 247, 340, 368, 425, 700, 702	368, 425, 511	582, 661
Dopamine	Dog	174		174, 175

duced reduction in blood flow is fairly small, being up to 20% in those studies in which total cerebral blood flow was measured. Changes of this magnitude will not be readily detected by many techniques used to measure cerebral blood flow, unless large series of experiments are performed to allow adequate statistical analysis. A few studies have reported very marked noradrenaline-induced decreases in cerebral blood flow but these investigations just serve to emphasise the necessity of isolating cerebral from extracerebral circulations. This precaution is of importance when examining the effects of procedures such as sympathetic stimulation or noradrenaline infusion, which may have differential actions upon very dissimilar tissue beds. With a chronically-implanted electromagnetic flowmeter on the internal maxillary artery of the unanesthetised goat, Lluch *et al.* (413) reported that intra-arterial injections of noradrenaline produced dose-dependent reductions in cerebral blood flow, this reduction being 55% with the highest dose (5 μg) examined. Earlier studies (17, 136), however, have pointed out that the internal maxillary artery in the goat feeds into an extracranial structure known as the rete mirabile which in turn supplies the circle of Willis. The intra-arterial administration of noradrenaline proximal to the rete effected a blood flow of the same order as seen in the study by Lluch *et al.* (413). On the other hand, when noradrenaline was injected distal to the rete (into the middle cerebral artery) then no decrease in blood flow was observed (136). The different findings are readily explained by the observation that only one fourth of the blood flow in the internal maxillary artery of the goat is destined for the cerebral circulation (468). When studied in baboons, the intracarotid infusions of adrenaline, noradrenaline, phenylephrine, and isoprenaline effected only minor changes in internal carotid artery blood flow (289).

There are a number of reasons which might explain the apparent insensitivity of the cerebral circulation to noradrenaline, and these reasons should be considered in any investigations that involve amines. Firstly, there is the existence of

blood-brain barrier mechanisms to amines which would limit the accessibility of cerebrovascular smooth muscle to circulating amines, as has been discussed in section III. Secondly, one should consider the "dual effects" hypothesis, advanced by Harper *et al.* (272). It states that the cerebral circulation can be described as two resistances in series: the extraparenchymal (pial) vessels are influenced to a greater extent by the autonomic nervous system or catecholamines, but the intraparenchymal vessels are regulated by intrinsic metabolic or myogenic mechanisms and, to a lesser extent, by catecholamines. This theory has been supported by a number of investigations reported in 1972, 1973, and 1976 (189, 241, 284, 507, 650). If the intraparenchymal vessels are near-maximally dilated, as during hypotension or hypercapnia, then sympathetic stimulation or the infusion of catecholamines will potentiate the reduction in total cerebral blood flow by constricting the extraparenchymal vessels. However, the recent demonstration of an adrenergic innervation to the intraparenchymal vessels may require a modification of the "dual effects" hypothesis.

Lastly, there is a regional heterogeneity in the blood flow response to adrenergic agents. This heterogeneity has been demonstrated between brain areas such as the caudate nucleus and the lateral geniculate body (615). Systemic injection of noradrenaline or adrenaline caused a reduction in



Receptor No.	Receptor type	Response	Inhibitors tested	Mode of inhibition
1	alpha	+	piperoxan phentolamine phenoxybenzamine dibenamine	competitive (reversible) " " competitive (irreversible) " "
2	$beta_1$	−	propranolol INPEA practolol	competitive " "
3	muscarinic	− and +	atropine	competitive
4	nicotinic	−	hexamethonium	competitive
5	histamine (non-spec.)	+	mepyramine chlorpheniramine	non-competitive "
6	histamine H2	−	burimamide	competitive
7	serotonin (non-spec.)	+	methysergide	non-competitive

+, contraction; −, dilation (inhibition in case of nicotinic receptors)

FIG. 2. Schematic representation of the postganglionic autonomic innervation and other sources of amines arranged around the circumference of a brain vessel. The corresponding receptors are also shown.

the flow to the caudate nucleus, but not to the lateral geniculate body. This decrease can be inhibited by phentolamine. Similarly, preganglionic stimulation of the sympathetic trunk below the superior cervical ganglion reduces the blood flow, and the effect is less pronounced in the lateral geniculate body than in the caudate nucleus. Furthermore, this decrease in flow can be abolished by previous *alpha*-receptor blockade. The amount of innervation in the two regions is strikingly well correlated with the local cerebral blood flow response (see section II). The existence of marked noradrenaline-induced changes in specific regions could well be masked in those studies where total, or hemispheric blood flow was measured.

The studies in which an increase in blood flow have been noted after the administration of noradrenaline (table 1) can best be explained by either a failure of autoregulation or a deliberate or unintentional disruption of the blood-brain barrier. If autoregulation is abolished (either at normotension or during hypotensive shock) then any pressor agent will passively increase cerebral blood flow. If the pressor response to noradrenaline is considerable then the upper limit of autoregulation may be exceeded, blood flow will increase and may remain increased after the return of blood pressure to normotensive levels (653). The study of James and MacDonell (313) is of interest as these authors have demonstrated an increase in cortical blood flow after infusion of noradrenaline intravenously or into the common carotid artery, although the infusion of noradrenaline into the internal carotid artery effected a decrease in cortical blood flow. However, every change in blood flow was accompanied by a change in cortical glucose and oxygen metabolism in the same direction. At least two explanations exist for these anomolous results; either the effects of noradrenaline were primarily on cerebral metabolism, or the small region of cortical tissue, examined by the ^{85}Kr technique, was not at all representative of perfusion in the remainder of brain. Furthermore, the dose of noradrenaline administered systemically in these studies resulted in a large pressor response which developed rapidly (424), the conditions under which hypertensive lesions of the blood-brain barrier occur. This criticism may apply to other investigations (442).

It seems probable that the cerebrovascular responses to noradrenaline are dependent on the integrity of the blood-brain barrier: noradrenaline increases blood flow after osmotic disruption of the barrier (268); intraventricular noradrenaline increases cerebral blood flow (427) and the direct injection of noradrenaline into the hypothalamus can increase blood flow (582). The intravenous administration of catecholamines to foetal and newborn lambs increases cerebral blood flow and it is unlikely that barrier mechanisms to monoamines had matured in these animals (540). These increases in cerebral blood flow, associated with noradrenaline when it bypasses the blood-brain barrier, occur concomitantly with an increase in cerebral metabolism (427).

Beta-adrenergic agents. The effect of the *beta*-receptor agonist, isoprenaline, has given consistent data both *in vitro* and *in vivo*. When isolated brain vessels are studied a contractile response usually occurs in vessels without tone (490). The effect is not antagonised by propranolol (a *beta* receptor blocking agent) but is inhibited by the *alpha*-receptor blocking agents, piperoxan and phenoxybenzamine (149). Therefore, in order to study the dilatatory action of *beta*-receptor agonists the vessels have to be given an active tone by 5-hydroxytryptamine, carbacholine, prostaglandin $F_{2\alpha}$ or KCl. During such conditions isoprenaline, adrenaline, noradrenaline, and terbutaline dilate the tonically contracted artery (provided that the contractile effects have previously been blocked by dibenamine or phenoxybenzamine administration) in a dose-dependent manner (149). The relative potency is isoprenaline > noradrenaline = adrenaline > terbutaline. The dilatation

produced by isoprenaline or terbutaline can be blocked competitively by propranolol (*beta*$_1$ and *beta*$_2$ receptor blocking agent) and by the selective *beta*$_1$-receptor agonist, practolol, given in low concentrations (149). That the interaction between propranolol and the receptor involved a bimolecular reaction was confirmed in Arunlakshana-Schild plots. The pA_2 value and the corresponding dissociation constant (K_b) for the receptor antagonist complex indicated that the dilatatory response was mediated by a *beta*-receptor. These results, together with the finding that noradrenaline was almost equipotent to adrenaline and that isoprenaline was about 2500 times more potent than terbutaline, show that the cerebrovascular *beta*-receptor is of the *beta*$_1$ type. This receptor type has been found in the coronary arteries, whereas other parts of the peripheral circulatory bed possess *beta*$_2$-receptors (212).

Isoprenaline has been shown to dilate brain vessels *in situ* after direct administration with the microapplication technique (687), the effect being antagonised by propranolol. Several authors have examined the effect of isoprenaline on cerebral blood flow and observed a dose-dependent increase in blood flow or vasodilatation (see table 3), the effect being more pronounced in the caudate nucleus than in the lateral geniculate body (615). The vasodilatatory effect of isoprenaline can be prevented by previous injection of the *beta*-antagonist, propranolol (289, 498, 616). Furthermore, it has been found that the *beta*$_2$-receptor agonist, terbutaline, is without effect on caudate blood flow although, like isoprenaline, it produced a slight fall in blood pressure (616). The selective *beta*$_1$-receptor antagonist, practolol, abolishes the isoprenaline-induced increase in blood flow in the caudate nucleus without affecting the slight hypotension. The findings corroborate the *in vitro* experiments and show that brain vessels possess *beta*$_1$-receptors which mediate vasodilatation and increase local cerebral blood flow in regions well-supplied by sympathetic nerves.

Sympatholytic agents. Much interest has been paid to the question whether the brain vessels are under a tonic nervous influence, and it has been anticipated that this would be revealed immediately after a sympathetic denervation, as has been discussed earlier. The results from experiments in which adrenergic receptor blockers have been used are not consistent. The *alpha*-receptor antagonists, phentolamine (116, 242, 369, 374, 631), phenoxybenzamine (116, 291, 313, 417), and thymoxamine (105, 291) were found to be without effect on vessel tone or on resting blood flow, but antagonised the reduction in the pial vessel calibre or reduced the flow response to phenylephrine, adrenaline, and noradrenaline (116, 369, 374, 413, 417). The discrepancy in response between the findings from nerve section and *alpha*-receptor blockade experiments might be due to difficulties for the antagonists to reach the receptors in sufficient concentrations. As was discussed in section II, it is necessary to maintain the antagonist close to the receptor for a considerable time to obtain an adequate inhibition. This is difficult to achieve during *in vivo* conditions. However, the conclusion must be that the resting vasomotor tone is low in the cerebral circulation although some localised regions may well be under a significant adrenergic tone. *Beta*-receptor blocking agents have little cerebral circulatory effects during resting conditions (426, 687). Notably, propranolol has been described as reducing cerebral oxygen consumption and also as being able to reduce the CO_2 response of the cerebral circulation in baboons (426). However, the vasodilatatory action of isoprenaline is inhibited both by propranolol (313, 413, 417, 498, 615, 687) and practolol (616).

C. Stimulation and Section of the VIIth Cranial Nerve

Only a limited number of experiments have been undertaken to reveal the role of

nonadrenergic nerves. The evidence so far collected has examined cholinergic innervation (supposedly *via* the VIIth cranial nerve) on the regulation of cerebral blood flow.

Histochemistry and electronmicroscopy have demonstrated the presence of a cholinergic nerve supply to the pial vessels where the cholinergic nerve network is as well developed as the adrenergic innervation (145). The cholinergic fibres are considered to originate in the brain stem, and then follow the facial nerve to the geniculate ganglion where they either synapse and/or continue along the greater superficial petrosal nerve to the plexus of the internal carotid artery and further to cerebral vessels (96).

Stimulation of the facial nerve near the medulla oblongata in the sympathectomised monkey resulted in a slight vasodilatation of pial arteries in the parietal cortex (96). This effect seems to be strictly ipsilateral, and is likewise obtained when the geniculate ganglion is stimulated (202). Furthermore, this same effect can be abolished by local application of the cholinergic receptor antagonist, atropine (200). Stimulation of the vagal nerve has also resulted in pial vasodilatation, but the effect is accompanied by a reduction in arterial pressure which thus might indicate that the effect is secondary to a fall in arterial pressure (99, 200, 498). Quantitative measurements of cerebral blood flow during stimulation of the VIIth cranial nerve cause an increase in regional flow, provided the centripetal effects of stimulation are prevented by sectioning of the central afferent part of the nerve (591). Other research groups have reported flow effects in this direction, but the response has been both inconstant and inconsistent (314, 460). When the *intact* facial nerve is stimulated any vasodilatation could be masked by the effects of stimulating brain stem structures. The effects of section of the VIIth cranial nerve on the cerebral circulation would seem to be insignificant at normoxia (290, 535) and at hypercapnia and hypoxia (290).

D. Cholinomimetic and Cholinolytic Drugs

In contrast to the small number of studies involving section and stimulation of the cholinergic nerves, many pharmacological studies have been undertaken during the last decade on the effects of cholinergic drugs on the cerebral circulation (tables 2 and 3). Acetylcholine has a dual effect on isolated pial vessels, involving both dilatation and contraction (138, 139, 144, 145, 490, 666). Both effects are directly on the smooth musculature, since the responses are unaffected by previous sympathectomy. The dilatatory response occurs at low concentrations (between 10^{-8}-10^{-6} M), whereas the contractile action is first seen at concentrations about 3×10^{-6} M acetylcholine. Both effects were inhibited by atropine in a competitive manner (139). The antagonism by atropine and the fact that hexamethonium does not affect the acetylcholine-induced response suggests that these two effects are mediated by cholinergic receptors of the muscarinic type. It is conceivable that the cholinergic vascular receptors mediate vasodilatation during physiological conditions, whereas high, pharmacological doses of parasympathomimetics produce vasoconstriction.

Microapplication of the parasympathomimetic agent, carbamylcholine, into the perivascular space of single pial arteries by Kuschinsky *et al.* (371) has demonstrated a dose-dependent dilatation with a maximum of about 15%. Atropine administered during the same conditions prevented the carbachol-induced dilatation, but the antagonist had no effect of its own on untreated pial vessels under their experimental conditions (371).

Lowe and Gilboe (418) have demonstrated a reduction in cerebrovascular resistance in constantly perfused brains after intracarotid injection of acetylcholine. Similarly, intra-arterial administration of metacholine caused a weak vasodilatatory response as measured by the venous outflow method (443). Increased cortical flow has been observed after the intra-

carotid administration of acetylcholine (367).

The intravertebral administration of acetylcholine increases cerebral blood flow by 27% while reducing the oxygen consumption by 19% (124). On the other hand, intracarotid infusion of the amine has been shown to increase cerebral blood flow only by 8% (124). Another report from the same laboratory has described no effect of acetylcholine on vertebral flow, while the internal carotid artery flow is reduced (263).

Scremin *et al.* (611) have demonstrated that cortical blood flow increases by about 50% after the topical application of carbachol, arecoline, acetylcholine, and pilocarpine in the presence of eserine, a cholinesterase inhibitor. These effects were counteracted by atropine.

If the results mentioned above are considered together with the earlier findings on the effects of acetylcholine reviewed by Sokoloff (641), which showed dilatation of pial vessels, increase in brain volume, raised cerebrospinal fluid pressure, and increased blood flow, it becomes evident that the choline esters are capable of relaxing cerebrovascular smooth muscle.

The adrenergic and cholinergic nerve terminals lie close together within the same Schwann cell sheath, and are separated by only a 25 nm distance (145, 492). This arrangement opens the possibility for an interaction between the two neuron (adrenergic and cholinergic) systems at the axoaxonal level. Studies on peripheral tissues (lacking cholinergic nerves) have shown that the adrenergic fibres possess muscarinic inhibitory receptors (205). This conclusion has been reached on the basis of experiments which have shown that a variety of muscarinic agonists selectively inhibit the vasoconstriction evoked by periarterial nerve stimulation. The noradrenaline release, evoked by transmural stimulation of pial arteries under the influence of parasympathomimetic compounds, has been studied in an efflux system (139) in order to elucidate the functional significance of this relationship between the two neuron systems. Electrical field stimulation increased the tritium efflux by approximately 125%, the effect being enhanced in the presence of hexamethonium. In contradistinction, both acetylcholine and nicotine inhibited the effect of stimulation so that the tritium efflux was not significantly higher than that occurring during the resting state. This inhibitory action of the parasympathomimetics was counteracted by hexamethonium, but not by atropine. These experiments demonstrate the existence (but not physiological role) of a functional interaction between the two types of autonomic nerve terminals, the cholinergic nerves being capable of inhibiting the adrenergic activity through a nicotinic receptor (139). A similar finding has been reported recently by Toda (667) who observed a dilatation of pial vessels in response to 10^{-4} M nicotine. In his experiments the effect could be abolished by hexamethonium. Quantitative measurements of cerebral blood flow, either after tobacco smoking or during the intravenous administration of nicotine, enhances blood flow but does not affect the oxygen consumption of the brain (634, 695).

Thus, acetylcholine liberated from the cholinergic nerves may, under physiological conditions, induce pial vasodilatation by a combination of (a) direct effects on muscarinic receptors in the vascular smooth muscle, and (b) through axoaxonal interaction with the nicotinic receptors in the adrenergic nerves causing inhibition of noradrenaline release (137).

Nonetheless, the bulk of the evidence would support the conclusion that the cholinergic component to the tone of cerebrovascular smooth muscle is minimal under resting conditions. One would stress that conditions of normoxia, normocapnia, and normotension might not reveal the functional significance of this system.

E. 5-Hydroxytryptamine

Although 5-hydroxytryptamine has been implicated frequently in the pathogenesis of a number of intracranial, vascu-

lar diseases, an adequate description of the pharmacological and physiological effects of 5-hydroxytryptamine is still waiting. The release of 5-hydroxytryptamine is said to occur after stroke (471), trauma (515), cold injury lesions (107), and ischaemia (701). Similarly, 5-hydroxytryptamine has been postulated to be a candidate in the pathogenesis of cerebral vasospasm (562, 563) and migraine (18, 111, 337, 599, 629). In the body, 5-hydroxytryptamine is located mainly in blood platelets (217), in central neuronal systems (see section III), and in the cerebral mast cells of certain species (577). It is possible that 5-hydroxytryptamine could be released from such sites and so affect the vascular smooth musculature.

When serotonin is applied directly to isolated cerebral vessels a constriction occurs (8, 53, 131, 141, 392, 490, 532, 660, 668, 677, 720), and this response can be inhibited by various concentrations of the serotonin antagonists, methysergide (141), and lysergic acid diethylamide (677). The contraction elicited by 5-hydroxytryptamine can be blocked not only by the classical antiserotonin drugs, *e.g.*, methysergide, pizotifen, cyproheptadine, but also by increasing doses of *beta*-haloalkylamines such as phenoxybenzamine (141). After complete inhibition of the 5-hydroxytryptamine contractile effect, and provided that the pial arteries have been given an active tone, 5-hydroxytryptamine produces a dose-dependent dilatation. This dilatation is inhibited in a competitive way by propranolol, suggesting that 5-hydroxytryptamine may interact with *beta*-receptors (141, 451). It is, therefore, possible that the contradictory actions of 5-hydroxytryptamine, dilatation and constriction, might be due to the activation of two types of receptors. A dilatation occurs when the *beta*-receptors predominate in relation to the constrictory 5-hydroxytryptamine receptors and a constriction in the reverse case. The action that will predominate in a given situation could be due to species differences, regional variations in receptor availability, or be dependent on the tone of the vessel (254). The perivascular application (into the subarachnoid space and thought not to affect the underlying cortical metabolism) of 5-hydroxytryptamine to pial vessels effects *tone*-dependent changes in calibre: large, conducting vessels constrict, while the small, resistance arterioles dilate. The serotonin-induced arteriolar dilatation can be abolished by reducing the systemic arterial pressure and so abolishing the tone of the smaller vessels (275b). Very large conducting vessels such as the internal carotid artery show a marked vasoconstriction in response to systemically administered 5-hydroxytryptamine (123, 247, 275a, 551, 700).

When 5-hydroxytryptamine is applied topically to the surface of the cerebral cortex, it causes a vasoconstriction of the pial arteries (33, 563, 579, 580). However, since circulating serotonin is taken up poorly by the brain (502), the effect produced by topical application does not necessarily mean that the same response will be achieved after intra-arterial administration. Furthermore, the intracarotid infusion of 5-hydroxytryptamine, after osmotic disruption of the blood brain barrier, results in a reduction in both blood flow to, and oxygen consumption of, the brain (275a). Similar effects were obtained when 5-hydroxytryptamine was injected directly into hypothalamic tissue (581).

A number of cerebral circulatory studies have been performed. Karlsberg *et al.* (340) described a marked serotonin-induced reduction in cerebral perfusion. In another series of experiments the cerebral blood flow was found to be reduced, during infusion of 1 μg/kg per min of 5-hydroxytryptamine, by 17% at normocapnia and by about 35% during hypercapnia (123). A more pronounced vasoconstrictor effect of 5-hydroxytryptamine (up to 62%) has been noted during arterial hypoxia (169). These authors were unable to affect this contriction by phentolamine, methysergide, or propranolol. Grimson *et al.* (247) observed

a decrease in internal carotid artery flow by 58% after 10 μg/kg per min after 5-hydroxytryptamine, without any change in arterial pressure, heart rate, or blood gas tensions during the infusion. These observations have been confirmed by Welch *et al.* (700, 702), who observed a decrease in internal carotid artery flow after the infusion of 20 μg/kg per min of 5-hydroxytryptamine. The intraperitoneal administration of 5-hydroxytryptamine (5.8 mg/kg) reduces cerebral blood flow slightly in the rat (368). These animal studies are somewhat at variance with the observations in patients where no effect on flow has been observed after a low dose of 5-hydroxytryptamine (511). However, in three of the five patients studied a change in the regional distribution of tracer took place.

The cerebral circulatory effects of serotonin are clearly complex. The overall response to the administration of 5-hydroxytryptamine would tend to be a reduction in cerebral perfusion, although this reduction could well be confused due to the simultaneous increase in extracranial perfusion (123, 247, 661, 702). Other complicating factors could be the existence of dilatatory and constrictory 5-hydroxytryptamine receptors at different levels of the cerebrovascular bed and possible actions of the amine on both cerebral metabolism and the blood-brain barrier.

F. Dopamine

Dopamine crosses the blood-brain barrier poorly (37, 502), unlike the dopamine agonists, apomorphine and piribedil, and the postulated dopamine antagonists, haloperidol and pimozide. The administration of such agonists and antagonists results usually in a variety of stereotyped behavioural responses in animals (14, 104, 108, 141) and man (92, 372). Dopamine agonists and antagonists have marked effects on the electroencephalogram (EEG): *e.g.*, haloperidol increases the incidence of spontaneous EEG spikes and enhances the paroxysmal EEG activity during photic stimulation (450). In addition to the electrocortical and behavioural effects of dopamine, the catecholamine stimulates the production of cyclic adenosine 3′,5′-monophosphate in cerebral and, especially, striatal tissue (308, 343, 470). Adenyl cyclase obtained from the caudate nucleus is highly sensitive to L-dopa while adenyl cyclase derived from the cerebellum (which has no central dopinergic innervation) does not respond to L-dopa (219). The dopamine-induced stimulation is less effective than the noradrenaline-induced stimulation of cyclic adenosine 3′,5′-monophosphate, when compared on an equimolar basis (185, 308, 405).

In the renal circulation, dopamine effects, firstly, a vasoconstriction which is believed to be mediated by an *alpha*-adrenergic mechanism and, second, a sustained vasodilatation which is believed to be mediated by specific dopamine receptors (232, 233). A similar series of responses has been reported on the cerebral circulation (174). The specific dopamine agonist, apomorphine, increases cerebral blood flow; an effect which could be abolished by the intravenous infusion of pimozide (175). However, the *in vivo* studies on the cerebral effects of dopamine have all been performed in dogs and blood flow has been measured by the intravertebral ^{85}Kr technique. As an important amount of vertebral blood goes to the extracranial muscles in this species (703), the results obtained to date with dopaminergic agents must be treated with caution. Dopamine has been shown to constrict cerebral vessels *in vitro* (723), an observation which is consistent with the effects of dopamine on isolated coronary arteries (669). These effects are antagonised by phenoxybenzamine and, should the vessel have an active tone, dopamine invariably dilates (234). It is possible that the observed cerebral circulatory effects of L-dopa (168) are due to the activation of dopaminergic mechanisms: the amino acid is converted rapidly into dopamine both in peripheral tissues and in the walls of brain capillaries (267).

The intracisternal injection of dopamine evokes a vasoconstrictory response in the basilar artery, as seen by vertebral angiography (711).

In view of the wide-ranging biological activities of dopamine (232, 233, 664), future research should give consideration to the possible effects that a "vasoactive" agent, such as dopamine, might have on the underlying cerebral metabolism and neuronal function. Furthermore, regional variations in the vascular response to dopamine may well be noted, depending upon the extent of the cerebral dopaminergic innervation.

G. Histamine

There is considerable experimental evidence to suggest that the histamine in brain is stored in intracerebral neurons (608), although this has not yet been confirmed by direct visualization of histamine in nerve fibres. Fluorescence histochemical and chemical studies have shown that histamine is present in cerebral mast cells, often with a perivascular localisation (577). This opens the obvious possibility that there could be a local action of histamine on brain vessels and, for this reason, experiments have been performed to characterise histamine receptors. Several research groups have studied the contractile effect of histamine on cerebral vessels (8, 150, 154, 392, 490, 532, 660, 677).

The contractile effect of histamine has been studied in the presence of 10^{-4} burimamide to avoid interference with dilatatory mechanisms (150, 154). In extracranial arteries histamine produced a strong contraction, whereas the contractile response of the intracranial arteries was only about one third of that and the ED50 concentration was high. These responses and the finding that the classical antihistamines, chlorpheniramine and mepyramine, reduced the slope and maximum response of histamine in the middle cerebral artery, would indicate that the cerebrovascular contraction was not mediated by specific histamine receptors. In extracranial arteries these antagonists produced a parallel shift of the histamine-induced contraction, demonstrating the presence of histamine H_1-receptors (150).

The dilatatory response to histamine has been analysed after the arteries had been given a tonic contraction and mepyramine to block the contractile effect of histamine (150, 154). Under such conditions, histamine causes a dilatation with a low ED50 in both intra- and extracranial vessels. A parallel shift in the dose-response curves was obtained with graded doses of burimamide, demonstrating that the dilatation was mediated by histamine H_2-receptors.

Based on these findings, it has been concluded that the specific vasomotor action of histamine in the brain involves only histamine H_2-receptors, whereas the contractile effect of histamine is nonspecific. This is in contrast to extracranial arteries in which the presence of both contractile (H_1) and dilatatory (H_2) histamine receptors has been established during *in vitro* conditions. These observations open the possibility that histamine will mediate both vasoconstriction and vasodilatation, depending on the experimental conditions.

Angiography of the anterior cerebral artery of the monkey (694) has revealed that histamine in a dose of 50 μg/kg induces a marked dilatation. When the dose is increased to 150 μg/kg of histamine the vessel diameter is not changed. However, 300 μg/kg of histamine produces a uniform constriction of the anterior cerebral artery. This study substantiates the importance of the two types of histamine receptors that have been observed in the *in vitro* studies cited above.

Early studies on the intravenous administration of histamine have shown uniformly a vasodilatation in the cerebral vascular bed (641). The intra-arterial injection of this amine (in a total dose of about 14 μg) in patients, produces an immediate vasodilation reaching its maximum response within 10 sec and lasting less than 1 min (665). Andersson and Ku-

bicek (16) observed an increased blood flow to the brain after histamine administration (12–25 μg/kg). That Olesen and Skinhøj (511) have not obtained any increase in regional cerebral blood flow might be explained by the following facts: low dosage; the studies were performed in geriatric patients; and the intra-arterial ^{133}Xe technique has a long time constant. Furthermore, an increase in cerebrospinal fluid pressure is observed commonly after the administration of histamine (224, 511).

Taken together, the findings point to vascular effect of systemically-administered histamine that is both transient and rapid in onset. However, there is some evidence of an action of the amine on the larger cerebral vessels without significantly affecting cerebral tissue perfusion (511).

H. General Brain Stem Effects

The effects of selective stimulation and ablation of various brain stem centres have been studied extensively in a number of experimental models. Brain stem stimulation, sufficient to provoke the electrocortical "arousal" reaction, simultaneously increased cortical blood flow in the cat (303). With a nonquantitative technique for the measurement of cerebral blood flow, Molnár and Szántó (474) have reported that stimulation of the bulbar vasomotor centres increased cortical perfusion although, in their instance, cortical desynchronization did not invariably occur. Stimulation of diffuse regions throughout the pons and medulla oblongata resulted in an increase in cerebral blood flow in the monkey despite an arterial depressor response (379). The stimulation of the ascending reticular formation in the brain stem has been shown consistently to increase cerebral blood flow in the anaesthetised primate. Furthermore, such increases in blood flow were accompanied, or caused, by increases in cerebral oxygen consumption and, less invariably, by desynchronization of the electroencephalogram (456, 460).

The preceeding five studies (303, 379, 456, 460, 474) have a number of common features. In the first instance, the brain areas in which stimulation evoked an increase in cerebral perfusion were generally sited caudal to the mesencephalon and rostral to the upper third of the pons. The approximate distribution of these areas, transferred to the human brain, is shown in fig. 3. These areas can be compared to the known localisation of the ascending reticular activating system and the telencephalic projections of the locus coeruleus, also shown in fig. 3. Secondly, the increases in blood flow were accompanied usually by an increase in cerebral metabolism or by activation of the electroencephalogram, were either of those parameters measured. Accordingly, most workers would consider that the increased perfusion associated with pontine stimulation is an example of the ability of the cerebral vasculature to respond to changing metabolic requirements. Many examples of such a response can be cited: the increase in blood flow in the visual pathways after photic stimulation (56, 341); the increase in blood flow in areas contiguous to an epileptogenic focus (674); the increase in regional cerebral blood flow after spatial and verbal tests in awake man (571); and the decreases and increases in blood flow in slow wave and paradoxical sleep respectively (28, 565, 671).

A different cerebrovascular pattern emerges from the placement of brain lesions (fig. 3). High medullary, pontine, and mesencephalic lesions reduce both metabolism and blood flow in the cerebrum, as well as greatly attenuating the cerebrovascular responsiveness to induced hypercapnia. A most marked depression of cerebral blood flow and oxygen consumption has been noted in a patient with well-defined lesion in the upper brain stem (301, 304) and this finding has been confirmed in series of comatose patients with less precisely located lesions (280). Destructive lesions in the brain stem decrease the cerebral circulatory responsive-

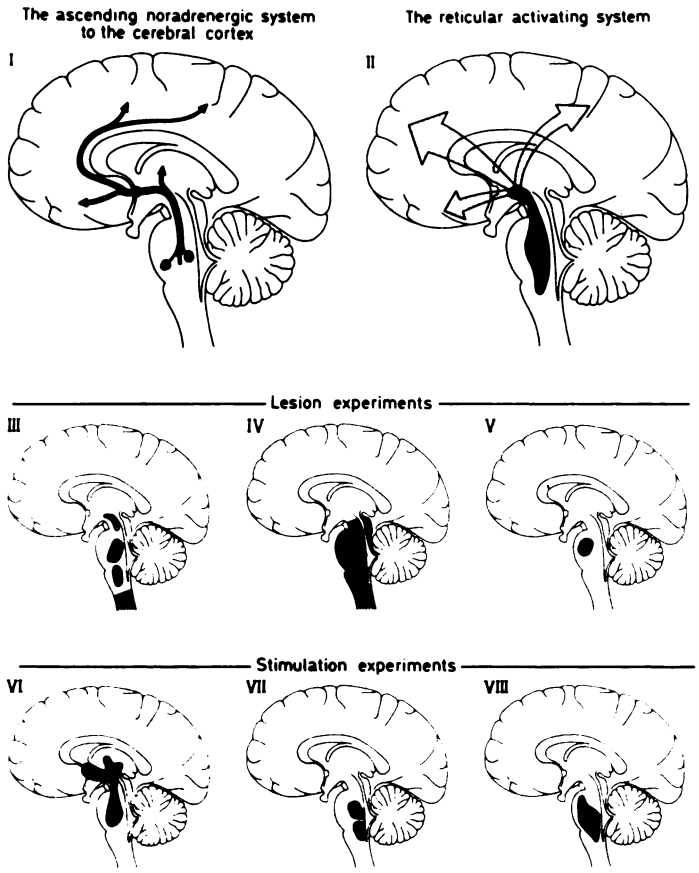


FIG. 3. Representation of some cerebral circulatory studies in which either stimulation or lesions of the brain stem have been examined. In order to allow comparison, the various studies have been transferred to a midsagittal section of the human brain. Sections I and II indicate the positions of the ascending noradrenergic system and the ascending reticular activating system respectively. In section III the blocked areas show those lesioned sites which abolished the cerebral CO_2 reactivity in dogs (623). The stippled areas in this, and the remaining sections, are those areas in which no effect was noted. Brain stem transections (81) and pontine cold lesions (183) abolished CO_2 reactivity in cats, as shown in sections IV and V respectively. Sections VI to VIII illustrate some studies in rhesus monkeys and baboons which demonstrated brain stem sites, the stimulation of which resulted in an increase in cerebral blood flow and metabolism (379, 456, 460).

ness to pCO_2 in anaesthetised dogs (623), although these studies were based on arteriovenous oxygen content differences and the results must accordingly be qualified. Cold injury lesions to the lateral aspect of the pons firstly increase blood flow in the contralateral hemisphere and then, along with the establishment of brain stem oedema, decrease the reactivity of the cerebral circulation to changing arterial pCO_2 (183). Brain stem transections rostral, but not caudal, to the pontomedullary junction would seem to abolish the cerebrovascular CO_2 reactivity (81). Such studies might indicate that there is a brain stem centre, responsive to changing pCO_2, which mediates the cerebral circulatory responses to hypo- and hypercapnia. However, such a possibility is ruled out by the investigation of Skinhøj and Paulson (636) who demonstrated that the intravertebral infusion of hypercapnic blood did not affect cerebral blood flow through the frontal and parietal regions but did increase cerebellar blood flow, although the intracarotid infusion of the same blood increased cerebral perfusion. Therefore, the most acceptable and simplest explanation for the brain stem

effects on the cerebral circulatory responsivenss to CO_2 must be that there is a brain stem system which, although not in itself sensitive to CO_2, sensitises cerebrovascular smooth muscle to carbon dioxide. This brain stem system is probably part of the ascending reticular activating system and, possibly, is one of the ascending monoaminergic pathways. This theory would be supported by the fact that barbiturates decrease the CO_2 reactivity of the cerebral circulation (210, 250). Other agents such as propranolol (426) and the prostaglandin inhibitor, indomethacin (530), are able to reduce, or abolish, the CO_2 response for reasons unexplained as yet.

Hereto, few studies have examined the specific influence of the ascending aminergic systems on the cerebral circulation. Raichle *et al.* (545) have reported that "selective" stimulation of the locus coeruleus with carbachol decreased cerebral blood flow and that the intraventricular administration of the *alpha*-receptor blocking agent phentolamine, had the opposite effect. However, there is little to support the thesis that direct injection of carbachol into an area as complex as the brain stem would specifically stimulate central noradrenergic neurons. Furthermore, the observations of Raichle *et al.* (545) were performed on an extremely limited number of experiments. A second investigation found that stimulation of the intracerebral noradrenergic pathway increased hypothalamic blood flow, as measured by the ^{133}Xe injection technique. The disadvantages and limitations of this method have been mentioned earlier (583). The results of these two studies (545, 583) are most interesting but it must be stressed that biochemical (324, 400, 690) or histochemical (400) proof of selective interference with the aminergic pathways must be preferred. Histological evidence of proximity to these pathways is *not* sufficient, especially when species other than the rat (in which the majority of the research has been performed) are used to study the central aminergic systems. The profound effects of brain stem stimulation and ablations on the EEG, perhaps with secondary cerebral metabolic and respiratory effects, again emphasises for the necessity of control data in central aminergic investigations (208, 406, 475, 476).

VII. Involvement of Aminergic Mechanisms

A. Autoregulation to Changing Arterial and Intracranial Pressure

The cerebral circulation displays autoregulation, a phenomenon which may be defined as the intrinsic ability of an organ or tissue to maintain a relatively constant blood flow in the face of moderate changes in perfusion pressure (the difference between mean arterial pressure and intracranial pressure). Autoregulation ensures, firstly, that the supply of oxygen, glucose, and other essential nutrients is maintained constant, and secondly, that cerebral capillary pressure is maintained within normal limits.

The constancy of cerebral blood flow is achieved by the dilatation of cerebral arterioles in response to a reduction in perfusion pressure. The converse occurs when perfusion pressure is increased. However, when perfusion pressure is reduced there is a point at which the arteriolar dilatation is near maximal and further reductions in perfusion pressure will result in a fall in cerebral blood flow. This point is termed the lower limit of autoregulation. Similarly, as perfusion pressure is increased there is a point at which the increase in cerebrovascular resistance is maximal and further increases in perfusion pressure result in an increase in cerebral blood flow. This point is termed the upper limit of autoregulation. These upper and lower limits of autoregulation are not absolute, unchangeable values, since the limits may be affected by diverse factors such as chronic hypertension and the degree of activity in the sympathetic nerves that innervate the cerebral vessels.

Autoregulation may be impaired or abolished by a number of situations that would include severe hypercapnia, reactive hyperaemia (or, in general, any form of hypoxia), diabetes mellitis, and carotid artery ligation or vasospasm. In almost all types of intracranial pathology (embolic, ischaemic, and neoplastic), a disturbed autoregulation will be noted. Furthermore, autoregulation is a sensitive and fragile mechanism and may readily be impaired by a number of experimental manoeuvres.

Nature of autoregulation. Autoregulation is a fundamental cardiovascular phenomenon and, as such, has been noted in almost every organ or type of tissue. Without exception, autoregulation is believed to be an intrinsic feature of these tissues and, in organs such as skeletal muscle and kidney, autoregulation can *only* be demonstrated after either surgical denervation or the use of sympatholytic agents (for review, see 199). With the kidney as an example, a reduction in perfusion pressure by haemorrhage results in renal vasoconstriction (32, 350, 361, 692). However, in the isolated kidney when autonomic and humoral influences have been removed, constancy of blood flow is seen after a reduction in perfusion pressure (198, 288). Similarly, autoregulation to graded haemorrhage is noted in kidneys treated by sympathectomy (361) or after the administration of a ganglionic blocking agent (32). A reduction in renal perfusion pressure by graded occlusion of the abdominal aorta does not affect autoregulation of renal blood flow (32).

From such investigations has arisen the concept that renal autoregulation is essentially an intrinsic mechanism; but autoregulation may be overridden by the profound renal vasoconstriction, mediated by the adrenergic innervation and the increased levels of circulating catecholamines which accompanies haemorrhagic shock.

Neither acute nor chronic superior cervical sympathectomy alters the normal pressure/flow relationship of the cerebral circulation (163, 189, 654, 691). Neither does administration of *alpha*-adrenergic blocking agents, such as phentolamine and phenoxybenzamine, impair autoregulation (189, 459, 480, 631). Cerebral autoregulation is still present after the induction of hypotension with ganglionic blocking agents, such as pentolinium, hexamethonium, and trimetaphan (87, 134, 188, 296): Such agents will presumably interrupt both sympathetic and parasympathetic transmission, including that of the cholinergic innervation of the cerebral circulation.

Autoregulation in the spinal cord remains intact after high cervical cord transection—in other words, after separation of the spinal cord from the cerebral control of the sympathetic nervous system (347, 354, 355). In patients with physiologically complete cervical cord transection, cerebral blood flow remained constant during induced hypo- and hypertension (485). These studies reinforce the viewpoint that control of autoregulation is independent of the cervical sympathetic pathways. With care, even isolated perfused brain preparations can display autoregulation (376).

The pressure in a cannulated branch of the middle cerebral artery can be changed although constancy of blood flow is noted in the vein of Labbé, which drains the area supplied by that arterial branch (663). This manoeuvre can be accomplished without affecting systemic arterial pressure and, hence, baroreceptor activity. The classical studies of Fog (193, 194, 196) and Forbes *et al.* (201) demonstrated pial arteriolar constriction (after induced hypertension) and dilatation (after induced hypotension): responses which were not impaired either by superior cervical ganglionectomy or by section of the vagus, aortic depressor, or carotid sinus nerves.

The venous-arteriolar response has been described in the cerebral circulation (172) which supports the opinion that autoregulation is a phenomenon inherent to the cerebral circulation. Earlier investiga-

tions have demonstrated that, with proportionate reductions of perfusion pressure, the cerebrovascular resistance was consistently higher when the reduction in perfusion pressure was effected by an increase in venous pressure when compared to a reduction effected by a decrease in arterial pressure (166, 171): this phenomenon is defined as the venous-arteriolar response. Such differences in cerebrovascular resistance imply the existence of a venous-arteriolar mechanism. However, in other investigations the acute elevation of cerebral venous pressure was without effect on blood flow through the brain (312, 546).

Much of the discussion about a neurogenic *control* of autoregulation is based on the eristic studies of James *et al.* (314) and Ponte and Purves (535). These workers have advanced the hypothesis that the characteristic pressure/flow relationship is reflexly controlled with the carotid sinus baroreceptors being the afferent components and the cervical sympathetic and VIIth cranial nerves being the efferent components of this reflex arc. The investigations by Purves and his colleagues (314, 535) have prompted a number of laboratories to examine the contribution of neural reflexes to the physiological responses of the cerebral circulation. However, Heistad and Marcus (281) and others (162, 550) have been unable to demonstrate any change in either focal or regional cerebral blood flow after either selective stimulation or denervation of the peripheral arterial baroreceptors.

One factor not discussed in such studies is the profound effects that selective baroreceptor stimulation can have on electrocortical activity. Carotid sinus stimulation can reduce cortical electrical activity, while occlusion below a carotid sinus blind sac induces outburst of electrocortical sham rage (26, 58, 100, 441). Such changes were potentiated by a bilateral vagotomy and abolished by section of Hering's nerves. Bearing this information in mind, it must be considered of cardinal importance to monitor electrocardial activity and cerebral metabolism during cerebral circulatory experiments that involve peripheral baroreceptive function.

The study of James *et al.* (314) would suggest that the adrenergic innervation of the cerebrovascular bed is essential for the maintenance of autoregulation. However, a later investigation (189) strongly implies that the linear pressure/flow relationship after cervical sympathectomy found by James *et al.* (314) was due to an experimental artifact—that of posthypoxic reactive hyperaemia—rather than due to the sympathectomy *per se* (207, 357, 383, 658, 659).

Cholinergic mechanisms. Some studies have implied that the autoregulatory vasodilatation to induced hypotension may be affected by the, presumably, cholinergic fibres of the VIIth cranial nerve. Support for the concept of a parasympathetic vasodilatation can be adduced from the observations of Mchedlishvili and Nikolaishvili (445) who found that the intravenous administration of atropine and other postganglionic cholinergic inhibitors abolished the autoregulatory dilatation to haemorrhagic hypotension. However, such studies are fraught with difficulties; the repeated lowering of systemic arterial pressure, by itself, will tend to attenuate or completely abolish the appropriate changes in pial vessel calibre. Although the systemic administration of atropine does not affect cerebral autoregulation (342, 584), the anticholinesterase agent, neostigmine, is able to decrease the constrictor response to an increase in cerebral perfusion pressure (19). A further caution is required. Many of these studies "quantify" an impairment in autoregulation through the use of an autoregulation index (19, 342, 508). This index is no more than:

$$\frac{\Delta CBF}{\Delta CPP}$$

where CBF is cerebral blood flow and CPP is the cerebral perfusion pressure (although this latter term is usually unjusti-

fiably simplified to the systemic arterial pressure). The fallacy in the use of an autoregulatory index, to describe an impairment in autoregulation, is that it treats the pressure/flow relationship of the cerebral circulation as a linear function. In reality, this relationship is a cubic function and the points of inflection of this function (the lower and upper limits of autoregulation) may be modulated by the factors as diverse as the degree of adrenergic nerve activity (46, 153, 189), the existence of essential hypertension (325, 652, 655), and the degree of respiratory alkalosis or acidosis (170, 269).

Shy-Drager syndrome. Patients with chronic idiopathic autonomic insufficiency, variously termed idiopathic orthostatic hypotension and the Shy-Drager syndrome, have been investigated in a number of laboratories (85, 239, 458, 485, 486, 635) in an attempt to gain further insight into the role of the autonomic innervation of the cerebral circulation. Unfortunately, this further insight has not been forthcoming and the various conflicting reports have tended to greatly confuse the issue. These discrepancies might be due in part to the fact that in some of the patients the arterial pressure was increased or decreased to levels outside the range of autoregulation in normal man. Again, it must be emphasised that the use of autoregulation "indices" will tend to obscure, rather than clarify, the issue. Furthermore, these patients show degenerative changes in the ascending and descending spinal tracts as well as in a number of brain stem nuclei (609, 624, 628, 678), including the nuclei that give rise to the central monoaminergic pathways. Because of the extreme hypotensive episodes that occur in these patients, it is to be expected that ischaemic cell changes will occur in the arterial boundary zones of the cerebral and cerebellar cortices (4, 65, 628) and autoregulation will be abolished in the ischaemic tissues (261, 524, 632). Finally, it is speculatively possible that morphological adaptations of vascular smooth muscle occur in patients with idiopathic autonomic insufficiency. In patients with chronic hypertension there is a medial hypertrophy which has marked effects on fundamental haemodynamic phenomena, such as autoregulation. Could, by analogy, there be a medial atrophy in patients with long-lasting, severe hypotension and could this affect cerebral autoregulation? When methodological artifacts, the existence of widespread neuropathological lesions, and the possibility of vascular adaptations are taken into account, one must come regrettably to the conclusion that studies in patients with idiopathic orthostatic hypotension are unlikely to shed light on the cerebrovascular role of the autonomic nervous system in man.

Chronic hypertension. In chronic hypertension there are structural vascular changes (197, 422, 630) which occur in the cerebral vascular walls and which make hypertensive subjects less tolerant to low arterial pressures: at the same time, this "structural" tone makes them more tolerant to high arterial pressures and reduces the risk of a damaging vascular crisis (326, 385). In passing, it should be noted that there is a true supersensitivity and a vascular hyper-reactivity to noradrenaline in the peripheral beds of animals with chronic renovascular hypertension (101, 187). Such phenomena have yet to be described in the cerebral circulation.

Role of the sympathetic nervous system. Notwithstanding the many negative studies, some unanimity is appearing regarding the role of the cerebrovascular sympathetic innervation in the autoregulation of cerebral blood flow. It is probable that the sympathetic nervous system imparts "functional" tone (i.e., adrenergic nervous activity) to the cerebral circulation, somewhat analogous to the "structural" tone (i.e., hypertrophy of the medial musculature) which is imparted by chronic hypertension. Activation of the sympathetic nervous system or the existence of essential hypertension can shift the upper and lower limits of autoregulation to higher

absolute levels of systemic arterial pressure in a qualitatively similar manner (fig. 4).

Fitch *et al.* (189) have demonstrated that the lower limit of autoregulation is approximately 65 mm Hg to controlled haemorrhage. Under identical experimental conditions the lower limit of autoregulation was approximately 35 mm Hg when either an acute cervical sympathectomy was performed, or the *alpha*-adrenergic blocking agent, phenoxybenzamine, was administered intravenously. The implication of such a study is that the indiscriminate sympathoadrenal discharge, which accompanies haemorrhagic hypotension, curtails the ability of the cerebral arteries to dilate at low systemic arterial pressures. When this discharge is removed, then the arteries can dilate to their maximum capacity. An independent investigation has confirmed that phenoxybenzamine treatment prevents the decrease in cerebral blood flow at low, haemorrhage-induced arterial pressures (364). A fall in arterial pressure, caused by decompressing the lower half of the body, effects a constriction, not a dilatation, of the larger cerebral arteries (60). In studies which compared profound hypotension induced by haemorrhage or by momentary cardiac arrest with hypotension induced by a ganglion blocker (trimetaphan camsylate), it was found that the cerebral angiographic circulation time was maintained at a lower absolute level of arterial pressure with the ganglionic blocking agent (401, 402). This finding has been confirmed with a more direct measure of cerebral blood flow (188). Also, in support, Hernandéz-Pérez *et al.* (284) have shown that superior cervical ganglionectomy shifted the lower limit of cerebral autoregulation to a lower absolute level of mean arterial pressure, again hypotension being induced by graded haemorrhage. An *in vitro* study by Farrar (179) has shown that, when arterial resistance is increased by noradrenaline,

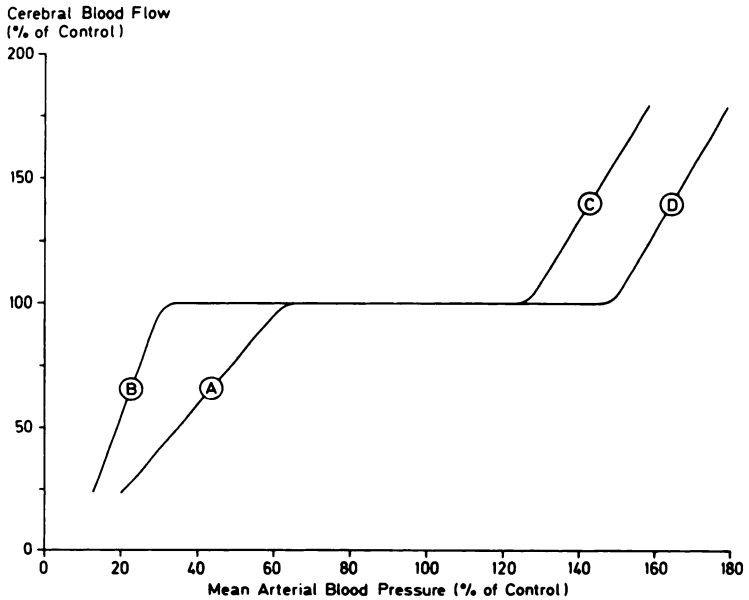


FIG. 4. A graph to illustrate the modifying effect of sympathetic nervous activity on the autoregulation of cerebral blood flow. A: The lower limit of autoregulation during haemorrhage, *i.e.*, accompanied by a marked sympathoadrenal discharge. B: The lower limit of autoregulation during haemorrhage *with* either *alpha*-adrenergic blockade or cervical sympathectomy. The lower limit of autoregulation to intracranial hypertension occurs also around this point. C: The upper limit of autoregulation to drug-induced hypertension. D: The upper limit of autoregulation to drug-induced hypertension along with stimulation of the cervical sympathetic trunk.

the lower limit of autoregulation (or "critical transmural pressure") is increased to higher values of perfusion pressure.

The concept that adrenergic nerve activity, by increasing the tone of cerebrovascular smooth muscle, can reset the range of cerebral blood flow autoregulation might explain some discrepancies between the lower limit of autoregulation to haemorrhagic hypotension and the lower limit of autoregulation to intracranial hypertension. Significant differences between the lower limits of autoregulation have been found in two comparative studies (251, 257). The former would seem to occur at perfusion pressures between 60 to 70 mm Hg (163, 188, 189, 251, 257, 269, 281, 469), whereas the latter occurs at perfusion pressure of approximately 30 mm Hg (251, 323, 469, 726). The significant difference between the two manoeuvres to alter perfusion pressure is the sympathico-adrenal system discharges throughout haemorrhagic hypotension but discharges only when extreme intracranial hypertension is reached. The Cushing type of sympathico-adrenal discharge occurs when the intracranial pressure reaches the level of the mean or even systolic arterial pressures (31, 279, 365, 380, 698), *i.e.*, at perfusion pressures far below the lower limit of autoregulation to intracranial hypertension.

Thus it would seem that, under conditions of haemorrhagic hypotension, an adrenergic-mediated vasconstriction decreases the possible range of cerebral autoregulation. An extension of such findings would be that the cerebral circulation is at a greater risk during a state of haemorrhagic or cardiogenic shock than it is when deliberate hypotension is induced during anaesthesia by autonomic blocking agents.

The effect of the sympathetic nervous system on the upper limit of autoregulation has been examined in only three investigations so far. Strandgaard *et al.* (654) were unable to demonstrate any effect of sympathetic denervation on the upper limit of autoregulation of cerebral blood flow. In retrospect, this negative result is to be expected because there would be little sympathetic activity as hypertension was induced by the intravenous infusion of angiotensin. These findings (654) are in accordance with the observation of Byrom (78) that bilateral cervical sympathectomy neither prevented nor relieved the development of hypertensive encephalopathy in rats with extreme renovascular hypertension.

The more satisfactory experiment (46) was to *stimulate* the cervical sympathetic trunk during induced hypertension (46). The stimulation shifted the upper limit of autoregulation to higher absolute levels of arterial pressure. These observations have been confirmed and extended in an investigation in anaesthetised rats (153). It would thus seem that cervical adrenergic activity can prevent or forestall the undesirable cerebral sequelae obtained in non-stimulated animals during extreme hypertension, namely hyperperfusion (180, 319, 429, 653, 654), loss of autoregulation (653), blood-brain barrier lesions (180, 258, 266, 320, 321, 429), and depressed electroencephalographic activity (320). Bevan *et al.* (43) first demonstrated that arterial pressure in normotensive man rises throughout the day to pressures that would be considered previously to be above the upper limit of cerebral autoregulation (637, 654, 655). Some of the "physiological" hypertensive episodes that were cited by Bevan *et al.* (43) included driving in traffic, heated arguments, babysitting, and coitus. The question therefore arises: Why should coitus not result in hypertensive encephalopathy? However, such hypertensive episodes are mediated by the sympathetic nervous system which is simultaneously increasing cerebrovascular resistance and so preventing breakthrough of autoregulation.

In conclusion, most workers would consider that the basic pattern of blood flow regulation in the brain is essentially the same as is found in other vascular beds; namely, there is an inherent stability of

the vessels, and the regulation of their calibre in response to local metabolic requirements is the apposition and interaction of mechanisms that involve vascular smooth muscle directly (myogenic or Bayliss responses) (29), and mechanisms that involve metabolic or mediator substances. The extrinsic adrenergic and cholinergic effects may be superimposed upon such intrinsic, basic mechanisms. Neurogenic influences may moderate, but not control, autoregulation.

B. Reactivity of the Cerebral Circulation to Changing Blood Gas Tensions

The involvement of the autonomic nervous system in the well-documented reactivity of the cerebral circulation to changes in the arterial CO_2 tension is much debated. Very little is known about possible neurogenic influences in the cerebral circulatory responses to changes in arterial oxygen content.

There are a number of experimental studies which would suggest that the cerebrovascular sensitivity to carbon dioxide is essentially a local and intrinsic phenomenon. The arteriolar dilatation that follows an increase in the arterial CO_2 tension is believed to be mediated *via* an increase in the hydrogen ion concentration of the milieu around resistance vessels in the brain. Some experiments provide strong support for such a local mechanism: the pial arteriolar dilatation after the topical injection of acid cerebrospinal fluid (CSF) solutions (685); and the blood flow increase which occurs in paraventricular tissues after the ventriculocisternal perfusion of acidic CSF (520). Additional supportive evidence for this local CO_2 hypothesis can be found in many other investigations (552, 617, 636) which, however, have yet to be reconciled with the possibility of brain stem effects on the CO_2 sensitivity of the cerebral circulation, as discussed in section VI, H.

In peripheral tissues, the local reaction of resistance vessels is to dilate in response to respiratory acidosis, but this local mechanism is overridden by central adrenergic mechanisms (118, 132). In general, both cardiac and peripheral vascular reactivity to sympathomimetic amines are reduced during hypercapnia (20, 77). A similar phenomenon has been described in the cerebral circulation as the pial arteriolar sensitivity to noradrenaline is reduced considerably when the amine is applied in an acidic CSF solution (688).

The administration of *alpha*-adrenergic blocking agents (phenoxybenzamine, phentolamine, and thymoxamine) has been shown to have little or no effect on the CO_2 sensitivity of the cerebral circulation, and especially the vasoconstriction induced by hypocapnia (291, 459, 631). In contrast, Corbett *et al.* (105) have claimed that *alpha*-adrenergic blockade can attenuate the hypocapnic vasoconstriction. A second study by this group (161) asserted that patients with a high cervical cord transection (and thus no sympathetic outflow) also failed to show a decrease in cerebral blood flow during hypocapnia. Both of these investigations (105, 161) have been strongly criticized on the grounds that the inhalation method of measuring cerebral blood flow led to artifactual results due to extracranial contamination (291, 633).

Although superior cervical sympathectomy would seem to have a minimal effect on cerebrovascular CO_2 sensitivity (651, 691), the stimulation of the cervical sympathetic trunk can effect a significant reduction in blood flow during hypercapnia (272, 314, 353). The blood flow reduction is not, however, below the base-line, normocapnic levels of blood flow. The decrease seen with both sympathetic stimulation and noradrenaline infusions during hypercapnia has led to the formulation of the "dual effects" hypothesis (270, 272, 507), which states that when the cerebral vessels are near maximally dilated as in hypercapnia, then the vasoconstrictor properties of sympathetic stimulation will be unmasked.

The involvement of the parasympathetic nervous system in cerebrovascular CO_2 reactivity has been examined to a very

limited extent. The circulatory response to hypercapnia is depressed by atropine (342, 584) and the response is enhanced by eserine (584) or by the intravertebral administration of neostigmine (19). The response to hypercapnia seemed to be unaltered by unilateral or bilateral transection of the VIIth cranial nerve which putatively contains the parasympathetic fibres, innervating the pial vasculature (290).

In any experimental study there are various factors which should be considered, as they may affect the relationship between aminergic systems and cerebrovascular CO_2 reactivity. Hypercapnia, although at narcotic concentrations of CO_2, can increase the penetrability of the blood-brain barrier (112, 235). The CO_2 reactivity is directly related to the resting oxygen utilization of the brain (210; see fig. 5). Experimental spasm or ligation of the major extracranial arteries reduces the CO_2 sensitivity (273), as does moderate hypotension (274). Extreme hypotension abolishes the CO_2 sensitivity (274). Finally, it should be remembered that metabolic acidosis or alkalosis will not affect cerebral blood flow (271) unless the blood-brain barrier is disrupted (519).

The possibility that the cerebral circulatory responses to changing arterial gases are reflex, and not local, in nature has been opened by the study by Ponte and Purves in 1974 (535). These workers suggested that the response of the cerebral blood vessels to hypercapnia and, especially, hypoxia was reflexly controlled *via* the peripheral arterial chemoreceptors. However, two later investigations have been unable to show any effect of chemodenervation or the cerebral circulatory responses to hypoxia (282, 672), and, moreover, selective stimulation of the carotid chemoreceptors was unable to effect any changes in cerebral blood flow (282). It would also seem that pial arterioles will dilate when hypoxic solutions of CSF are applied directly to them (553). Hypoxia will still elicit an increase in cerebral blood flow after bilateral section of the VIIth cranial nerve (290), the proposed efferent limb of the chemoreceptor reflex.

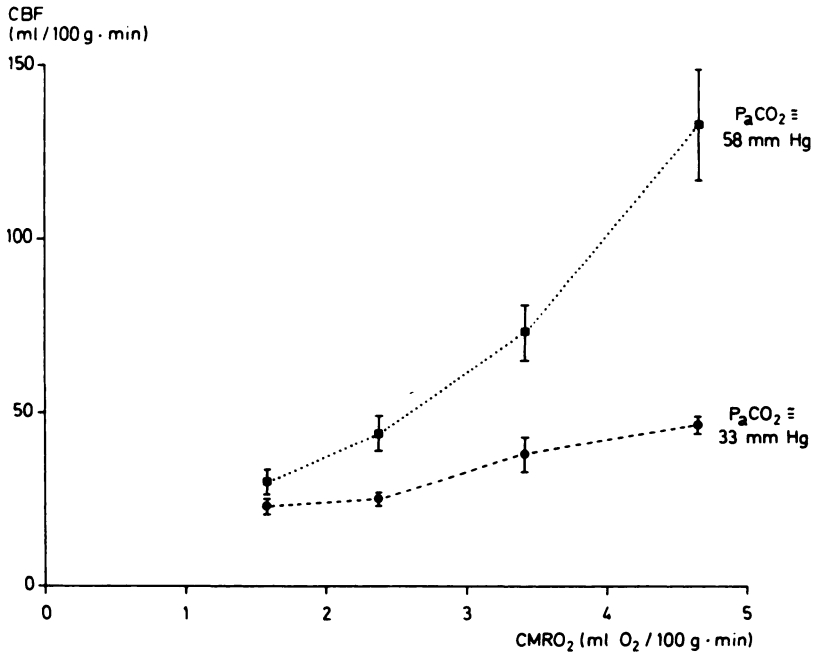


FIG. 5. The relationship between blood flow and metabolism in the dog brain, both at normocapnia and at hypercapnia. Cerebral oxygen consumption was decreased by barbiturate anaesthesia [modified from Fujishima *et al.* (210)].

Apart from the involvement of hypoxia in the chemoreceptor reflex, there has been no examination of the relationship between aminergic mechanisms and the cerebral circulatory responses to changing arterial O_2 tensions. The basic hypoxic response, with its threshold at a pO_2 between 50 and 60 mm Hg, has been well described (358, 444). Likewise, carbon monoxide intoxication increases cerebral blood flow in a graded manner (430). In peripheral tissues hypoxia relaxes vascular smooth muscle both *in vitro* (86, 125) and *in vivo* (119, 132). However, *in vitro* investigations are complicated frequently by changing arterial pressure during exposure to hypoxia and it should be noted that hypoxia results in a loss of cerebrovascular autoregulation (357).

C. Intracranial Pressure and CSF Formation

The cerebral blood volume and the rate of formation of CSF are two factors that could influence intracranial pressure. In this context, it is convenient to look upon the choroid plexus as part of the cerebrovascular bed with special functions involved in another cerebral circulatory system, namely that of the CSF. There is reason to believe that both factors in turn could be influenced by the autonomic nervous system. The venous system of the brain—as the main capacitance component, containing the greater fraction of the total cerebral blood volume—receives sympathetic fibres that have been demonstrated by fluorescence histochemistry (137, 489, 516). The pial system has, furthermore, been shown to possess a cholinergic innervation of similar density as the adrenergic system (145). Light microscopy has shown that in the choroid plexus tissue adrenergic (148) and cholinergic (143) nerve terminals run adjacent both to the epithelial cells which produce CSF and to the choroidal vessels. Electronmicroscopic studies on cat and rabbit plexuses have revealed nonmyelinated axon terminals in close relation both to epithelial cells (distance 20 nm) and to smooth muscle cells (distances less than 100 nm) of small arterioles (140). These nerve terminals fulfil the ultrastructural criteria necessary for a true innervation.

The observation that ventricular fluid pressure is reduced to below base-line levels 1 day after sympathectomy would tend to confirm the fact that noradrenaline can stimulate cerebrovascular receptors during the early stage of degeneration (157). When the sympathetic nerves have lost their noradrenaline, 3 to 6 days postoperatively, the ventricular fluid pressure is higher than in the control state (157). The pressure returns to base-line levels about 2 weeks after the sympathectomy (157) which could be due to the progressive development of denervation supersensitivity (378).

When comparing the changes in ventricular fluid pressure after sympathectomy with the sequence of corresponding changes in cerebral blood volume it is evident that the patterns resemble each other closely (147, 155). It should be noted that the cerebral blood volume measurements were performed on smaller animals (mice rather than rabbits) and the denervation effects occur more rapidly.

Measurements of choroidal carbonic anhydrase activity have been performed and used as a functional parameter of CSF production, to which carbonic anhydrase activity is related (140). The enzyme activity increases after the elimination of noradrenaline from the choroidal plexuses either by reserpine treatment or by sympathetic denervation (140). The enzyme activity returns to normal when denervation supersensitivity develops 1 week later (140). These observations show that the choroid plexus is innervated by sympathetic nerves from the superior cervical ganglia that inhibit the production of CSF.

D. Functional Activity

Rather than reviewing the enormous field that associates aminergic mechanisms with behaviour, it was considered

worthwhile to examine a few, well-documented situations in which amines are related to marked changes in neuronal activity and these, in turn, are related to changes in cerebral perfusion. These situations are anxiety, stress, sleep, intellectual effort, and the behavioural changes resulting from the administration of either amphetamine or lysergic acid diethylamide (LSD). Common to all these situations is that objective evidence of changes in brain function can be obtained. In many of these functional states, there are clear changes in cerebral metabolism as well as blood flow.

Brain amines are released during stressful conditions. Swimming and running exhaustion cause a decrease in brain serotonin and noradrenaline levels (23). Other types of stressful conditions (foot shocks, fighting, self-stimulation, exposure to cold, and immobilisation) increase brain noradrenaline turnover (360) and decrease total brain noradrenaline (50, 440). It is widely accepted that the ascending catecholamine neurons participate in the maintenance of wakefulness. The dopamine neurons of the nigrostriatal system are of importance for normal behaviour (behavioural arousal), while the noradrenergic neurons of the locus coeruleus, projecting *via* the dorsal tegmental catecholamine bundle to certain forebrain areas such as the cerebral cortex, are of importance for the electrocortical aspects of wakefulness, that is, cortical arousal (398, 399).

Furthermore, conditions such as immobilisation stress have been observed to be accompanied by an increase in brain oxygen consumption and blood flow (83). These effects were abolished almost completely by adrenalectomy or by the administration of the *beta*-receptor blocking agent, propranolol (83). Such findings indicate that peripheral, as well as central, catecholamines might be involved in the activation of the cerebral circulation to stress. As it has been demonstrated that catecholamines can cross the blood-brain barrier to a certain extent (268, 502), the amines which are released from peripheral storage sites (adrenal gland, sympathetic nerves) may well affect cerebral blood flow directly or indirectly. Electrocortical activation results from the intravenous infusion of catecholamines and from drug-induced hypertension (58, 437, 538) and this observation might, in part, account for the cerebral circulatory responses to stress.

Amphetamine is used commonly in behavioural studies. The central excitation caused by amphetamine is mediated *via* catecholamine mechanisms (106) and these effects are thought to be due to the release of central noradrenaline and dopamine (106). Abreu *et al.* (1) and Shenkin (625) found no consistent effect on brain oxygen consumption or on cerebral blood flow after the administration of amphetamine. This lack of effect is not surprising, as the dose used (less than 0.4 mg/kg) is a fraction of the amount subsequently employed in studies of monoamine metabolism. If amphetamine is given, enormous increases in both oxygen consumption and blood flow occur (84). The effects produced by amphetamine are as great as those observed during the extremes of hypercapnia, hypoxia, and epileptic seizures (Siesjö, personal communication). Similarly, the hallucinogen, lysergic acid diethylamide, increases blood flow in specific areas of the brain, notably the frontal and parietal cortices and the cerebellum (236).

Brain amines are implicated in the functional changes of sleep. Sleep can be divided into two types: one synchronised phase ("slow wave sleep") and one desynchronised phase ("paradoxical or rapid eye movement (REM) sleep"). It seems that slow wave sleep is controlled by the serotonin-containing neurons of the raphé system (93, 331, 473) and wakefulness is controlled by catecholamine-containing neurons of the reticular activating system of pons and mesencephalon (362, 363). The exact role of amines in paradoxical sleep is not determined, but there is an involve-

ment of noradrenaline as well as acetylcholine neuron systems (339, 537). A small increase in blood flow was reported by Mangold *et al.* (436) during sleep, the increase being unrelated to any change in PCO_2 and overall cerebral metabolism. Cerebral blood flow is enhanced markedly during paradoxical sleep (28, 565, 620, 671). This increase in regional blood flow was less pronounced in man (620, 671) than it was in cats where flow doubled in some regions (565).

The solution of arithmetical problems—as a model for mental effort—on brain circulation and metabolism has been studied (642). Hereto, no changes in total flow or metabolism have been noted. Thus, it seems that even concentrated mental effort does not lead to a noticeable increase in total cerebral blood flow. Risberg and Ingvar (572), on the other hand, have observed a redistribution of regional cerebral blood flow during psychological tasks. This observation indicates that an increase in activity in some parts of the brain may be accompanied by a reduction in others, overall cerebral blood flow being unchanged. Such differences in cerebrovascular reactivity have been observed, as certain brain regions respond well to adrenergic agents although other regions respond to a much lesser extent (615).

In normal brain there are unequivocal relationships between neuronal activity and blood flow, and it is the factors that cause these relationships that are proving to be the greatest problem in cerebral circulatory physiology. What are the factors that link activity, metabolism, and flow in the brain? Because of their wide-ranging functional, metabolic, and vascular effects it would be unwise to dismiss amines, and they should be considered as candidates for these physiological linkages. One further associationship might be considered: there is a voluminous literature which relates dysfunction of the central monoaminergic systems to the affective disorders, such as mania and depression, and to schizophrenia (61, 120, 126, 601, 602). The pattern of regional cerebral blood flow is markedly different from normal in patients with dementia or schizophrenia (253, 300).

VIII. Conclusions

A large number of factors must be considered in every experimental study into the relationship between amines and the cerebral circulation. We have tried to discuss these factors in a critical manner and fig. 6 is our attempt at summarising them.

There is abundant evidence that larger ("inflow tract") arteries and pial arterioles are innervated by both adrenergic and cholinergic fibres. There can be little doubt that the intraparenchymal arterioles receive a sympathetic innervation. It is currently a matter of debate as to whether the cerebral capillaries are innervated by fibres from the central noradrenergic pathways. If so, such an arrangement would be a unique and intriguing feature.

The blood-brain barrier to amines and amine precursors could be thought of as two very differing entities. There is both a structural barrier (an anatomical continuum of cerebral capillary endothelial cells) and an enzymatic barrier (dopa decarboxylase, monoamine oxidase, and other enzymes are connected within these endothelial cells). The extent of these barrier mechanisms is not yet known conclusively and, likewise, it is not known whether they protect the cerebrovascular smooth muscle of all the cerebral resistance vessels from circulating amines. Amines and amine precursors penetrate the barrier to varying degrees. Not only does the barrier affect the passage of amines, but some amines could well affect the integrity of the barrier. Some factors, such as hypertension, can disrupt the barrier and these are important in understanding the difference between a number of experimental studies.

It should be remembered that the cerebral parenchyma contains many aminergic cell systems which, although probably not vasomotor in nature, could influ-

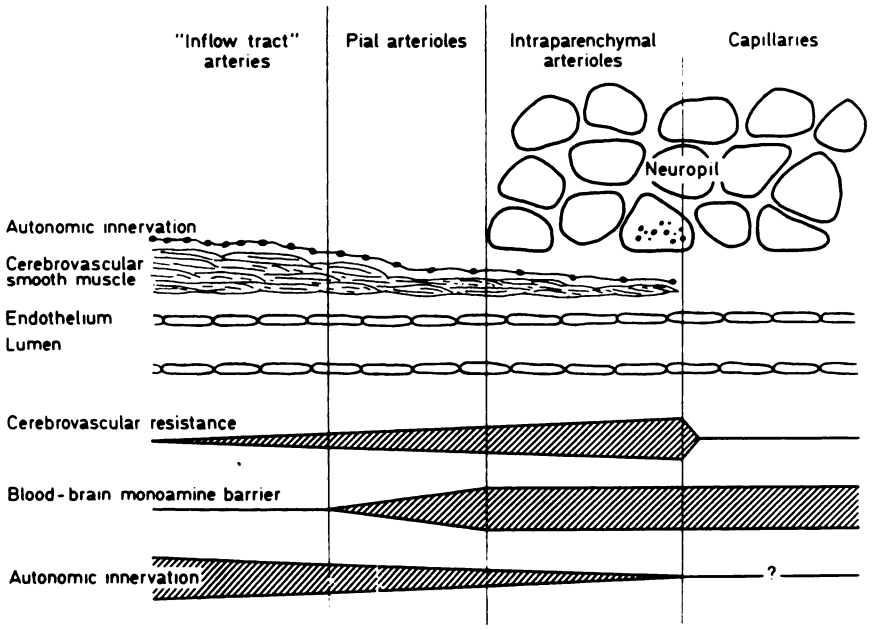


FIG. 6. Schematic diagram of the factors to be considered in the relationship between amines and the cerebral circulation. See text for details.

ence cerebrovascular smooth muscle either by diffusion of their contents through the interstitial fluid or by secondary effects on other parenchymal cells. It is widely accepted that the endogenous amines can stimulate carbohydrate metabolism in most tissues of the body, including the brain. Numerous investigations would tend to suggest that the metabolic stimulation by the catecholamines is mediated by *beta*-adrenoreceptors. The linkages between brain metabolism and blood flow are not understood, and we suggest that the possible involvement of amines in the intrinsic relationship between flow, metabolism, and functional activity is worthy of further attention.

The findings of any particular study on the cerebral circulation will be no better than the method used. A multitude of techniques exist that purport to measure cerebral blood flow. Very few of them do so. The reliability and accuracy of each technique must be examined critically before any weight can be placed on the biological importance of the findings. In the majority of experimental animals, and to a lesser extent primates, including man, considerable difficulties can arise because of inability to differentiate adequately between the cerebral and the extracranial circulations. Another experimental artifact that has to be borne in mind is the effect of trauma associated with a number of techniques. Those methods that are based upon the Fick principle have yielded the most meaningful results in the past. However, techniques designed to measure blood flow in discrete regions of the brain might well prove to be the most revealing in future investigations.

A number of amine receptors have been demonstrated through the use of *in vitro* and *in vivo* techniques. The existence of these receptors satisfies the fundamental criterion for a functional role for amines in the vasculature. Nevertheless, correctly designed experiments have yet to be performed that would examine the interactions between amines and vascular smooth muscle under physiological conditions. Little can be said about the involvement of amines in pathological conditions.

Most of the current knowledge about aminergic nerves relates to the sympathetic system, few studies having exam-

ined the cholinergic system. It might be profitable to pay more attention to the cholinergic and central amine systems. The use of neurotoxic agents and selective lesions might elucidate the influence of brain stem centres (and, especially, the aminergic components of the reticular system) or the cerebral circulation. However, just as peripheral hypersensitivity is a confusing factor in the studies on the autonomic nervous system, so might the phenomenon of central denervation supersensitivity complicate studies on the parenchymal amine systems.

The sympathetic system has a modulating role in autoregulation. It could well be that, were the extremes of the cerebral circulatory responses to carbon dioxide and hypoxia examined, further intricate roles of the autonomic nervous system might possibly be elucidated.

We find it disturbing that this review has had to concentrate on problems of interpretation and approach, rather than positive findings, regarding amine mechanisms in the cerebral circulation. However, this balance reflects the complexity of the problem, and it is evident that the more complex the problem the more elusive the solution.

Acknowledgments. We would like to thank our colleagues in Lund and Glasgow who gave many helpful suggestions during the preparation of this manuscript and, in particular, Jan-Erik Hardebo, Olle Lindvall and Jack O. Rowan. Our thanks go also to our secretaries and, especially, to Margaret Stewart and Alan Young, who obtained and checked the references.

We are indebted greatly to our mentors, Christer Owman and A. Murray Harper, who have given us enormous support, advice, encouragement, and criticism throughout.

REFERENCES

1. Abreu, B. E., Liddle, G. W., Butkes, A. L., Sutherland, V., Elliott, H. W., Simon, A. and Margolis, L.: Influence of amphetamine sulfate on cerebral metabolism and blood flow in man. J. Amer. Pharm. Ass. Sci. Ed. 38: 186–188, 1949.
2. Adachi, M. and Feigin, I.: Cerebral oedema and the water content of normal white matter. J. Neurol. Neurosurg. Psychiat. 29: 446–450, 1966.
3. Adachi, M., Rosenblum, W. I. and Feigin, I.: Hypertensive disease and cerebral oedema. J. Neurol. Neurosurg. Psychiat. 29: 451–455, 1966.
4. Adams, J. H., Briebley, J. B., Connor, R. C. R. and Treip, C. S.: The effects of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. Brain 89: 235–268, 1966.
5. Albert, S. N., Albert, C. A. and Fazekas, J. F.: A rapid and simple method for measuring the rate of cerebral blood flow in humans with krypton^{85}. J. Lab. Clin. Med. 56: 473–482, 1960.
6. Alexander, S. C., Wollman, H., Cohen, P. J., Chase, P. E., Melman, E. and Behar, M.: Krypton^{85} and nitrous oxide uptake of the human brain during anesthesia. Anesthesiology 25: 37–42, 1964.
7. Alksne, J. F.: The passage of colloidal particles across the dermal capillary wall under the influence of histamine. Quart. J. Exp. Physiol. Cog. Med. Sci. 44: 51–66, 1959.
8. Allen, G. S., Henderson, L. M., Chou, S. N. and French, L. A.: Cerebral arterial spasm. Part I: *In vitro* contractile activity of vasoactive agents on canine basilar and middle cerebral arteries. J. Neurosurg. 40: 433–441, 1974.
9. Alm, A.: Radioactively labelled microspheres in regional cerebral blood flow determinations. A study on monkeys with 15 + 35 μm spheres. Acta Physiol. Scand. 95: 60–65, 1975.
10. Alm, A. and Bill, A.: The effect of stimulation of the cervical sympathetic chain on retinal oxygen tension and on unveal, retinal and cerebral blood flow in cats. Acta Physiol. Scand. 88: 84–94, 1973.
11. Alman, R. W., Rosenberg, M. and Fazekas, J. F.: Effects of histamine on cerebral hemodynamics and metabolism. Arch. Neurol. Psychiat. (Chicago) 67: 354–356, 1952.
12. Andén, N.-E., Dahlström, A., Fuxe, K., Larsson, K., Olson L. and Ungerstedt, U.: Ascending monoamine neurons to the telencephalon and diencephalon. Acta Physiol. Scand. 67: 313–326, 1966.
13. Andén, N.-E., Engel, J. and Rubenson, A.: Mode of action of L-DOPA on central noradrenaline mechanisms. Naunyn-Schmiedeberg's Arch. Pharmakol. Exp. Pathol. 273: 1–10, 1972.
14. Andén, N.-E., Rubenson, A., Fuxe, K. and Hökfelt, T.: Evidence for dopamine receptor stimulation by apomorphine. J. Pharm. Pharmacol., 19: 627–629, 1967.
15. Anderson, R. E., Waltz, A. G., Yamaguchi, T. and Ostrom, R. D.: Assessment of cerebral circulation (cortical blood flow) with an infra-red microscope. Stroke 1: 100–103, 1970.
16. Anderson, W. D. and Kubicek, W. G.: Effects of betahistine HCl, nicotinic acid and histamine on basilar blood flow in anesthetized dogs. Stroke 2: 409–415, 1971.
17. Anderssón, B. and Jewell, P. A.: The distribution of carotid and vertebral blood in the brain and spinal cord of the goat. Quart. J. Exp. Physiol. Cog. Med. Sci. 41: 462–474, 1956.
18. Anthony, M., Hinterberger, H. and Lance, J. W.: Plasma serotonin in migraine and stress. Arch. Neurol. 16: 544–552, 1967.
19. Aoyagi, M., Meyer, J. S., Deshmukh, V. D., Ott, E. O., Tagashira, Y., Kawamura, Y., Matsuda, M., Achari, A. N. and Chee, A. N. C.: Central cholinergic control of cerebral blood flow in the baboon. J. Neurosurg. 43: 689–705, 1975.
20. Atkinson, J. M. and Rand, M. J.: Reduction of cardiovascular responses to some sympathomimetic amines during hypercapnia. Eur. J. Pharmacol. 18: 166–173, 1972.
21. Barr, S.: Recording of microvascular dimensions with an image-splitter television microscope. J. Appl. Physiol. 21: 299–301, 1966.
22. Bannister, R. G. and Romanul, F. C. A.: The localization of alkaline phosphatse activity in cerebral blood vessels. J. Neurol. Neurosurg. Psychiat. 26: 333–340, 1963.
23. Barchas, J. D. and Freedman, D.: Brain amines:

Response to physiological stress. Biochem. Pharmacol. 12: 1232–1235, 1963.
24. Barrett, R. E., Fraser, R. A. R. and Stein, B. M.: A fluorescence histochemical survey of monoaminergic innervation of cerebral blood vessels in primate and humans. Trans. Amer. Neurol. Assoc. 96: 39–45. 1971.
25. Bartholini, G., Constantinidis, J., Tissot, R. and Pletscher, A.: Formation of monoamines from various amino acids in the brain after inhibition of extracerebral decarboxylase. Biochem. Pharmacol. 20: 1243–1247, 1971.
26. Bartorelli, C., Bizzi, E., Libretti, A. and Zanchetti, A.: Inhibitory control of sinocarotid pressoceptive afferents on hypothalamic autonomic activity and sham rage behaviour. Arch. Ital. Biol. 98: 308–326, 1960.
27. Baudry, M., Martres, M.-P. and Schwartz, J.-C.: H_1 and H_2 receptors in the histamine-induced accumulation of cyclic AMP in guinea pig brain slices. Nature (London) 253: 362–364, 1975.
28. Baust, W.: Local blood flow in different regions of the brain-stem during natural sleep and arousal. Electroencephalogr. Clin. Neurophysiol. 22: 365–372, 1967.
29. Bayliss, W. M.: On the local actions of the arterial wall to changes of internal pressure. J. Physiol. (London) 28: 220–231, 1902.
30. Becker, N. H., Hirano, A. and Zimmerman, H. M.: Observations of the distribution of exogenous peroxidase in the rat cerebrum. J. Neuropathol. Exp. Neurol. 27: 439–452, 1968.
31. Bees, J. W. F.: Effects of increased supratentorial pressure in cats. J. Neurol. Neurosurg. Psychiat. 37: 627–630, 1974.
32. Bell, G. and Harper, A. M.: Effects of haemorrhage on blood flow through renal cortex of dog. J. Appl. Physiol. 28: 583–588, 1970.
33. Bell, W. H., Sundt, T. M., Jr. and Nofzinger, J. D.: The response of cortical vessels to serotonin in experimental cerebral infarction. J. Neurosurg. 26: 203–212, 1967.
34. de Bellerochе, J. S., Das, I. and Bradford, H. F.: Absence of an effect of histamine, noradrenaline and depolarizing agents on the levels of adenosine 3′,5′-monophosphate in nerve endings isolated from cerebral cortex. Biochem. Pharmacol. 23: 835–843, 1974.
35. Benzi, G. and Villa, R. F.: Adenyl cyclase system and cerebral energy state. J. Neurol. Neurosurg. Psychiat. 39: 77–83, 1976.
36. Berne, R. M., Rubio, R. and Curnish, R. R.: Release of adenosine from ischemic brain. Effect on cerebral vascular resistance and incorporation into cerebral adenine nucleotides. Circ. Res. 35: 262–271, 1974.
37. Bertler, A., Falck, B., Owman, Ch. and Rosengren, E.: The localization of monoaminergic blood-brain barrier mechanisms. Pharmacol. Rev. 18: 369–385, 1966.
38. Bertler, A., Falck, B. and Rosengren, E.: The direct demonstration of a barrier mechanism in the brain capillaries. Acta Pharmacol. Toxicol. 20: 317–321, 1962.
39. Betz, A. L. and Gilboe, D. D.: Effect of pentobarbital on amines, acid and urea flux in the isolated dog brain. Amer. J. Physiol. 224: 580–587, 1973.
40. Betz, A. L., Gilboe, D. D., Yudilevich, D. L. and Drewes, L. R.: Kinetics of unidirectional glucose transport into the isolated dog brain. Amer. J. Physiol. 225: 586–592, 1973.
41. Betz, E.: Measurements of local blood flow by means of heat clearance. *In* Blood Flow through Organs and Tissues, ed. by W. H. Bain and A. M. Harper, pp. 169–176, Livingstone, Edinburgh, 1968.
42. Betz, E., Enzenross, H. G. and Vlahov, V.: Interaction of H^+ and Ca^{++} in the regulation of local pial vascular resistance. Pflügers Arch. 343: 79–88, 1973.
43. Bevan, A. T., Honour, A. J. and Stott, F. H.: Direct arterial recording in unrestricted man. Clin. Sci. (London) 36: 329–344, 1969.
44. Bevan, J. A. and Bevan, R. D.: Localized neurogenic vasoconstriction of the basilar artery. Stroke 4: 760–763, 1973.
45. Bienmüller, H. and Betz, E.: Die Regulation der lokalen corticalen Gehirndurchblutung bei Injection von Noradrenalin, Pentobarbital und Adrenolitico. Arzneimittel-Forschung, 24: 97–111, 1970.
46. Bill, A. and Linder, J.: Sympathetic control of cerebral blood flow in acute arterial hypertension. Acta Physiol. Scand. 96: 114–121, 1976.
47. Björklund, A., Falck, B. and Owman, Ch.: Fluorescence microscopic and microspectrofluorometric techniques for the cellular localization and characterization of biogenic amines. *In* Methods of Investigative and Diagnostic Endocrinology, ed. by S. A. Berson. vol. 1, The Thyroid and Biogenic Amines, ed. by J. E. Rall and I. J. Kopin, pp. 318–368, North Holland Publishing Co., 1972.
48. Björklund, A., Nobin, A. and Stenevi, U.: The use of neurotoxic dihydroxytryptamines as tools for morphological studies and localized lesioning of central indolamine neurons. Z. Zellforsch. Mikroskop. Anat. 145: 479–501, 1973.
49. Blasberg, R. G., Patlak, C. and Fenstermacher, J. D.: Intrathecal chemotherapy: Brain tissue profiles after ventriculo-cisternal perfusion. J. Pharmacol. Exp. Ther. 195: 73–83, 1975.
50. Bliss, E. L. and Zwanziger, J.: Brain amines and emotional stress. J. Psychiat. Res. 4: 189–198, 1966.
51. Bodenheimer, T. S. and Brightman, M. W.: A blood-brain barrier to peroxidase in capillaries surrounded by perivascular spaces. Amer. J. Anat. 122: 249–268, 1968.
52. Bodor, N., Shek, E. and Higuchi, T.: Delivery of a quaternary pyridinium salt across the blood-brain barrier by its dihydropyridine derivative. Science 190: 155–156, 1975.
53. Bohr, D. F., Goulet, P. L. and Taquini, A. C., Jr.: Direct tension recording from smooth muscle of resistance vessels from various organs. Angiology 12: 478–485, 1961.
54. Bolwig, T. G., Hertz, M. M., Paulson, O. B., Spotoft, H., Rafaelsen, O. J. and Lassen, N. A.: Blood-brain barrier permeability during hyperosmolality and during electrically induced seizures in man. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 3.3–3.7. Churchill Livingstone, Edinburgh, 1975.
55. Bolwig, T. G. and Lassen, N. A.: The diffusion permeability to water of the rat blood-brain barrier. Acta Physiol. Scand. 93: 415–422, 1975.
56. Bondy, S. C., Lehman, R. A. W. and Purdy, J. L.: Visual attention affects brain blood flow. Nature (London) 248: 440–441, 1974.
57. Bondy, S. C. and Purdy, J. L.: Selective regulation of the blood-brain barrier by sensory input. Brain Res. 76: 542–545, 1974.
58. Bonvallet, M., Dell, P. and Hiebel, G.: Tonus sympathique et activité électrique corticale. Electroencephalogr. Clin. Neurophysiol. 6: 119–144, 1954.
59. Borodulya, A. V. and Pletchkova, E. K.: Distribution of cholinergic and adrenergic nerves in the internal carotid artery. Acta Anat. 86: 410–425, 1973.
60. du Boulay, G., Symon, L., Shah, S., Dorsch, N. and Ackerman, R.: Cerebral arterial reactivity and spasm after subarachnoid haemorrhage. Proc. Roy. Soc. Med. 65: 80–82, 1972.
61. Boulton, A. A.: Biochemical research in schizophre-

nia. Nature (London) 231: 22–28, 1971.
62. Bradbury, M. W. B., Patlak, C. S. and Oldendorf, W. H.: Analysis of brain uptake and loss of radiotracers after intracarotid injection. Amer. J. Physiol. 229: 1110–1115, 1975.
63. Brawley, B. W.: Construction of a regional cerebral blood flow probe using a peltier device. J. Surg. Res. 9: 395–398, 1969.
64. Brierley, J. B.: The penetration of ^{32}P into the nervous tissues of the rabbit. J. Physiol. (London) 116: 24–25P, 1952.
65. Brierley, J. B., Brown, A. W., Excell, B. J. and Meldrum, B. S.: Brain damage in the Rhesus monkey resulting from profound arterial hypotension. I. Its nature, distribution and general physiological correlates. Brain Res. 13: 68–100, 1969.
66. Brightman, M. W.: The distribution within the brain of ferritin injected into cerebrospinal fluid compartments. I. Ependymal distribution. J. Cell Biol. 26: 99–123, 1965.
67. Brightman, M. W.: The distribution within the brain of ferritin injected into cerebrospinal fluid compartments. II. Parenchymal distribution. Amer. J. Anat. 117: 193–220, 1965.
68. Brightman, M. W., Hori, M., Rapoport, S. I., Reese, T. S. and Westergaard, E.: Osmotic opening of tight junctions in cerebral endothelium. J. Comp. Neurol. 152: 317–326, 1973.
69. Brightman, M. W. and Reese, T. S.: Junctions between intimately apposed cell membranes in ther vertebrate brain. J. Cell Biol. 40: 648–677, 1969.
70. Broman, T., Forssman, B. and Olsson, O.: Further experimental investigations of injuries from contrast media in cerebral angiography. Acta Radiol. (Stockholm) 34: 135–145, 1950.
71. Broman, T. and Olsson, O.: The tolerance of cerebral blood vessels to a contrast medium of the diodrast group. An experimental study of the effect on the blood-brain barrier. Acta Radiol. (Stockholm) 30: 326–342, 1948.
72. Broman, T. and Olsson, O.: Experimental study of contrast media for cerebral angiography with reference to possible injurious effects on the cerebral blood vessels. Acta Radiol. (Stockholm) 31: 321–334, 1949.
73. Browning, E. T.: Metabolic effects of norepinephrine and papaverine in C-6 astrocytoma cells. Fed. Proc. 32: 679, 1973.
74. Bulat, M. and Supek, Z.: The penetration of 5-hydroxytryptamine through the blood-brain barrier. J. Neurochem. 14: 265–271, 1967.
75. Bulat, M. and Supek, Z.: Passage of 5-hydroxytryptamine through the blood-brain barrier; its metabolism in the brain and alimination of 5-hydroxyindoleacetic acid from the brain tissue. J. Neurochem. 15: 383–389, 1968.
76. Burkard, W. P.: Adenylate cyclase in the central nervous system. Progr. Neurobiol. 4: 241–267, 1975.
77. Bygdeman, S. and von Euler, U. S.: The effect of respiratory acidosis upon the peripheral vascular reactivity to noradrenaline in the cat. Acta Physiol. Scand. 54: 138–146, 1962.
78. Byrom, F. B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. Lancet ii: 201–211, 1954.
79. Cameron, B. D.: Determination of regional cerebral cortical blood flow using a heat clearance technique. Phys. Med. Biol. 15: 715–722, 1970.
80. Cameron, I. R., Davson, H. and Segal, M. B.: The effect of hypercapnia on the blood-brain barrier to sucrose in the rabbit. Yale J. Biol. Med. 42: 241–247, 1970.
81. Capon, A.: Effects of acute sections of the brain stem on hypercapnic vasodilatation of cerebral and spinal vessels. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennet, J. D. Miller and J. O. Rowan, pp. 1.16–1.17, Churchill Livingstone, Edinburgh, 1975.
82. Cappelen, C., Jr. and Hall, K. V.: Electromagnetic blood flowmetry in clinical surgery. Acta Chir. Scand. 368: 1–27, 1967.
83. Carlsson, Ch., Hägerdal, M. and Siesjö, B. K.: Increase in cerebral oxygen uptake and blood flow in immobilization stress. Acta Physiol. Scand. 95: 206–208, 1976.
84. Carlsson, Ch., Hägerdal, M. and Siesjö, B. K.: Influence of amphetamine sulphate on cerebral blood flow and metabolism. Acta Physiol. Scand. 94: 128–129, 1976.
85. Caronna, J. J. and Plum, F.: Cerebrovascular regulation in preganglionic and postganglionic autonomic insufficiency. Stroke 4: 12–19, 1973.
86. Carrier, O., Jr., Walker, J. R. and Guyton, A. C.: Role of oxygen in autoregulation of blood flow in isolated vessels. Amer. J. Physiol. 206: 951–954, 1964.
87. Carter, L. P. and Atkinson, J. R.: Cortical blood flow in controlled hypotension as measured by thermal diffusion. J. Neurol. Neurosurg. Psychiat. 36: 906–913, 1973.
88. Cartoni, C., Giardini, V. and Carpi, A.: Effects of isoprenaline on intracranial hemodynamics. Pharmacol. Res. Commun. 6: 155–161, 1974.
89. Casley-Smith, J. R.: An electron microscopical demonstration of the permeability of cerebral and retinal capillaries to ions. Experientia (Basel) 25: 845–847, 1969.
90. Cervós-Navarro, J. and Matakas, F.: Electron microscopic evidence for innervation of intracerebral arterioles in the cat. Neurology 24: 282–286, 1974.
91. Chapman, B. J., Horn, N. M. and Rickaby, S. F.: The measurement of cerebral blood flow in the rat by ^{85}krypton washout. J. Physiol. (London) 251: 16P–18P, 1975.
92. Chase, T. N.: Central monoamine metabolism in man. Arch. Neurol. 29: 349–351, 1973.
93. Chase, T. N. and Murphy, D. L.: Serotonin and central nervous system function. Annu. Rev. Pharmacol. 13: 181–197, 1973.
94. Chasin, M., Mamrak, F., Samaniego, S. G. and Hess, S. M.: Characteristics of the catecholamine and histamine receptor sites mediating accumulation of cyclic adenosine 3′,5′-monophosphate in guinea pig brain. J. Neurochem. 21: 1415–1427, 1973.
95. Choi, B. H., Antanitus, D. S. and Lapham, L. W.: Fluorescence histochemical and ultrastructural studies of locus coeruleus of human fetal brain. J. Neuropathol. Exp. Neurol. 34: 507–516, 1975.
96. Chorobski, J. and Penfield, W.: Cerebral vasodilator nerves and their pathway from the medulla oblongata. Arch. Neurol. Psychiat. (Chicago) 28: 1257–1289, 1932.
97. Clark, R. B. and Perkins, U. P.: Regulation of adenosine 3′,5′-cyclic monophosphate concentration in cultured human astrocytoma cells by catecholamines and histamine. Proc. Nat. Acad. Sci. U.S.A. 68: 2757–2760, 1971.
98. Clemedson, C. J., Hartelius, H. and Holmberg, G.: The influence of carbon dioxide inhalation on the cerebral vascular permeability to trypan blue (the blood-brain barrier). Acta Pathol. Microbiol. Scand. 42: 137–149, 1958.
99. Cobb, S. and Finesinger, J. E.: Cerebral circulation. XIX. The vagal pathway of the vasodilator impulses. Arch. Neurol. Psychiat. (Chicago) 28: 1243–1256, 1932.
100. Coleridge, H. M., Coleridge, J. C. G. and Rosenthal, F.: Prolonged activation of cortical pyramidal

tract neurones in cats by distension of the carotid sinus. J. Physiol. (London) 256: 635–650, 1976.
101. Collis, M. G. and Alps, B. J.: Vascular reactivity to noradrenaline, potassium chloride and angiotensin II in the rat perfused mesenteric vasculature preparation, during the development of renal hypertension. Cardiovasc. Res. 9: 118–126, 1975.
102. Constantinides, J. and Geissbühler, F.: Problèmes de barrière capillaire pour les monoamines et leurs précurseurs. *In* Monoamines Noyaux Gris Centraux et Syndrome de Parkinson, ed. by J. de Ajuriaguerra and G. Gauthier, pp. 99–118, Masson et Cie, Paris, 1970.
103. Constantinides, J., de la Torre, J. C., Tissot, R. and Geissbühler, F.: La barrière capillaire pour la dopa dans le cerveau et les différents organes. Psychopharmacologia 15: 75–87, 1969.
104. Cools, A. R. and van Rossum, J. M.: Caudal dopamine and stereotype behaviour of cats. Arch. Int. Pharmacodyn. Thér. 187: 163–173, 1970.
105. Corbett, J. L., Edelman, B. H. and Debarge, O.: Modification of cerebral vasoconstriction with hyperventilation in normal man by thymoxamine. Lancet ii: 461–463, 1972.
106. Costa, E. and Garattini, S.: Amphetamine and Related Compounds, Raven Press, New York, 1970.
107. Costa, J. L., Ito, U., Spatz, M., Klatzo, I. and Demirjian, C.: 5-Hydroxytryptamine accumulation in cerebrovascular injury. Nature (London) 248: 135–136, 1974.
108. Costall, B. and Naylor, R. J.: The role of telencephalic dopaminergic systems in the mediation of apomorphine stereotyped behaviour. Eur.J. Pharmacol. 24: 8–24, 1973.
109. Csillik, B., Janscó, G., Tóth, L., Kozma, M., Kálmán, G. and Karcsu, S.: Adrenergic innervation of hypothalamic blood vessels. A contribution to the problem of central thermodetectors. Acta Anat. 80: 142–151, 1971.
110. Cunha-Vaz, J. G., Shakib, M. and Ashton N.: Studies on the permeability of the blood-retinal barrier. I. On the existence, development and site of a blood-retinal barrier. Brit. J. Ophthal. 50: 441–453, 1966.
111. Curran, D. A., Hinterberger, H. and Lance, J. W.: Total plasma serotonin, 5-hydroxyindoleacetic acid and *p*-hydroxy-*m*-methoxymandelic acid excretion in normal and migrainous subjects. Brain 88: 997–1010, 1965.
112. Cutler, R. W. P. and Barlow, C. F.: The effect of hypercapnia on brain permeability to protein. Arch. Neurol. 14: 54–63, 1966.
113. Dahl, E.: The innervation of the cerebral arteries. J. Anat. 115: 53–63, 1973.
114. Dahl, E.: The fine structure of intracerebral vessels. Z. Zellforsch. Mikroskop. Anat. 145: 577–586, 1973.
115. Dahlström, A. and Fuxe, K.: Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand., Suppl. 62: 1–55, 1964.
116. D'Alecy, L. G.: Sympathetic cerebral vasoconstriction blocked by adrenergic alpha receptor antagonists. Stroke 4: 30–37, 1973.
117. D'Alecy, L. G. and Feigl, E. O.: Sympathetic control of cerebral blood flow in dogs. Circ. Res. 31: 267–283, 1972.
118. Dalske, H. F., Harakal, C., Sevy, R. W. and Menkowitz, B. J.: Catecholamine content and response to norepinephrine of middle cerebral artery. Proc. Soc. Exp. Biol. Med. 146: 718–721, 1974.
119. Daugherty, R. M., Jr., Scott, J. B. and Haddy, F. J.: Effects of generalized hypoxemia and hypercapnia on forelimb vascular resistance. Amer. J. Physiol. 213: 1111–1114, 1967.
120. Davis, J. M.: Theories of biological etiology of affective disorders. Int. Rev. Neurobiol. 12: 145–175, 1970.
121. Davson, H.: Physiology of the Cerebrospinal Fluid, Churchill, London, 1967.
122. Dengler, H. J., Michaelson, I. A., Spiegel, H. G. and Titus, E.: The uptake of labeled norepinephrine by isolated brain and other tissues of the cat. Int. J. Neuropharmacol. 1: 23–38, 1962.
123. Deshmukh, V. D. and Harper, A. M.: The effect of serotonin on cerebral and extracerebral blood flow with possible implications in migraine. Acta Neurol. Scand. 49: 649–658, 1973.
124. Deshmukh, V. D., Meyer, J. S., Aoyagi, M., Matsuda, M. and Tagashira, Y.: Evidence for cholinergic influences on cerebral blood flow and metabolism. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 4.3–4.4. Churchill Livingstone, Edinburgh, 1975.
125. Detar, R. and Bohr, D. F.: Oxygen and vascular smooth muscle contraction. Amer. J. Physiol. 214: 241–244, 1968.
126. Dewhurst, W. G.: New theory of cerebral amine function and its clinical application. Nature (London) 218: 1130–1133, 1968.
127. Dismukes, R. K. and Daly, J. W.: Altered responsiveness of adenosine 3′,5′-monophosphates generating systems in brain slices from adult rats after neonatal treatment with 6-hydroxydopaine. Exp. Neurol. 49: 150–160, 1975.
128. Dobbing, J.: The blood-brain barrier. Physiol. Rev. 41: 130–188, 1961.
129. Dollison, J. R., Bloor, B. M., Figueroa, A. F., Jr. and Loar, C. R.: The effects of cervical sympathetic stimulation on cerebrovascular hemodynamics. Surg. Forum, 20: 416–417, 1969.
130. Donáth, T.: Monoaminergic innervation of extra and intracerebral vessels. Acta Morphol. Acad. Sci. Hung. 16: 285–293, 1968.
131. Duckles, S. P., Lee, T. J. F. and Bevan, J. A.: Histamine potentiation of contractile responses of rabbit basilar artery. Proc. West. Pharmacol. Soc. 17: 118–121, 1974.
132. Duling, B. R.: Changes in microvascular diameter and oxygen tension induced by carbon dioxide. Circ. Res. 32: 370–376, 1973.
133. Dumke, P. R. and Schmidt, C. F.: Quantitative measurements of cerebral blood flow in the macacque monkey. Amer. J. Physiol. 138: 421–431, 1943.
134. Eckenhoff, J. E., Enderby, G. E. H., Larson, A., Davies, R. and Judevine, D. E.: Human cerebral circulation during deliberate hypotension and head-up tilt. J. Appl. Physiol. 18: 1130–1138, 1963.
135. Eckman, W. W., Phair, R. D., Fenstermacher, J. D., Patlak, C. S., Kennedy, C. and Sokoloff, L.: Permeability limitation in estimation of local brain blood flow with [^{14}C] antipyrine. Amer. J. Physiol. 223: 215–221, 1975.
136. Edelman, N. H., Epstein, P., Cherniack, N. S. and Fishman, A. P.: Control of cerebral blood flow in the goat: role of the carotid rete. Amer. J. Physiol. 223: 615–619, 1972.
137. Edvinsson, L.: Neurogenic mechanisms in the cerebrovascular bed. Autonomic nerves, amine receptors and their effect on cerebral blood flow. Acta Physiol. Scand., Suppl. 427: 1–36, 1975.
138. Edvinsson, L., Aubineau, P., Owman, Ch., Sercombe, R. and Seylaz, J.: Sympathetic innervation of cerebral arteries. Prejunctional supersensitivity to norepinephrine of sympathectomy or cocaine treatmnt. Stroke 6: 525–530, 1975.
139. Edvinsson, L., Falck, B. and Owman, Ch.: Possibilities for cholinergic nerve action on smooth musculature and sympathetic axons in brain vessels me-

diated by muscarinic and nicotinic receptors. J. Pharmacol. Exp. Ther. 200: 117–126, 1977.

140. EDVINSSON, L., HÅKANSON, R., LINDVALL, M., OWMAN, CH. AND SVENSSON, K.-G.: Ultrastructural and biochemical evidence for a sympathetic neural influence on the choroid plexus. Exp. Neurol. 48: 241–251, 1975.
141. EDVINSSON, L. AND HARDEBO, J. E.: Characterization of serotonin-receptors in intracranial and extracranial vessels. Acta Physiol. Scand. 97: 523–525, 1976.
142. EDVINSSON, L., LINDVALL, M., NIELSEN, K. C. AND OWMAN, CH.: Are brain vessels innervated also by central (non-sympathetic) adrenergic neurones? Brain Res. 63: 496–499, 1973.
143. EDVINSSON, L., NIELSEN, K. C. AND OWMAN, CH.: Cholinergic innervation of choroid plexus in rabbits and cats. Brain Res. 63: 500–503, 1973.
144. EDVINSSON, L., NIELSEN, K. C. AND OWMAN, CH.: Influence of initial tension and changes in sensitivity during amine-induced contractions of pial arteries *in vitro*. Arch. Int. Pharmacodyn. Thér. 208: 235–242, 1974.
145. EDVINSSON, L., NIELSEN, K. C., OWMAN, CH. AND SPORRONG, B. L.: Cholinergic mechanisms in pial vessels. Histochemistry, electron microscopy and pharmacology. Z. Zellforsch. Mikroskop. Anat. 134: 311–325, 1972.
146. EDVINSSON, L., NIELSEN, K. C., OWMAN, CH. AND WEST, K. A.: Sympathetic neural influence on norepinephrine vasoconstriction in brain vessels. Arch. Neurol. 27: 492–495, 1972.
147. EDVINSSON, L., NIELSEN, K. C., OWMAN, CH. AND WEST, K. A.: Evidence of vasoconstrictor sympathetic nerves in brain vessels of mice. Neurology 23: 73–77, 1973.
148. EDVINSSON, L., NIELSEN, K. C., OWMAN, CH. AND WEST, K. A.: Adrenergic innervation of the mammalian choroid plexus. Amer. J. Anat. 139: 299–308, 1974.
149. EDVINSSON, L. AND OWMAN, CH.: Pharmacological characterization of adrenergic *alpha* and *beta* receptors mediating vasomotor response of cerebral arteries *in vitro*. Circ. Res. 35: 835–849, 1974.
150. EDVINSSON, L. AND OWMAN, CH.: A pharmacologic comparison of histamine receptors in isolated extracranial and intracranial arteries *in vitro*. Neurology 25: 271–276, 1975.
151. EDVINSSON, L. AND OWMAN, CH.: The measurement of regional cerebral blood flow in the rat by C^{14}-ethanol. Submitted for publication, 1977.
152. EDVINSSON, L., OMAN, CH., ROSENGREN, E. AND WEST, K. A.: Concentration of noradrenaline in pial vessels, choroid plexus, and iris during two weeks after sympathetic ganglionectomy or decentralization. Acta Physiol. Scand. 85: 201–206, 1972.
153. EDVINSSON, L., OWMAN, CH. AND SIESJÖ, B. K.: Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. Brain Res. 117: 519–523, 1976.
154. EDVINSSON, L., OWMAN, CH. AND SJÖBERG, N.-O.: Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study. Brain Res. 115: 377–394, 1976.
155. EDVINSSON, L., OWMAN, CH. AND WEST, K. A.: Changes in cerebral blood volume of mice at various time periods after superior cervical sympathectomy. Acta Physiol Scand. 82: 521–526, 1971.
156. EDVINSSON, L., OWMAN, CH. AND WEST, K. A.: Sympathetic influence of cerebral blood volume: time-dependent effect of decentralization of the superior cervical ganglia in mice. Experientia (Basel) 28: 790–791, 1972.
157. EDVINSSON, L., OWMAN, CH. AND WEST, K. A.: Influence of sympathetic denervation on intracranial pressure. *In* Intracranial Pressure II ed. by N. Lundberg, U. Ponten and M. Brock, pp. 453–459, Springer-Verlag, Berlin, Heidelberg, New York, 1975.
158. EDVINSSON, L. AND SERCOMBE, R.: Influence of pH and pCO_2 on *alpha*-receptor mediated contraction in brain vessels. Acta Physiol. Scand. 97: 325–331, 1976.
159. EDWARDS, C., NAHORSKI, S. R. AND ROGERS, K. J.: *In vivo* changes of cerebral cyclic adenosine 3′,5′-monophosphate induced by biogenic amines: association with phosphorylase activation. J. Neurochem. 22: 565–572, 1974.
160. EHRLICH, P.: Das Sauerstoff-Bedurfniss des Organismus. Eine farbenanalytische Studie, pp. 69–72, August Hirschwald, Berlin, 1885.
161. EIDELMAN, B. H., CORBETT, J. L., DEBARGE, O. AND FRANKEL, H.: Absence of cerebral vasconstriction with hyperventilation in tetraplegic man. Lancet ii: 457–460, 1972.
162. EIDELMAN, B. H., MCCALDEN, T. A. AND ROSENDORFF, C.: The role of the carotid body in mediating the cerebrovascular response to altered arterial carbon dioxide tension. Stroke 7: 72–76, 1976.
163. EKLÖF, B., INGVAR, D. H., KÅGSTRÖM, E. AND OLIN, T.: Persistence of cerebral blood flow autoregulation following chronic bilateral cervical sympathectomy in the monkey. Acta Physiol. Scand. 82: 172–176, 1971.
164. EKLÖF, B., LASSEN, N. A., NILSSON, L., NORBERG, K. AND SIESJÖ, B. K.: Blood flow and metabolic rate for oxygen in the cerebral cortex of the rat. Acta Physiol Scand. 88: 587–589, 1973.
165. EKLÖF, B., LASSEN, N. A., NILSSON, L., NORBERG, K., SIESJÖ, B. K. AND TORLÖF, P.: Regional cerebral blood flow in the rat measured by the tissue sampling technique; a critical evaluation using four indicators C^{14}-antipyrine, C^{14}-ethanol, H^3-water and $xenon^{133}$. Acta Physiol. Scand. 91: 1–10, 1974.
166. EKSTRÖM-JODAL, B.: On the relationship between blood pressure and blood flow in the canine brain with particular regard to the mechanism responsible for cerebral blood flow autoregulation. Acta Physiol. Scand., Suppl. 350: 1–28, 1970.
167. EKSTRÖM-JODAL, B., VON ESSEN, C. AND HÄGGENDAL, E.: Effects of noradrenaline on the cerebral blood flow in the dog. Acta Neurol. Scand. 50: 11–26, 1974.
168. EKSTRÖM-JODAL, B., VON ESSEN, C., HÄGGENDAL, E. AND ROOS, B.-E.: Effects of L-DOPA and L-tryptophan on the cerebral blood flow in the dog. Acta Neurol. Scand. 50: 3–10, 1974.
169. EKSTRÖM-JODAL, B., VON ESSEN, C., HÄGGENDAL, E. AND ROOS, B.-E.: Effects of 5-hydroxytryptamine on the cerebral blood flow in the dog. Acta Neurol. Scand. 50: 27–38, 1974.
170. EKSTRÖM-JODAL, B., HÄGGENDAL, E., LINDER, L.-E. AND NILSSON, N. J.: Cerebral blood flow autoregulation at high arterial pressures and different levels of carbon dioxide tension in dogs. Eur. Neurol. 6: 6–10, 1972.
171. EKSTRÖM-JODAL, B., HÄGGENDAL, E., NILSSON, N. J. AND NORBÄCK, B.: Changes of the transmural pressure – the probable stimulus to cerebral blood flow autoregulation. *In* Cerebral Blood Flow, ed. by M. Brock, C. Fieschi, D. H. Ingvar, N. A. Lassen and K. Schürmann, pp. 89–93, Springer-Verlag, Berlin, 1969.
172. EMERSON, T. E., JR. AND PARKER, J. L.: Effects of local increases of venous pressure on canine cerebral hemodynamics. *In* Cerebral Circulation and Metabolism, ed. by T. W. Langfitt, L. C. McHenry, Jr., M. Reivich and H. Wollman, pp. 10–13, Springer-Verlag, New York, 1975.
173. ESPAGNO, J. AND LAZORTHES, Y.: Measurement of re-

gional cerebral blood flow in man by local injections of xenon[133]. Acta Neruol. Scand., Suppl. 14: 58–62, 1965.

174. VON ESSEN, C.: Effects of dopamine on the cerebral blood flow in the dog. Acta Neurol. Scand. 50: 39–52, 1974.
175. VON ESSEN, C. AND ROOS, B.-E.: Further evidence for the existence of specific dopamine receptors in the cerebral vascular bed of the dog. Acta Pharmacol. Toxicol. 35: 433–435, 1974.
176. ESTLER, C.-J. AND AMMON, H. P. T.: The influence of the β-sympathicolytic agent, propranolol, on glycogenolysis and glycolysis in muscle, brain and liver of white mice. Biochem. Pharmacol. 15: 2031–2035, 1966.
177. ESTLER, C.-J. AND AMMON, H. P. T.: Antagonistic effects of dopa and propranolol on brain glycogen. J. Pharm. Pharmacol. 22: 146–147, 1970.
178. FALCK, B., MCHEDLISHVILI, G. I. AND OWMAN, CH.: Histochemical demonstration of adrenergic nerves in cortex-pia of rabbit. Acta Pharmacol. Toxicol. 23: 133–142, 1965.
179. FARRAR, J. K., JR.: Chronic cerebral arterial spasm: The role of intracranial pressure. J. Neurosurg. 43: 408–417, 1975.
180. FARRAR, J. K., JONES, J. V., GRAHAM, D. I., STRANDGAARD, S. AND MACKENZIE, E. T.: Evidence against cerebral vasospasm during acutely induced hypertension. Brain Res. 104: 176–180, 1976.
181. FAZEKAS, J. F., THOMAS, A., JOHNSON, J. V. V. AND YOUNG, W. K.: Effect of norepinephrine on cerebral hemodynamics in severe hypotension. Arch. Neurol. 2: 305–308, 1960.
182. FEIN, J. M., FLOR, W. J., COHAN, S. L. AND PARKHURST, J: Sequential changes of vascular ultrastructure in experimental cerebral vasospasm. J. Neurosurg. 41: 49–58, 1974.
183. FENSKE, A., HEYE, O., THEISS, R., REULEN, H. L. AND SCHÜRMANN, K.: Regional cortical blood flow in the early stage of brain stem edema. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 1.12–1.15, Churchill Livingstone, Edinburgh, 1975.
184. FENSTERMACHER, J. D., PATLAK, C. S. AND BLASBERG, R.: G.: Transport of material between brain extracellular fluid, brain cells and blood. Fed. Proc. 33: 2070–2074, 1974.
185. FERRENDELLI, J. A., KINSCHERF, D. A. AND CHANG, M.-M.: Comparison of the effects of biogenic amines on cyclic GMP and cyclic AMP levels in mouse cerebellum in vitro. Brain Res. 84: 63–73, 1975.
186. FERRIS, E. B., ENGEL, G. L., STEVENS, C. D. AND LOGAN, M.: The validity of internal jugular venous blood in studies of cerebral metabolism and blood flow in man. Amer. J. Physiol. 147: 517–521, 1946.
187. FINCH, L. AND HAEUSLER, G.: Vascular resistance and reactivity in hypertensive rats. Blood Vessels 11: 145–158, 1974.
188. FITCH, W., FERGUSON, G. G., SENGUPTA, D. AND GARIBI, J.: Autoregulation of cerebral blood flow during controlled hypotension. *In* Cerebral Circulation and Metabolism, ed. by T. W. Langfitt, L. C. McHenry, Jr., M. Reivich and H. Wollman, pp. 18–20, Springer-Verlag, New York, 1975.
189. FITCH, W., MACKENZIE, E. T. AND HARPER, A. M.: Effects of decreasing arterial pressure on cerebral blood flow in the baboon: Influence of the sympathetic nervous system. Circ. Res. 37: 550–557, 1975.
190. FLODMARK, S., HAMBERGER, A., HAMBERGER, B. AND STEINWALL, O.: Concurrent registration of EEG responses, catecholamine uptake and typan blue staining in chemical blood-brain barrier damage. Acta Neuropathol. 12: 16–22, 1969.
191. FLÖHR, H., POLL, W. AND BROCK, M.: Regulation of spinal cord blood flow. *In* Brain and Blood Flow, ed. by R. W. Ross Russell, pp. 406–409, Pitman, London, 1971.
192. FLUMERFELT, B. A., LEWIS, P. R. AND GWYN, D. G.: Cholinesterase activity in the rat brain. A light and electron microscopic study. Histochem. J. 5: 67–77, 1973.
193. FOG, M.: Cerebral circulation: The reaction of the pial arteries to a fall in blood pressure. Arch. Neurol. Psychiat. (Chicago) 37: 351–364, 1937.
194. FOG, M.: The relationship between the blood pressure and tonic regulation of the pial arteries. J. Neurol. Neurosurg. 1: 187–197, 1938.
195. FOG, M.: Cerebral circulation. I. Reaction of pial arteries to epinephrine by direct application and by intravenous injection. Arch. Neurol. Psychiat. (Chicago) 41: 109–118, 1939.
196. FOG, M.: Cerebral circulation. II. Reaction of pial arteries to increase in blood pressure. Arch. Neurol. Psychiat. (Chicago) 41: 260–268, 1939.
197. FOLKOW, B.: The haemodynamic consequences of adaptive structural changes of the resistance vessels in hypertension. Clin. Sci. (London) 41: 1–12, 1971.
198. FOLKOW, B. AND LANGSTON, J.: The interrelationship of some factors influencing renal blood flow autoregulation. Acta Physiol. Scand. 61: 165–176, 1964.
199. FOLKOW, B. AND NEIL, E.: Circulation, Oxford University Press, London, 1971.
200. FORBES, H. S. AND COBB, S.: Vasomotor control of cerebral vessels. Res. Publ. Ass. Nerv. Ment. Dis. 18: 201–207, 1938.
201. FORBES, H. S., FINLEY, H. K. AND NASON, G. I.: Cerebral circulation. XXIV. A. Action of epinephrine on pial vessels. B. Action of pituitary and pitressin on pial vessels. C. Vasomotor response in the pia and in the skin. Arch. Neurol. Psychiat. (Chicago) 30: 957–979, 1933.
202. FORBES, H. S., NASON, G. I., COBB, S. AND WORTMAN, R. C.: Cerebral circulation. XLV. Vasodilation in the pia following stimulation of the geniculate ganglion. Arch. Neurol. Psychiat. (Chicago) 37: 776–781, 1937.
203. FORRESTER, T., HARPER, A. M. AND MACKENZIE, E. T.: Effects of intracarotid adenosine triphosphate infusions in cerebral blood flow and metabolism in the anaesthetized baboon. J. Physiol. (London) 250: 38–39P, 1975.
204. FOX, J. L. AND YASARGIL, M. G.: The experimental effect of direct electrical current on intracranial arteries and the blood-brain barrier. J. Neurosurg. 41: 582–589, 1974.
205. FOZARD, J. R. AND MUSCHOLL, E.: Do adrenergic fibres have muscarinic inhibitory receptors? A reply. J. Pharm. Pharmacol. 26: 662–664, 1974.
206. FRANK, E. D., FRANK, H. A., JACOB, S., WEITZEL, H. A. E., KORMAN, H. AND FINE, J.: Effect of norepinephrine on circulation of the dog in hemorrhagic shock. Amer. J. Physiol. 186: 74–78, 1956.
207. FREEMAN, J. AND INGVAR, D. H.: Elimination by hypoxia of cerebral blood flow autoregulation and EEG relationship. Exp. Brain Res. 5: 61–71, 1968.
208. FRENCH, J. D. AND MAGOUN, H. W.: Effects of chronic lesions in central cephalic brain stem of monkeys. Arch. Neurol. Psychiat. (Chicago) 68: 591–604, 1952.
209. FUJISHIMA, M., REINUTH, O. M., KOGURE, K. AND SCHEINBERG, P.: The response of cerebral metabolism and flow to beta adrenergc blockade. Circulation 37 and 38: suppl. VI, 79, 1968.
210. FUJISHIMA, M., SCHEINBERG, P., BUSTO, R. AND REINMUTH, O. M.: The relation between cerebral oxygen consumption and cerebral vascular reactivity to carbon dioxide. Stroke 2: 251–257, 1971.
211. FURCHGOTT, R. F.: The pharmacological differentiation of adrenergic receptors. Ann. N.Y. Acad. Sci. 139: 553–570, 1967.

212. FURCHGOTT, R. F.: The classification of adrenoreceptors (adrenergic receptors). An evaluation from the standpoint of receptor theory. *In* Handbook of Experimental Pharmacology, ed. by H. Blaschko and E. Muscholl, vol. 33, pp. 283–335, Springer-Verlag, Berlin, 1972.
213. FUXE, K., HAMBERGER, B. AND HÖKFELT, T.: Distribution of noradrenaline nerve terminals in cortical areas of the rat. Brain Res. 8: 125–131, 1968.
214. FUXE, K. HÖKFELT, T., RITZÉN, M. AND UNGERSTEDT, U.: Studies on uptake of intraventricularly administered tritiated noradrenaline and 5-hydroxytryptamine with combined fluorescence histochemical and autoradiographic techniques. Histochemie 16: 186–194, 1968.
215. FUXE, K. AND JONSSON, G.: A modification of the histochemical fluorescence method for the improved localization of 5-hydroxytryptamine. Histochemie 11: 161–166, 1967.
216. GADO, M., EICHLING, J., GRUBB, R., JR., PHELPS, M., RAICHLE, M. AND TER-POGOSSIAN, M. M.: Appraisal of the angiographic circulation time as an index of cerebral blood flow. Radiology 115: 107–112, 1975.
217. GARATTINI, S. AND VALZELLI, L.: Serotonin, Elsevier, Amsterdam, 1965.
218. GARBARG, M., BARBIN, G., FEGER, J. AND SCHWARTZ, J.-C.: Histaminergic pathway in rat brain evidenced by lesions of the medial forebrain bundle. Science 186: 833–835, 1974.
219. GARELIS, E. AND NEFF, N. H.: Cyclic adenosine monophosphate: Selective increase in caudate nucleus after administration of L-dopa. Science 183: 532–533, 1973.
220. GEIGER, A. AND MAGNES, J.: The isolation of the cerebral circulation and the perfusion of the brain in the living cat. Amer. J. Physiol. 149: 517–537, 1947.
221. GERAUD, J., BES, A., DEPLA, M. AND MARC-VERGNES, J. P.: Cerebral arteriovenous oxygen differences. Reappraisal of their significance for evaluation of brain function. *In* Research on the Cerebral Circulation, ed. by J. S. Meyer, H. Lechner and O. Eichhorn, pp. 209–222, Charles C Thomas, Springfield, Ill., 1969.
222. GEY, K. F., RUTISHAUSER, M. AND PLETSCHER, R.: Suppression of glycolysis in rat brain *in vivo* by chlorpromazine, reserpine and phenobarbitol. Biochem. Pharmacol. 14: 507–514, 1965.
223. GIACOMELLI, F., WIENER, J. AND SPIRA, D.: The cellular pathology of experimental hypertension. V. Increased permeability of cerebral arterial vessels. Amer. J. Pathol. 59: 133–159, 1970.
224. GIARDINI, V., CARTONI, C. AND CARPI, A.: Quantitative relationships between CSF pressure changes and CBF changes caused by vasoactive agents. Eur. Neurol. 8: 69–73, 1972.
225. GIBBS, F. A., GIBBS, E. L. AND LENNOX, W. G.: The cerebral blood flow in man as influenced by adrenaline, caffein, amylnitrite and histamine. Amer. Heart J. 10: 916–924, 1935.
226. GILBOE, D. D., GLOVER, M. B. AND COTANCH, W. W.: Blood filtration and its effect on glucose metabolism by the isolated dog brain. Amer. J. Physiol. 213: 11–15, 1967.
227. GILMAN, A. G. AND NIRENBERG, M.: Effect of catecholamines on the adenosine 3′,5′-cyclic monophosphate concentrations of clonal satellite cells of neurons. Proc. Nat. Acad. Sci. U.S.A. 68: 2165–2168, 1971.
228. GJEDDE, A., ANDERSSON, J. AND EKLÖF, B.: Brain uptke of lactate, antipyrine, water and ethanol. Acta Physiol Scand. 93: 145–149, 1975.
229. GJEDDE, A., CARONNA, J. J., HINDFELT, B. AND PLUM, F.: Whole brain blood flow and oxygen metabolism in the rat during nitrous oxide anesthesia. Amer. J. Physiol. 229: 113–118, 1975.
230. GLASS, H. I. AND HARPER, A. M.: Measurement of regional blood flow in cerebral cortex of man through intact skull. Brit. Med. J. 1: 593, 1963.
231. GLEICHMANN, M., INGVAR, D. H., LASSEN, N. A., LÜBBERS, D. W., SIESJÖ, B. K. AND THEWS, G.: Regional cerebral cortical metabolic rate of oxygen and carbon dioxide, related to the EEG in the anesthetized dog. Acta Physiol. Scand. 55: 82–94, 1962.
232. GOLDBERG, L. I.: Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol. Rev. 24: 1–30, 1972.
233. GOLDBERG, L. I.: The dopamine vascular receptor. Biochem. Pharmacol. 24: 651–653, 1975.
234. GOLDBERG, L. I., TJANDRAMAGA, T. E., ANTON, A. H. AND TODA, N.: Continuing studies of the peripheral vascular actions of dopamine. Advan. Neurol. 5: 165–173, 1974.
235. GOLDBERG, M. A., BARLOW, C. F. AND ROTH, L. J.: Abnormal brain permeability in CO_2 narcosis. Arch. Neurol. 9: 498–507, 1966.
236. GOLDMAN, H., FISCHER, R., NICOLOV, N. AND MURPHY, S.: Lysergic acid diethylamide affects blood flow to specific areas of the conscious rat brain. Experientia (Basel) 31: 328–330, 1975.
237. GOLDMANN, E. E.: Vitalfarbung am Zentralnervensystem. Abh. preussischen Akad. Wiss. 1: 1–60, 1913.
238. GORDON, A. S.: Practical Aspects of Blood Flow Measurement, pp. 1–78, Statham Instruments Inc., California, 1971.
239. GOTOH, F., EBIHARA, S. I., TOYODA, M. AND SHINOHARA, Y.: Role of autonomic nervous system in autoregulation of human cerebral circulation. Eur. Neurol. 6: 203–207, 1972.
240. GOTOH, F., MEYER, J. S. AND TOMITA, M.: Hydrogen method for determining cerebral blood flow in man. Arch. Neurol. 15: 549–559, 1966.
241. GOTOH, F., MURAMATSU, F., FUKUUCHI, Y. AND AMANO, T.: Dual control of cerebral circulation: separate sites of action in vascular tree in autoregulation and chemical control. *In* Cerebral Circulation and Metabolism, ed: by T. W. Langfitt, L. C. McHenry, Jr., M. Reivich and H. Wollman, pp. 43–45, Springer-Verlag, New York. 1975.
242. GOTTSTEIN, U.: Der Hirnkreislaug unter dem Einfluss vasoaktiver Substanzen. A. Hüthig Verlag, Heidelberg, 1962.
243. GREEN, H. D. AND DENISON, A. B., JR.: Absence of vasomotor responses to epinephrine and arterenol in an isolated intracranial circulation. Circ. Res. 4: 565–573, 1956.
244. GREEN, J. P.: Histamine. *In* Handbook of Neurochemistry, vol. IV, pp. 221–250, Plenum Press, New York, 1970.
245. GREENFIELD, J. C. AND TINDALL, G. T.: Effect of norepinephrine and angiotensin on blood flow in the internal caotid artery of man. J. Clin. Invest. 47: 1672–1684, 1968.
246. GRIFFITH, R. P., TINDALL, G. T., IWATA, K., MCGRAW, C. P. AND VANDERVEER, R. W.: Response of cerebral metabolic rate of oxygen use to norepinephrine in head-injured patients. Surg. Forum, 21: 415–417, 1972.
247. GRIMSON, B. S., ROBINSON, S. C., DANFORD, E. T., RINDALL, G. T. AND GREENFIELD, J. C., JR.: Effect of serotonin on internal and external carotid artery blood flow in the baboon. Amer. J. Physiol. 216: 50–55, 1969.
248. GRUBB, R. L., JR., HERNÁNDEZ-PÉREZ, M. J., RAICHLE, M. E. AND PHELPS, M. E.: The effects of iodinated contrast agents on autoregulation of cerebral blood flow. Stroke 5: 155–160, 1974.
249. GRUBB, R. L., JR., PHELPS, M. E., RAICHLE, M. E. AND TER-POGOSSIAN, M. M.: The effects of arterial blood pressure on the regional cerebral blood volume

by x-ray fluorescence. Stroke 4: 390–399, 1973.
250. GRUBB, R. L., JR., RAICHLE, M. E., EICHLING, J. O. AND TER-POGOSSIAN, M. M.: The effect of changes in P_aCO_2 on cerebral blood volume, blood flow and vascular mean transit time. Stroke 5: 630–639, 1974.
251. GRUBB, R. L., JR., RAICHLE, M. E., PHELPS, M. E. AND RATCHESON, R. A.: Effects of increased intracranial pressure on cerebral blood volume, blood flow and oxygen utilization in monkeys. J. Neurosurg. 43: 385–398, 1975.
252. GUROFF, G. AND UDENFRIEND, S.: Studies on aromatic amino acid uptake by rat brain *in vivo*. J. Biol. Chem. *237*: 803–806, 1962.
253. GUSTAFSON, L. AND RISBERG, J.: Regional cerebral blood flow related to psychiatric symptoms in dementia with onset in the presenile period. Acta Psychiat. Scand. 50: 516–538, 1974.
254. HADDY, F. J., GORDON, P. AND EMANUEL, D. A.: The influence of tone upon responses of small and large vessels to serotonin. Circ. Res. 7: 123–130, 1959.
255. HAGEN, E. AND WITTKOWSKI, W.: Licht- und elektronemikroskopische Untersuchungen zur Innervation der Piagefässe. Z. Zellforsch. Mikroskop. Anat. 95: 429–444, 1969.
256. HÄGGENDAL, E.: Effects of some vasoactive drugs on the vessels of cerebral grey matter in the dog. Acta Physiol. Scand., Suppl. 258: 55–79, 1965.
257. HÄGGENDAL, E. AND JOHANSSON, B.: Effect of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. Acta Physiol. Scand., Suppl. 258: 27–53, 1965.
258. HÄGGENDAL, E. AND JOHANSON, B.: On the pathophysiology of the increased cerebrovascular permeability in acute arterial hypertension in cats. Acta Neurol. Scand. 48: 265–270, 1972.
259. HAINING, J. L., TURNER, M. D. AND PANTALL, R. M.: Measurement of local cerebral blood flow in the unanesthetized rat using a hydrogen clearance method. Circ. 23: 313–324, 1968.
260. HAINING, J. L., TURNER, M. D. AND PANTALL, R. M.: Local cerebral blood flow in young and old rats during hypoxia and hypercapnia. Amer. J. Physiol. 218: 1020–1024, 1970.
261. HALSEY, J. H. AND CLARK, L. C., JR.: Some regional circulatory abnormalities following experimental cerebral infarction. Neurology 20: 238–246, 1970.
262. HAMBERGER, A. AND HAMBERGER, B.: Uptake of catecholamines and penetration of trypan blue after blood-brain barrier lesions. Z. Zellforsch. Mikroskop. Anat. 70: 386–392, 1966.
263. HANDA, J., MEYER, J. S., AND YOSHIDA, K.: Regional pharmacologic esponses of the vertebral and internal carotid arteries. J. Pharmacol. Exp. Ther. 152: 251–267, 1966.
264. HANIG, J. P., AIELLO, E. AND SEIFTER, J.: Permeability of the blood-brain barrier to parenteral 5-hydroxytryptamine in the neonate chick. Eur. J. Pharmacol. 12: 180–182, 1970.
265. HANINGTON, E. AND HARPER, A. M.: The role of tryamine in the aetiology of migraine and related studies on the cerebral and extracerebral circulations. Headache 8: 84–97, 1968.
266. HANSSON, H.-A., JOHNSSON, B. AND BLOMSTRAND, C.: Ultrastructural studies on cerebrovascular permeability in acute hypertension. Acta Neuropathol. 32: 187–198, 1975.
267. HARDEBO, J.-E. EDVINSSON, L., FALCK, B., LINDVALL, M., OWMAN, CH., ROSENGREN, E. AND SVENGAARD, N.-A.: Experimental models for histochemical and chemical studies of the enzymatic blood-brain barrier for amine precursors. *In* The Cerebral Vessel Wall, ed. by J. Cervós-Navarro and F. Matakas, pp. 233–277, Raven Press, New York, 1976.
268. HARDEBO, J.-E., EDVINSSON, L., MACKENZIE, E. T. AND OWMAN, CH.: Regional brain uptake of noradrenoline following mechanical or osmotic opening of the blood-brain barrier. Brain Res., in press, 1977.
269. HARPER, A. M.: Autoregulation of cerebral blood flow: Influence of arterial pressure on blood flow through the cerebral cortex. J. Neurol. Neurosurg. Psychiat. 29: 398–403, 1966.
270. HARPER, A. M.: Autonomic control of cerebral blood flow. *In* Cerebral Vascular Diseases, ed. by J. P. Whisnant and B. A. Sandok, pp. 27–35, Grune & Stratton, Inc., New York, 1975.
271. HARPER, A. M. AND BELL, R. A.: The effect of metabolic acidosis and alkalosis on the blood flow through the cerebral cortex. J. Neurol. Neurosurg. Psychiat. 26: 341–344, 1963.
272. HARPER, A. M., DESHMUKH, V. D., ROWAN, J. O. AND JENNETT, W. B.: The influence of sympathetic nervous activity on cerebral blood flow. Arch. Neurol. 27: 1–6, 1972.
273. HARPER, A. M., DESHMUKH, V. D., SENGUPTA, D., ROWAN, J. O. AND JENNETT, W. B.: The effect of experimental spasm on the CO_2 responses of cerebral blood flow in primates. Neuroradiology, 3: 134–136, 1972.
274. HARPER, A. M. AND GLASS, H. I.: Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. J. Neurol. Neurosurg. Psychiat. 28: 449–452, 1965.
275. HARPER, A. M., LORIMER, A. R. AND THOMAS, D. L.: Methods of measuring blood flow. *In* Scientific Foundations of Anaesthesia, 2nd ed., ed. by S. Scurr and S. Feldman, pp. 53–70, Heinemann, London, 1974.
275a. HARPER, A. M. AND MACKENZIE, E. T.: Cerebral circulatory and metabolic effects of 5-hydroxytryptamine in anaesthetized baboons. J. Physiol. (London), in press, 1977.
275b. HARPER, A. M. AND MACKENZIE, E. T.: Effects of 5-hydroxytryptamine on pial arteriolar calibre in anaesthetized cats. J. Physiol. (London), in press, 1977.
276. HARPER, A. M., MACKENZIE, E. T. AND MCCULLOCH, J.: Pharmakologische Untersuchungen am Hirnkreislauf: Mögliche Fehlerquellen bei der Anwendung von Edelgas-Clearance-Methoden. *In* Hirnsloffwechsel und Hirndeuchblutung, ed. by S. Hoyer, pp. 26–28, Excerpta Medica, Amsterdam, in press, 1976.
277. HARTMAN, B. K., ZIDE, D. AND UDENFRIEND, S.: The use of dopamine β-hydroxylase as a marker for the central noradrenergic nervous system in rat brain. Proc. Nat. Acad. Sci. U.S.A. 69: 2722–2726, 1972.
278. HECK, A. F., REICHL, W. W., HALL, V. R. AND BOOTH, F. V. MCL.: Transient increases in intracranial pressure and the blood-brain barrier. Lancet, ii: 741, 1973.
279. HEDGES, T. R. AND WEINSTEIN, J. D.: Cerebrovascular responses to increased intracranial pressure. J. Neurosurg. 21: 292–297, 1964.
280. HEISS, W. D. AND JELLINGER, K.: Cerebral blood flow and brain stem lesions in comatose patients. Neuropathol. Pol. 12: 111–117, 1974.
281. HEISTAD, D. D. AND MARCUS, M. L.: Total and regional cerebral blood flow during stimulation of carotid baroreceptors. Stroke 7: 239–243, 1976.
282. HEISTAD, D. D., MARCUS, M. L., EHRHARDT, J. C. AND ABBOUD, F. M.: Effect of stimulation of carotid chemoreceptors on total and regional cerebral blood flow. Circ. Res. 38: 20–25, 1976.
283. HENNING, J.: Über die Speziesvariationen der regionalen Verteilung alkalischer Phosphatase im peripheren cerebrospinalen Nervensystem. Z. Zellforsch. Mikroskop. Anat. 123: 520–543, 1972.
284. HERNÁNDEZ-PÉREZ, M. J., RAICHLE, M. E. AND STONE, H. L.: The role of the peripheral sympathetic nerv-

ous system in cerebral blood flow autoregulation. Stroke 6: 284–292, 1975.
285. HERNÁNDEZ-PÉREZ, M. J. AND STONE, H. L.: Sympathetic innervation of the circle of Willis in the macaque monkey. Brain Res. 80: 507–511, 1974.
286. HERRSCHAFT, H., GLEIM, F. AND SCHMIDT, H.: Effects of angiographic contrast media on regional cerebral blood flow and haemodynamics in man. Neuroradiology, 7: 95–103, 1974.
287. HIMMS-HAGEN, J.: Sympathetic regulation of metabolism. Pharmacol. Rev. 19: 367–461, 1967.
288. HINSHAW, L. B., BALLIN, H. M., DAY, S. B. AND CARLSON, C. H.: Tissue pressure and autoregulation in the dextran-perfused kidney. Amer. J. Physiol. 197: 835–855, 1959.
289. HOBSON, R. W., WRIGHT, C. B. AND LAMOY, R. E.: Adrenergic mechanisms in the cephalic and cerebral circulations of the subhuman primate. Surgery 77: 304–310, 1975.
290. HOFF, J. T., MACKENZIE, E. T. AND HARPER, A. M.: Responses of the cerebral circulation to hypercapnia and hypoxia after VIIth cranial nerve transection in baboons, Circ. Res. 40: 258–262, 1977.
291. HOFF, J. T., SENGUPTA, D., HARPER, M. AND JENNETT, B.: Effect of alpha-adrenergic blockade on response of cerebral circulation to hypocapnia in the baboon. Lancet, ii: 1337–1339, 1972.
292. HOFFBRAND, B. I. AND FORSYTH, R. P.: Regional blood flow changes during norepinephrine, tyramine and methoxamine infusions in the unanesthetized Rhesus monkey. J. Pharmacol. Exp. Ther. 184: 656–661, 1973.
293. HÖKFELT, T., FUXE, K., GOLDSTEIN, M. AND JOHANSSON, O.: Evidence for adrenaline neurons in the rat brain. Acta Physiol. Scand. 89: 286–288, 1973.
294. HOLMQVIST, B., INGVAR, D. H. AND SIESJÖ, B.: Cerebral sympathetic vasoconstriction and EEG. Acta Physiol. Scand. 40: 146–160, 1957.
295. HOLMSTEDT, B.: A modification of the thiocholine method for the determination of cholinesterase. II. Histochemical application. Acta Physiol. Scand. 40: 331–337, 1957.
296. HOYER, S., HAMER, J., ALBERTI, E., STOECKEL, H. AND WEINHARDT, F.: The effect of stepwise arterial hypotension on blood flow and oxidative metabolism of the brain. Pflügers Arch. 351: 161–172, 1974.
297. HUANG, M. AND DALY, J. W.: Adenosine-elicited accumulation of cyclic AMP in brain slices: potentiation by agents which inhibit uptake of adenosine. Life Sci. 14: 489–503, 1974.
298. HUDGINS, W. R. AND GARCIA, J. H.: The effect of electrocautery, atmospheric exposure and surgical retraction on the permeability of the blood-brain barrier. Stroke 1: 375–380, 1970.
299. HUNTER, U. AND STEFANIK, P.: Sympathetic nervous system effects on rat brain metabolism. Life Sci. 17: 1381–1386, 1975.
300. INGVAR, D. H. AND FRANZÉN, G.: Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiat. Scand. 50: 425–462, 1974.
301. INGVAR, D. H., HÄGGENDAL, E., NILSSON, N. J., SOURANDER, P., WICKBOM, I. AND LASSEN, N. A.: Cerebral circulation and metabolism in a comatose patient. Arch. Neurol. 11: 13–21, 1964.
302. INGVAR, D. H. AND LASSEN, N. A.: Regional blood flow of the cerebral cortex determined by Krypton^{85}. Acta Physiol. Scand. 54: 325–338, 1962.
303. INGVAR, D. H. AND SÖDERBERG, U.: Cortical blood flow related to EEG patterns evoked by stimulation of the brain stem. Acta Physiol. Scand. 42: 130–143, 1958.
304. INGVAR, D. H. AND SOURANDER, P.: Destruction of the reticular core of the brain stem. Arch. Neurol. 23: 1–8, 1970.
305. IN-NAMI, H., KAWAGUCHI, T., KOSUGI, I., YAMAGUCHI, Y., OKADA, K., KAWASHIMA, Y. AND YAMAMURA, H.: Effects of acute administration of isoproterenol on the systemic and regional blood flow in the dog. Resuscitation 3: 285–297, 1974.
306. ISHII, T.: Acetylcholinesterase activity in the perivascular nerve plexus of the basilar and labyrinthine arteries. Acta Oto-laryngol 72: 281–287, 1971.
307. ISHII, T. AND FRIEDE, R. L.: Distribution of a catecholamine-binding mechanism in rat brain. Histochemie, 9: 126–135, 1967.
308. IVERSEN, L. L., HORN, A. S. AND MILLER, R. J.: Actions of dopaminergic agonists on cyclic AMP production in rat brain homogenates. Advan. Neurol. 5: 197–212, 1975.
309. IWAYAMA, T.: Ultrastructural changes in the nerves innervating the cerebral artery after sympathectomy. Z. Zellforsch. Mikroskop. Anat. 109: 465–480, 1970.
310. IWAYAMA, T., FURNESS, J. B. AND BURNSTOCK, G.: Dual adrenergic and cholinergic innervation of the cerebral arteries of the rat. Circ. Res. 26: 635–646, 1970.
311. JACKSON, R. T., CLAIRMONT, A. A. AND POLLOCK, R. A.: The effect of carbon dioxide inhalation on cerebral blood flow: a two-hour duration study in dogs with microspheres. Stroke 5: 344–349, 1974.
312. JACOBSON, I., HARPER, A. M. AND MCDOWALL, D. G.: Relationship between venous pressure and cortical blood flow. Nature (London) 200: 173–175, 1963.
313. JAMES, I. M. AND MACDONNELL, L.: Factors affecting the cerebrovascular response to noradrenaline in the dog. Brit. J. Pharmacol. 54: 129–143, 1975.
314. JAMES, I. M., MILLAR, R. A. AND PURVES, M. J.: Observations on the extrinsic neural control of cerebral blood flow in the baboon. Circ. Res. 25: 77–93, 1969.
315. JENNETT, W. B.: Cerebral blood flow measurement in clinical practice. Int. Anesthesiol. Clin. 7: 579–596, 1969.
316. JENNETT, W. B. AND ROWAN, J. O.: Transit time as an index of the cerebral circulation. Progr. Brain Res. 35: 365–374, 1971.
317. JENSEN, K. B., HØEDT-RASMUSSEN, K., SVEINSDOTTIR, E., STEWART, B. M. AND LASSEN, N. A.: Cerebral blood flow evaluated by inhalation of ^{133}Xe and extracranial recording: a methodological study. Clin. Sci. (London) 30: 485–494, 1966.
318. JEPPSSON, P. G. AND OLIN, T.: Cerebral distribution of contrast medium and the paradoxical location of lesions of the blood-brain barrier in the rabbit. Acta Radiol. Diag. 16: 577–584, 1975.
319. JOHANSSON, B.: Regional cerebral blood flow in acute experimental hypertension. Acta Neurol. Scand. 50: 366–372, 1974.
320. JOHANSSON, B., LI, C.-L., OLSSON, Y. AND KLATZO, I.: The effect of acute arterial hypertension on the blood-brain barrier to protein tracers. Acta Neuropathol. 16: 117–124, 1970.
321. JOHANSSON, B. AND LINDER, L.-E.: Blood-brain barrier dysfunction in acute arterial hypertension induced by clamping of the thoracic aorta. Acta Neurol. Scand. 50: 360–365, 1974.
322. JOHNSON, A. E. AND GOLLAN, F.: Cerebral blood flow monitoring the external detection of inhaled radioactive xenon. J. Nucl. Med. 6: 679–686, 1965.
323. JOHNSTON, I. H., ROWAN, J. O., HARPER, A. M. AND JENNETT, W. B.: Raised intracranial pressure and cerebral blood flow. 2. Supratentorial and infratentorial mass lesions in primates. J. Neurol. Neurosurg. Psychiat. 36: 161–170, 1973.
324. JONES, B. E., BOBILLIER, P., PIN, C. AND JOUVET, M.: The effect of lesions of catecholamine-containing neurons upon monoamine content of the brain and EEG and behavioural waking in the cat. Brain Res. 58: 157–177, 1973.
325. JONES, J. V., FITCH, W., MACKENZIE, E. T., STRAND-

GAARD, S. AND HARPER, A. M.: Lower limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. Circ. Res. 39: 555–557, 1976.

326. JONES, J. V., MACKENZIE, E. T. AND STRANDGAARD, S.: Hypertension and the cerebral circulation. Scot. Med. J. 21: 103–105, 1976.
327. JOÓ, F.: Increased production of coated vesicles in the brain capillaries during enhanced permeability of the blood-brain barrier. Brit. J. Exp. Pathol. 52: 646–649, 1971.
328. JOÓ, F.: Effect of N^6O^2-dibutyryl cyclic 3′, 5′-adenosine monophosphate on the pinocytosis of brain capillaries of mice. Experientia (Basel) 28: 1470–1471, 1972.
329. JOÓ, F., RAKONCZAY, S. AND WOLLEMANN, M.: cAMP-mediated regulation of the permeability in the brain capillaries. Experientia (Basel) 31: 582–583, 1975.
330. JOÓ, F., VÁRKONYI, T. AND CSILLIK, B.: Developmental alterations in the histochemical structures of brain capillaries: a histochemical contribution to the problem of the blood-brain barrier. Histochemie 9: 140–148, 1967.
331. JOUVET, M.: Neurophysiology of the states of sleep. Physiol. Rev. 47: 117–177, 1969.
332. KAJIKAWA, H.: Fluorescence histochemical studies on the distribution of adrenergic nerve fibres to intracranial blood vessels. Arch. Jap. Chir. 37: 473–482, 1968.
333. KAJIKAWA, H.: Mode of the sympathetic innervation of the cerebral vessels demonstrated by the fluorescent histochemical technique in rats and cats. Arch. Jap. Chir. 38: 227–235, 1969.
334. KAKIUCHI, S. AND RALL, T. W.: The influence of chemical agents on the accumulation of adenosine 3′, 5′-phosphate in slices of rabbit cerebellum. Mol. Pharmacol. 4: 367–378, 1968.
335. KAKIUCHI, S. AND RALL, T. W.: Studies on adenosine, 3′, 5′-phosphate in rabbit cerebral cortex. Mol. Pharmacol. 4: 379–388, 1968.
336. KAKIUCHI, S., RALL, T. W. AND MCILWAIN, H.: The effect of electrical stimulation upon the accumulation of adenosine 3′, 5′-phosphate in isolated cerebral tissue. J. Neurochem. 16: 485–491, 1969.
337. KANGASNIEMI, P., SONNINEN, V. AND RINNE, U. K.: Excretion of free and conjugated 5-HIAA and VMA in urine and concentration of 5-HIAA and VMA in CSF during migraine attacks and free intervals. Headache 12: 62–65, 1972.
338. KANZOW, E.: Quantitative fortlaufende Messung von Durchblutungsänderungen in der Hirnrinde. Pflügers Arch. 273: 199–209, 1961.
339. KARCZMAR, A. G., LONGO, V. G. AND SCOTTI DE CAROLIS, A.: A pharmacological model of paradoxical sleep: the role of cholinergic and monamine systems. Physiol. Behav. 5: 175–182, 1970.
340. KARLSBERG, P., ELLIOTT, H. W. AND ADAMS, J. E.: Effect of various pharmacologic agents on cerebral arteries. Neurology 13: 772–778, 1963.
341. KATO, M., UENO, H. AND BLACK, P.: Reginal cerebral blood flow of the main visual pathways during photic stimulation of the retina in intact and split-brain monkeys. Exp. Neurol. 42: 65–77, 1974.
342. KAWAMURA, Y., MEYER, J. S., HIROMOTO, H., AOYAGI, M., TAGASHIRA, Y. AND OTT, E. O.: Neurogenic control of cerebral blood flow in the baboon. J. Neurosurg. 43: 676–688, 1975.
343. KEBABIAN, J. W., PETZOLD, G. L. AND GREENGARD, P.: Dopamine-sensitive adenylate in caudate nucleus of rat brain, and its similarity to the "dopamine receptor". Proc. Nat. Acad. Sci. U.S.A. 69: 2145–2149, 1972.
344. KETY, S. S.: Blood flow and metabolism of the human brain in health and disease. Trans. Stud. Coll. Physicians Philadelphia 18: 103–108, 1950.
345. KETY, S. S.: Circulation and metabolism of the human brain in health and disease. Amer. J. Med. 8: 205–217, 1950.
346. KETY, S. S. AND SCHMIDT, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Amer. J. Physiol. 143: 53–66, 1945.
347. KINDT, G. W.: Autoregulation of spinal cord blood flow. Eur. Neurol. 6: 19–23, 1972.
348. KING, B. D., SOKOLOFF, L. AND WECHSLER, R. L.: The effects of l-ephinephrine and l-nor-epinephrine upon cerebral circulation and metabolism in man. J. Clin. Invest. 31: 273–279, 1952.
349. KING, L. J., CARL, J. L. AND LAO, L.: Cocaine and amphetamine modification of cerebral energy metabolism *in vivo*. Psychopharmacologia 44: 43–45, 1975.
350. KIRKEBÖ, A. AND TYSSEBOTN, I.: Distribution of renal cortical blood flow during hemorrhagic hypotension in conscious dogs. Acta Physiol. Scand. 91: 22–31, 1974.
351. KLAINER, L. M., CHI, Y.-M., FRIEDBERG, S. L., RALL, T. W. AND SUTHERLAND, E. W.: Adenyl cyclase. IV. The effects of neurohormones on the formation of adenosine 3′,5′-phosphate by preparations from brain and other tissues. J. Biol. Chem. 237: 1239–1243, 1962.
352. KLASSEN, A. C., RESCH, J. A., LOKEN, M. K. AND JOHNSON, E. A.: Cerebral circulation studies using inhaled ^{133}Xenon and the gamma camera. Stroke 1: 7–13, 1970.
353. KOBAYASHI, S., WALTZ, A. G. AND RHOTON, A. L., JR.: Effects of stimulation of cervical sympathetic nerves on cortical blood flow and vascular reactivity. Neurology 21: 297–302, 1971.
354. KOBRINE, A. I. AND DOYLE, T. F.: Physiology of spinal cord blood flow. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 4.16–4.19, Churchill Livingstone, Edinburgh, 1975.
355. KOBRINE, A. I., DOYLE, T. F. AND RIZZODI, H. V.: Spinal cord blood flow as affected by changes in systemic arterial pressure. J. Neurosurg. 44: 12–15, 1976.
356. KOELLE, G. B.: Cytological distributions and physiological functions of cholinesterases. *In* Handbook of Experimental Pharmacology, ed. by G. B. Koelle, vol. 15, pp. 187–298, Springer-Verlag, Berlin, Göttingen and Heidelberg, 1963.
357. KOGURE, K., SCHEINBERG, P., FUJISHIMA, M., BUSTO, R. AND REINMUTH, O. M.: Effects of hypoxia on cerebral autoregulation. Amer. J. Physiol. 219: 1393–1396, 1970.
358. KOGURE, K., SCHEINBERG, P., REINMUTH, O. M., FUJISHIMA, M. AND BUSTO, R.: Mechanisms of cerebral vasodilatation in hypoxia. J. Appl. Physiol. 29: 223–229, 1970.
359. KOPIN, I. J., AND GORDON, E. K.: Metabolism of norepinephrine-H^3 released by tyramine and reserpine. J. Pharmacol. Exp. Ther. 138: 351–359, 1962.
360. KORF, J., AGHAJANIAN, G. K. AND ROTH, R. H.: Increased turnover of norepinephrine in the rat cerebral cortex during stress: Role of the locus coeruleus. Neuropharmacology 12: 933–938, 1973.
361. KORNER, P. I., STOKES, G. S., WHITE, S. W. AND CHALMERS, J. P.: Role of the autonomic nervous system in the renal vasoconstriction response to hemorrhage in the rabbit. Circ. Res. 20: 676–685, 1967.
362. KOSTOWSKI, W. AND DOLFINI, E.: Prolonged pentobarbitol narcosis in rats with lesions of midbrain raphé. Eur. J. Pharmacol. 6: 71–73, 1969.
363. KOSTOWSKI, W., GIACALONE, E., GARATTINI, S. AND VALZELLI, L.: Electrical stimulation of midbrain raphé: biochemical, behavioral and bioelectrical effects. Eur. J. Pharmacol. 7: 170–175, 1969.

364. KOVÁCH, A. G. B., HAMAR, J., NYÁRY, I., SÁNDOR, P., REIVICH, M., DÓRA, E., GYULAI, L. AND EKE, A.: Cerebral blood flow and metabolism in hemorrhagic shock in the baboon. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 2.17-2.19, Churchill Livingstone, Edinburgh, 1975.
365. KRAMER, W. AND TUYNMANN, J. A.: Acute intracranial hypertension – an experimental investigation. Brain Res. 6: 686–705, 1967.
366. KROG, J.: The effect of cervical sympathetic stimulation on cerebral blood flow in the rabbit. J. Oslo City Hosp. 13: 185–200, 1963.
367. KROG, J.: A comparative study of the effect of cervical sympathetic stimulation on cerebral blood flow. Doctoral Thesis, University of Oslo, 1964.
368. KUNA, P.: Brain blood flow in rats following cystamine, AET, serotonin and 5-methoxytryptamine. Radiobiol. Radiother. (Berlin) 6: 757–759, 1973.
369. KUSCHINSKY, W. AND WAHL, M.: Alpha-receptor stimulation by endogenous and exogenous norepinephrine and blockade by phentolamine in pial arteries of cats. Circ. Res. 37: 168–174, 1974.
370. KUSCHINSKY, W., WAHL, M., BOSSE, O. AND THURAU, K.: Perivascular potassium and pH as determinants of local pial arterial diameter in cats. Circ. Res. 31: 240–247, 1972.
371. KUSCHINSKY, W., WAHL, M. AND NEISS, A.: Evidence for cholinergic dilatatory receptors in pial arteries of cats. Pflügers Arch. 347: 199–208, 1974.
372. LAL, S. AND DE LA VEGA, C. E.: Apomorphine and psychopathology. J. Neurol. Neurosurg. Psychiat. 38: 722–726, 1975.
373. LANDERS, J. W., CHASON, J. L., GONZALEZ, J. E. AND PALUTKE, W.: Morphology and enzymatic activity of rat cerebral capillaries. Lab. Invest. 11: 1153–1259, 1962.
374. LANG, R. AND ZIMMER R.: Neurogenic control of cerebral blood flow. Exp. Neurol. 43: 143–161, 1974.
375. LANG, R., ZIMMER, R. AND OBERDÖRSTER, G.: Postischaemic O_2-availability and O_2-consumption of the isolated perfused brain of the dog. Pflügers Arch. 334: 103–113, 1972.
376. LANG, R., ZIMMER, R. AND OBERDÖRSTER, G.: Impairment of cerebrovascular autoregulation by theophylline. Exp. Neurol. 40: 661–674, 1973.
377. LANGELIER, P., PARENT, A. AND POIRER, L. J.: Decarboxylase activity of the brain capillary walls and parenchyma in the rat, cat and monkey. Brain Res. 45: 622–629, 1972.
378. LANGER, S. Z., DRASKÓCZY, P. R. AND TRENDELENBURG, U.: Time course of the development of supersensitivity to various amines in the nictitating membrane of the pithed cat after denervation or decentralization. J. Pharmacol. Exp. Ther. 157: 255–273, 1967.
379. LANGFITT, T. W. AND KASSELL, N. F.: Cerebral vasodilatation produced by brain-stem stimulation. Neurogenic control vs. autoregulation. Amer. J. Physiol. 215: 90–97, 1968.
380. LANGFITT, T. W., KASSELL, N. F. AND WEINSTEIN, J. D.: Cerebral blood flow with intracranial hypertension. Neurology 15: 761–773, 1965.
381. LASANSKY, A.: Nervous function at the cellular level: glia. Annu. Rev. Physiol. 33: 241–256, 1971.
382. LASSEN, N. A.: Cerebral blood flow and oxygen consumption in man. Physiol. Rev. 39: 183–238, 1959.
383. LASSEN, N. A.: Luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. Lancet ii: 1113–1115, 1966.
384. LASSEN, N. A.: Control of cerebral circulation in health and disease. Circ. Res. 34: 749–760, 1974.
385. LASSEN, N. A. AND AGNOLI, A.: The upper limit of autoregulation of cerebral blood flow – on the pathogenesis of hypertensive encephalopathy. Scand. J. Clin. Lab. Invest. 30: 113–115, 1972.
386. LASSEN, N. A., HØEDT-RASMUSSEN, K., SØRENSEN, S. C., SKINHØJ, E., CRONQVIST, S., BODFORSS, B. AND INGVAR, D. H.: Regional cerebral blood flow in man determined by krypton 85. Neurology 13: 719–727, 1963.
387. LASSEN, N. A. AND INGVAR, D. H.: Radioisotopic assessment of regional cerebral blood flow. Progr. Nucl. Med. 1: 376–409, 1972.
388. LASSEN, N. A. AND LANE, M. H.: Validity of internal jugular blood for study of cerebral blood flow and metabolism. J. Appl. Physiol. 16: 313–320, 1961.
389. LASSEN, N. A. AND SEJRSEN, P.: Monoexponential extrapolation of tracer clearance curves in kinetic analysis. Circ. Res. 29: 76–87, 1971.
390. LAUBIE, M. AND DROUILLAT, M.: Action de l'isoprotérénol sur l'hémodynamique et le métabolisme cérébral du chien. Arch. Int. Pharmacodyn. Thér. 170: 93–98, 1967.
391. LAVRENTIEVA, N. B., MCHEDLISHVILI, G. I. AND PLECHKOVA, E. K.: Distribution and activity of cholinesterase in the nervous structures of the pial arteries (a histochemical study). Byull. Eksp. Biol. Med. 64: 110–113, 1968.
392. LEE, T. J.-F. AND BEVAN, J. A.: The effect of nerve stimulation and pharmacological agents on the contractile activity of the isolated basilar artery of the rabbit. Proc. West. Pharmacol. Soc. 17: 129–131, 1974.
392a. LEE, T. J.-F., SU, C. AND BEVAN, J. A.: Neurogenic sympathetic vasoconstriction of the rabbit basilar artery. Circ. Res. 39: 120–126, 1976.
393. LEFKOWITZ, R. J.: Molecular pharmacology of beta-adrenergic receptors – a status report. Biochem. Pharmacol. 23: 2069–2076, 1974.
394. LENDING, M., SLOBODY, L. B. AND MESTERN, J.: Effect of hyperoxia, hypercapnia and hypoxia on blood-cerebrospinal fluid barrier. Amer. J. Physiol. 200: 959–962, 1961.
395. LENNOX, W. G. AND GIBBS, E. L.: The blood flow in the brain and the leg of man, and the change induced by alteration of blood gases. J. Clin. Invest. 11: 1155–1177, 1932.
396. LEONARD, B. E.: The effect of some β-adrenergic receptor blocking drugs on carbohydrate metabolism in mouse brain. Neuropharmacology 10: 127–144, 1971.
397. LEONARD, B. E.: A comparison between the effects of phenoxybenzamine, phentolamine and propranolol on mouse brain glycolysis. Biochem. Pharmacol. 21: 109–113, 1972.
398. LIDBRINK, P.: The effect of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Brain Res. 74: 19–40, 1974.
399. LIDBRINK, P.: Studies on central catecholamine neurons with special reference to their role in wakefulness. Thesis, University of Stockholm, 1974.
400. LIDBRINK, P. AND JONSSON, G.: Noradrenal nerve terminals in the cerebral cortex: Effects of noradrenaline uptake and storage following axonal lesions with 6-hydroxydopamine. J. Neurochem. 22: 617–626, 1974.
401. LIN, S. R.: Cerebral angiography inducing momentary cardiac arrest and systemic hypotension in the dog. Amer. J. Roentogenol. 122: 485–494, 1974.
402. LIN, S. R.: Cerebral angiography in systemic hypotension: An experimental study in the dog. Neuroradiology 8: 157–162, 1974.
403. LINDENBAUM, A., MARCHER, K., WEPIERRE, J. AND COHEN, Y.: Barrière hemato-encephalique II: Cinétique de distribution de la parahydroxyamphetamine ^3H dans les structures du cerveau de rat après administration intraveineuse. Arch. Int. Pharmacodyn. Thér. 215: 168–176, 1975.
404. LINDL, T. AND CRAMER, H.: Formation, accumulation and release of adenosine 3′,5′-monophosphate in-

duced by histamine in the superior cervical ganglion of the rat *in vitro*. Biochim. Biophys. Acta 343: 182–191, 1974.

405. LINDL, T. AND CRAMER, H.: Evidence against dopamine as the mediator of the rise of cyclic AMP in the superior cervical ganglion of the rat. Biochem. Biophys. Res. Commun. 65: 731–739, 1975.
406. LINDSLEY, D. B., BOWDEN, J. W. AND MAGOUN, H. W.: Effects upon the EEG of acute injury to the brain stem activating system. Electroencephalogr. Clin. Neurophysiol. 1: 475–486, 1949.
407. LINDVALL, M., CERVOS-NAVARRO, J., EDVINSSON, L., OWMAN, CH. AND STENEVI, U.: Non-sympathetic perivascular nerves in the brain. Origin and mode of innervation studies by fluorescence and electron microscopy combined with stereotaxic lesions and sympathectomy. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 1.7–1.9, Churchill Livingstone, Edinburgh, 1975.
408. LINDVALL, O.: Mesencephalic dopaminergic afferents to the lateral septal nucleus of the rat. Brain Res. 87: 89–95, 1975.
409. LINDVALL, O. AND BJÖRKLUND, A.: The glyoxylic acid fluorescence histochemical method: A detailed account of the methodology for the visualization of central catecholamine neurons. Histochemistry 39: 97–127, 1974.
410. LINDVALL, O. AND BJÖRKLUND, A.: The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol. Scand., Suppl. 412: 1–48, 1974.
411. LINDVALL, O., BJÖRKLUND, A., MOORE, R. Y. AND STENEVI, U.: Mesencephalic dopamine neurons projecting to neocortex. Brain Res. 81: 325–331, 1974.
412. LLUCH, S., GÓMEZ, B., ALBORCH, E. AND URQUILLA, P. R.: Adrenergic mechanisms in cerebral circulation of the goat. Amer. J. Physiol. 228: 985–989, 1975.
413. LLUCH, S., REIMANN, C. AND GLICK, G.: Evidence for the direct effect of adrenergic drugs on the cerebral vascular bed of the unanesthetized goat. Stroke 4: 50–56, 1973.
414. LÖFGREN, J., VON ESSEN, C. AND ZWETNOW, N. N.: The pressure volume curve of the cerebrospinal fluid space in dogs. Acta Neurol. Scand. 49: 557–574, 1973.
415. LOIZOU, L. A.: Uptake of monoamines into central neurones and the blood-brain barrier in the infant rat. Brit. J. Pharmacol. 40: 800–813, 1970.
416. LORENZO, A. V., SHIRAHIGE, I., LIANG, M. AND BARLOW, C. F.: Temporary alterations of cerebrovascular permeability to plasma protein during drug-induced seizures. Amer. J. Physiol. 223: 268–277, 1972.
417. LOWE, R. F. AND GILBOE, D. D.: Demonstration of alpha and beta adrenergic receptors in canine cerebral vasculature. Stroke 2: 193–200, 1971.
418. LOWE, R. F. AND GILBOE, D. D.: Canine cerebrovascular response to nitroglycerin, acetylcholine, 5-hydroxytryptamine and angiotensin. Amer. J. Physiol. 225: 1333–1338, 1973.
419. LUBSEN, N.: Experimental studies on the cerebral circulation of the unanesthetized rabbit. Arch. Neer. Physiol. 25: 287–305, 1941.
420. LUDWIGS, N. AND SCHNEIDER, M.: Über den Einfluss des Hals-sympathicus auf die Gehirndurchblutung. Pflügers Arch. 5: 261–268, 1954.
421. LUNDERBERG, D.: Some aspects of the pharmacology of the degeneration contraction of rat periorbital smooth muscle after sympathetic denervation. Abstr. Uppsala Diss. Sci. 79: 1–10, 1970.
422. LUNDGREN, Y., HALLBACK, M., WEISS, L. AND FOLKOW, B.: Rate and extent of adaptive cardiovascular changes in rats during experimental renal hypertension. Acta Physiol. Scand. 91: 103–115, 1974.
423. LUNDHOLM, L., MOHME-LUNDHOLM, E. AND SVEDMYR, N.: Metabolic effects of catecholamines – introductory remarks. Pharmacol. Rev. 18: 255–272, 1966.
424. MACDONELL, L.: Effects of noradrenaline on blood flow and metabolism in the cerebral cortex of the dog. Ph.D. Thesis, University of London, 1974.
425. See Ref. 275a.
426. MACKENZIE, E. T., MCCULLOCH, J. AND HARPER, A. M.: Influence of endogenous norepinephrine on cerebral blood flow and metabolism. Amer. J. Physiol. 231: 489–494, 1976.
427. MACKENZIE, E. T., MCCULLOCH, J., O'KEANE, M., PICKARD, J. D. AND HARPER, A. M.: Cerebral circulation and norepinephrine: Relevance of the blood-brain barrier. Amer. J. Physiol. 231: 483–488, 1976.
428. See Ref. 275b.
429. MACKENZIE, E. T., STRANDGAARD, S., GRAHAM, D. I., JONES, J. V., HARPER, A. M. AND FARRAR, J. K.: Effects of acutely induced hypertension in the cat on pial arteriolar caliber, local cerebral blood flow and the blood-brain barrier. Circ. Res. 39: 33–41, 1976.
430. MACMILLAN, V.: Regional cerebral blood flow of the rat in acute carbon monoxide intoxication. Can. J. Physiol. Pharmacol. 53: 644–650, 1975.
431. MAEDA, T., PIN, C., SALVERT, D., LIGIER, M. AND JOUVET, M.: Les neurones contenant des catécholamines du tegmentum pontique et leurs voies de projection chez le chat. Brain Res. 57: 119–152, 1973.
432. MAJNO, G., SHEA, S. M. AND LEVENTHAL, M.: Endothelial contraction induced by histamine-type mediators. J. Cell Biol. 42: 647–672, 1969.
433. MALLETT, B. L. AND VEALL, N.: The measurement of regional cerebral clearance rates in man using xenon-133 inhalation and external recording. Clin. Sci. (London) 29: 179–191, 1965.
434. MALMFORS, T. AND SACHS, C.: Direct studies on the disappearance of the transmitter and changes in the uptake-storage mechanisms of degenerating adrenergic nerves. Acta Physiol. Scand. 64: 211–223, 1964.
435. MAMO, H., SEYLAZ, J., CARON, J.-P. AND HOUDART, R.: Mesure de débit sanguin du cortex de l'homme par une méthode semi-quantitative continue et focale. Rev. Neurol. (Paris) 117: 689–713, 1967.
436. MANGOLD, R., SOKOLOFF, L., CONNER, E. L., KLEINERMAN, J., THERMAN, P. G. AND KETY, S. S.: The effects of sleep and lack of sleep on the cerebral circulation and metabolism of young men. J. Clin. Invest. 34: 1092–1100, 1955.
437. MANTEGAZZINI, P., POECK, K. AND SANTIBAÑEZ, G.: The action of adrenaline and nor-adrenaline on the cortical electrical activity of the "encéphale isolé" cat. Arch. Ital. Biol. 97: 222–242, 1959.
438. MARS, H.: Modification of levodopa effects by systemic decarboxylase inhibition. Arch. Neurol. 28: 91–95, 1973.
439. MARTRES, M.-P., BAUDRY, M. AND SCHWARTZ, J.-C.: Subsensitivity of noradrenaline-stimulated cyclic AMP accumulation in brain slices of *d*-amphetamine-treated mice. Nature (London) 255: 731–733, 1975.
440. MAYNERT, E. W. AND LEVI, R.: Stress-induced release of brain norepinephrine and its inhibition by drugs. J. Pharmacol. Exp. Ther. 143: 90–95, 1967.
441. MAZZELLA, H., MULLIN, R. G. AND AUSTT, E. G.: Effect of carotid sinus stimulation on the EEG. Acta Neurol. Lat. Amer. 3: 361–364, 1957.
442. MCCALDEN, T. A. AND EIDELMAN, B. H.: The cerebrovascular response to infused noradrenaline and its modification by a catecholamine metabolism blocker. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B Jennett, J. D. Miller and J. O. Rowan, pp. 2.10–2.11, Churchill Livingstone, Edinburgh, 1975.
443. MCCLURE, C., JR. AND GREEN, H. D.: Cerebral venous outflow in the dog: influence of adrenergic and cho-

linergic substances. Amer. J. Physiol. 197: 1183–1190, 1959.

444. McDowall, D. G.: Interrelationships between blood oxygen tensions and cerebral blood flow. *In* Oxygen Measurements in Blood and Tissues, ed. by J. P. Payne and D. W. Hill, pp. 205–219, Churchill, London, 1966.

445. Mchedlishvili, G. I. and Nikolaishvili, L. S.: Evidence of a cholinergic mechanism mediating the autoregulatory dilatation of the cerebral blood vessels. Pflügers Arch. 315: 27–37, 1970.

446. McHenry, L. C., Jr.: Quantitative cerebral blood flow determination. Application of krypton^{85} desaturation technique in man. Neurology 14: 785–793, 1964.

447. McIlwain, H.: Cyclic AMP and tissues of the brain. *In* Effects of Drugs on Cellular Control Mechanisms, ed. by B. R. Rabin and R. B. Freedman, pp. 281–302, Macmillan Co., London, 1971.

448. McIlwain, H.: Adenosine in neurohumoral and regulatory roles in the brain. *In* Central Nervous System—Studies on Metabolic Regulation and Function, ed. by E. Genazzani and H. Herken, pp. 3–11, Springer-Verlag, New York, 1974.

449. Meier, P. and Zierler, K. L.: On the theory of the indicator-dilution method for measurement of blood flow and volume. J. Appl. Physiol. 6: 731–744, 1954.

450. Meldrum, B., Anlezark, G. and Trimble, M.: Drugs modifying dopaminergic activity and behaviour, the EEG and epilepsy in *Papio papio*. Eur. J. Pharmacol. 32: 203–213, 1975.

451. Mena, M. A. and Vidrio, H.: On the mechanism of the coronary dilator effect of serotonin in the dog. Eur. J. Pharmacol. 36: 1–5, 1976.

452. Meyer, J. S., Gotoh, F., Akiyama, M. and Yoshitake, S.: Monitoring cerebral blood flow, oxygen and glucose metabolism. Circulation 36: 197–211, 1967.

453. Meyer, J. S., Ishikawa, S. and Lee, T. K.: Electromagnetic measurement of internal jugular venous flow in the monkey. Effect of epilepsy and other procedures. J. Neurosurg. 21: 524–539, 1964.

454. Meyer, J. S., Ishikawa, S., Lee, T. K. and Thal, A.: Quantitative measurement of cerebral blood flow with electromagnetic flowmeters. Trans. Amer. Neurol. Ass. 88: 78–83, 1963.

455. Meyer, J. S., Lavy, S., Ishikawa, S. and Symon, L.: Effects of drugs and brain metabolism on internal carotid arterial flow. Amer. J. Med. Electron. 3: 169–180, 1964.

456. Meyer, J. S., Nomura, F., Sakamoto, K. and Kondo, A.: Effect of stimulation of the brain stem reticular formation on cerebral blood flow and oxygen consumption. Electroencephalogr. Clin. Neurophysiol. 26: 125–132, 1969.

457. Meyer, J. S., Okamoto, S., Shimazu, K., Koto, A., Ohuchi, T., Sari, A. and Ericsson, A. D.: Cerebral metabolic changes during treatment of sub-acute cerebral infarction by alpha and beta adrenergic blockage with phenoxybenzamine and propranolol. Stroke 5: 180–195, 1974.

458. Meyer, J. S., Shimazu, K., Fukuuchi, Y., Ohuchi, T., Okamoto, S., Koto, A. and Ericsson, A. D.: Cerebral dysautoregulation in central neurogenic orthostatic hypotension (Shy-Drager syndrome). Neurology 23: 262–273, 1973.

459. Meyer, J. S., Shimazu, K., Okamoto, S., Koto, A., Ohuchi, T., Sari, A. and Ericsson, A. D.: Effects of alpha adrenergic blockade on autoregulation and chemical vasomotor control of CBF in stroke. Stroke 4: 187–200, 1973.

460. Meyer, J. S., Teraura, T., Sakamoto, K. and Kondo, A.: Central neurogenic control of cerebral blood flow. Neurology 21: 247–262, 1971.

461. Meyer, J. S., Welch, K. M. A., Okamoto, S. and Shimazu, K.: Disordered neurotransmitter function: Demonstration by measurement of norepinephrine and 5-hydroxytryptamine in CSF of patients with recent cerebral infarction. Brain 97: 655–664, 1974.

462. Meyer, J. S., Yoshida, K. and Sakamoto, K.: Autonomic control of cerebral blood flow measured by electromagnetic flowmeters. Neurology 17: 638–648, 1967.

463. Meyer, M. W. and Klassen, A. C.: Regional brain blood flow during sympathetic stimulation. *In* Cerebral Blood Flow and Metabolism, ed. by T. W. Langfitt, L. C. McHenry, Jr., M. Reivich and H. Wollman, pp. 459–461, Springer-Verlag, New York, 1975.

464. Meyer, M. W., Tschetter, T., Klassen, A. C. and Resch, J.: Regional cerebral blood flow estimated by using particle distribution and isotope clearance methods. *In* Cerebral Blood Flow, ed. by M. Brock, C. Fieschi, D. H. Ingvar, N. A. Lassen and K. Schürmann, pp. 50–52, Springer-Verlag, Berlin, 1969.

465. Meyer, M. W. and Werth, L. J.: Error analysis of a convolution integral approach to estimate local blood flow. J. Appl. Physiol. 35: 631–634, 1973.

466. Meyers, S. H., Jawetz, E. and Goldfien, A.: A Review of Medical Pharmacology, 3rd ed., Blackwell Scientific Publications, Oxford, 1967.

467. Michenfelder, J. D., Messick, J. M., Jr. and Theye, R. A.: Simultaneous cerebral blood flow measured by direct and indirect methods. J. Surg. Res. 8: 475–481, 1968.

468. Miletich, D. J., Ivankovic, A. D., Albrecht, R. F. and Toyooka, E. T.: Cerebral hemodynamics following internal maxillary artery ligation in the goat. J. Appl. Physiol. 38: 942–945, 1975.

469. Miller, J. D., Stanek, A. and Langfitt, T. W.: Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. Progr. Brain Res. 35: 411–432, 1971.

470. Miller, R., Horn, A., Iversen, L. and Pinder, R.: Effects of dopamine-like drugs on rat striatal adenyl cyclase have implications for CNS dopamine receptor topography. Nature (London) 250: 238–241, 1974.

471. Misra, S. S., Singh, K. S. P. and Bhargava, K. P.: Estimation of 5-hydroxytryptamine (5-HT) level in cerebrospinal fluid of patients with intracranial or spinal lesions. J. Neurol. Neurosurg. Psychiat. 30: 163–165, 1967.

472. Mitchell, G., Scriven, D. R. L. and Rosendorff, C.: Adrenoreceptors in intracerebral resistance vessels. Brit. J. Pharmacol. 54: 11–15, 1975.

473. Modigh, K.: Functional aspects of 5-hydroxytryptamine turnover in the central nervous system. Acta Physiol. Scand., Suppl. 403: 1–56, 1974.

474. Malnár, L. and Szántó, J.: The effect of electrical stimulation of the bulbar vasomotor centre on the cerebral blood flow. Quart. J. Exp. Physiol. Cog. Med. Sci. 49: 184–193, 1964.

475. Moruzzi, G.: Reticular influences on the EEG. Electroencephalogr. Clin. Neurophysiol. 16: 2–17, 1964.

476. Moruzzi, G. and Magoun, H. W.: Brain stem reticular formation and activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 1: 455–473, 1949.

477. Motavkin, P. A. and Dovbish, T. V.: Histochemical characteristics of acetylcholinesterase of the nerves innervating the brain vessels. Acta Morphol. Acad. Sci. Hung. 19: 159–173, 1971.

478. Motavkin, P. A. and Palashchenko, L. D.: Cholinergic and adrenergic nerves in the extramedullary arteries of the spinal cord. Acta Morphol. Acad. Sci. Hung. 21: 227–238, 1973.

479. Moyer, J. H., Morris, G. and Snyder, H.: A comparison of the cerebral hemodynamic response to aramine and norepinephrine in the normotensive and hypertensive subject. Circulation 10: 265–270, 1954.

480. Moyer, J. H., Snyder, H. and Miller, S. I.: Cerebral hemodynamic response to blood pressure reduction with phenoxybenzamine (Dibenzyline-688A). Amer.

J. Med. Sci. 228: 563–567, 1954.
481. MURPHY, D. J.: Cerebrovascular permeability after meglumine iothalamate administration. Neurology 23: 926–936, 1973.
482. NAHORSKI, S. R. AND ROGERS, K. J.: *In vivo* effects of amphetamine on metabolites and metabolic rate in brain. J. Neurochem. 21: 679–686, 1973.
483. NAHORSKI, S. R. AND ROGERS, K. J.: The role of catecholamines in the action of amphetamine and L-dopa on cerebral energy metabolism. Neuropharmacology 14: 283–290, 1975.
484. NAHORSKI, S. R., ROGERS, K. J. AND SMITH, B. M.: Histamine H_2 receptors and cyclic AMP in brain. Life Sci. 15: 1887–1894, 1974.
485. NANDA, R. N., WYPER, D. J., HARPER, A. M. AND JOHNSON, R. H.: Cerebral blood flow in paraplegia. Paraplegia 12: 212–218, 1974.
486. NANDA, R., WYPER, D. J., HARPER, A. M. AND JOHNSON, R. H.: Cerebral blood flow during hypotension and hypocapnia in patients with disorders affecting sympathetic pathways. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 2.22–2.23, Chruchill Livingstone, Edinburgh, 1975.
487. NELSON, E. AND RENNELS, M.: Innervation of intracranial arteries. Brain 93: 475–490, 1970.
488. NELSON, E. AND RENNELS, M.: Neuromuscular contacts in intracranial arteries of the cat. Science 167: 301–302, 1970.
489. NIELSEN, K. C. AND OWMAN, CH.: Adrenergic innervation of pial arteries related to the circle of Willis in the cat. Brain Res. 6: 773–776, 1967.
490. NIELSEN, K. C. AND OWMAN, CH: Contractile response and amine receptor mechanisms in isolated middle cerebral artery of the cat. Brain Res. 27: 33–42, 1971.
491. NIELSEN, K. C., OWMAN, CH. AND SPORRONG, B.: Sympathetic nervous control of pial arteries: tyramine-induced contraction of the isolated middle cerebral aretery of the cat. *In* Brain and Blood Flow, ed. by R. W. Ross Russell, pp. 244–247, Pitman Medical, London, 1971.
492. NIELSEN, K. C., OWMAN, CH. AND SPORRONG, B.: Ultrastructure of the autonomic innervation apparatus in the main pial arteries of rats and cats. Brain Res. 27: 25–32, 1971.
493. NILSSON, B.: Measurement of overall blood flow and oxygen consumption in rat brain. Acta Physiol. Scand. 92: 142–144, 1974.
494. NILSSON, B. AND SIESJÖ, B. K.: A method for determining blood flow and oxygen consumption in the rat brain. Acta Physiol. Scand. 96: 72–82, 1976.
495. NOBIN, A. AND BJÖRKLUND, A.: Topography of the monoamine neuron systems in the human brain as revealed in fetuses. Acta Physiol. Scand., Suppl. 288, 1–40, 1973.
496. NORBERG, K. AND SIESJÖ, B. K.: Quantitative measurement of blood flow and oxygen consumption in rat brain. Acta Physiol. Scand. 91: 154–164, 1974.
497. NORBERG, K.-A.: Transmitter histochemistry of the sympathetic adrenergic nervous system. Brain Res. 5: 125–170, 1967.
498. OBERDÖRSTER, G., LANG, R. AND ZIMMER, R.: Direct effects of α- and β-sympathomimetic amines on the cerebral circulation of the dog. Pflügers Arch. 340: 145–160, 1973.
499. OBERDÖRSTER, G., LANG, R. AND ZIMMER, R.: Influence of adenosine and lowered cerebral blood flow on the cerebrovascular effects of theophylline. Eur. J. Pharmacol. 30: 197–204, 1975.
500. OBRIST, W. D., THOMPSON, H. K., JR., KING, C. H. AND WANG, H. S.: Determination of regional cerebral blood flow by inhalation of ^{133}xenon. Circ. Res. 20: 124–135, 1967.
501. OHGUSHI, N.: Adrenergic fibres to the brain and spinal cord vessels in the dog. Arch. Jap. Chir. 37: 294–303, 1968.
502. OLDENDORF, W. H.: Brain uptake of radiolabeled amino acids, amines and hexoses after arterial injection. Amer. J. Physiol. 221: 1629–1639, 1971.
503. OLDENDORF, W. H.: Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. Amer. J. Physiol. 224: 1450–1453, 1973.
504. OLDENDORF, W. H.: Stereospecificity of blood-brain barrier parmeability to amino acids. Amer. J. Physiol. 224: 967–969, 1973.
505. OLDENDORF, W. H.: Brain concentrations of ^{14}C-nicotine and ^{14}C-antipyrine after intravenous injection. *In* Cerebral Circulation and Metabolism, ed. by T. W. Langfitt, L. C. McHenry, Jr., M. Reivich and H. Wollman, pp. 132–134, Springer-Verlag, New York, 1975.
506. OLDENDORF, W. H. AND SZABO, J.: Amino acid assignment to one of three blood-brain barrier amino acid carriers. Amer. J. Physiol. 230: 94–98, 1976.
507. OLESEN, J.: The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. Neurology 22: 978–987, 1972.
508. OLESEN, J.: Quantitative evaluation of normal and pathologic cerebral blood flow regulation to perfusion pressure. Arch. Neurol. 28: 143–149, 1973.
509. OLESEN, J.: Cerebral blood flow methods for measurement, regulation, effects of drugs and changes in disease. Acta Neurol. Scand., Suppl. 57: 1–134, 1974.
510. OLESEN, J.: Effect of intracarotid isoprenaline, propranolol and prostaglandin E_1 on regional cerebral blood flow in man. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 4.10–4.11, Churchill Livingstone, Edinburgh, 1975.
511. OLESEN, J. AND SKINHØJ, E.: The influence of certain vasoactive amines on the regional cerebral blood flow in man. International Headache Symposium, Sandoz, Basle, pp. 145–152, 1971.
512. OLSSON, Y., RINDER, L., LINDGREN, S. AND STALHAMMAR, D.: Studies on vascular permeability changes in experimental brain concussion. Acta Neuropathol. 19: 225–233, 1971.
513. ONOYAMA, K. AND OMAE, T.: Leakage of serum proteins in brain tissues in experimentally induced renal hypertension. Acta Neurol. Scand. 49: 339–344, 1973.
514. OPLER, L. A. AND MAKMAN, M. H.: Mediation by cyclic AMP of hormone-stimulated glycogenolysis in cultured rat astrocytoma cells. Biochem. Biophys. Res. Commun. 46: 1140–1145, 1972.
515. OSTERHOLM, J. L., BELL, J., MEYER, R. AND PYENSON, J.: Experimental effects of free serotonin on the brain and its relation to brain injury. J. Neurosurg. 31: 408–421, 1969.
516. OWMAN, CH., EDVINSSON, L., FALCK, B. AND NIELSEN, K. C.: Amine mechanisms in brain vessels, with particular regard to autonomic innervation and blood-brain barrier. *In* Pathology of Cerebral Microcirculation, ed. by J. Cervós-Navarro, pp. 184–199, Walter de Gruyter, Berlin, 1974.
517. OWMAN, CH. AND ROSENGREN, E.: Dopamine formation in brain capillaries—an enzymatic blood-brain barrier mechanism. J. Neurochem. 14: 547–550, 1967.
518. PAGE, W. R., GERMAN, W. J. AND NIMS, L. F.: The nitrous oxide method for measurement of cerebral blood flow and cerebral gaseous metabolism in dogs. Yale J. Biol. Med. 23: 462–472, 1951.
519. PANNIER, J. L. AND LEUSEN, I.: Cerebral blood flow in cats after an acute hypertensive insult with damage to the blood-brain barrier. Stroke 6: 188–198, 1975.
520. PANNIER, J. L., WEYNE, J., DEMEESTER, G. AND LEUSEN, I.: Influence of changes in the acid-base composition of the ventricular system on cerebral blood

flow in cats. Pflügers Arch. 333: 337–351, 1972.
521. PARDRIDGE, W. M. AND CONNOR, J. D.: Saturable transport of amphetamine across the blood-brain barrier. Experientia (Basel) 29: 302–304, 1973.
522. PARDRIDGE, W. M., CONNOR, J. D. AND CRAWFORD, I. L.: Permeability changes in the blood-brain barrier: causes and consequences. CRC Crit. Rev. Toxicol. 3: 159–199, 1975.
523. PARDRIDGE, W. M., CRAWFORD, I. L. AND CONNOR, J. D.: Permeability changes in the blood-brain barrier induced by nortriptyline and chlorpromazine. Toxicol. Appl. Pharmacol. 26: 49–57, 1973.
524. PAULSON, O. B.: Cerebral apoplexy (stroke): pathogenesis, pathophysiology and therapy as illustrated by regional cerebral blood flow measurements in the brain. Stroke 2: 327–360, 1971.
525. PEASE, D. C. AND MOLINARI, S.: Electron microscopy of muscular arteries; pial vessels of the cat and monkey. J. Ultrastruct. Res. 3: 447–468, 1960.
526. PEERLESS, S. J. AND YASARGIL, M. G.: Adrenergic innervation of the cerebral blood vessels in the rabbit. J. Neurosurg. 35: 148–154, 1971.
527. PERKINS, J. P. AND MOORE, M. M.: Characterization of the adrenergic receptors mediating a rise in cyclic 3′,5′-adenosine monophosphate in rat cerebral cortex. J. Pharmacol. Exp. Ther. 185: 371–378, 1973.
528. PETERS, A.: The surface fine structure of the choroid plexus and ependymal lining of the rat lateral ventricle. J. Neurocytol. 3: 99–108, 1974.
529. PICKARD, J. D., DURITY, F. WELSH, F. A., LANGFITT, T. W., HARPER, A. M. AND MACKENZIE, E. T.: Osmotic opening of the blood-brain barrier: value in pharmacological studies on the cerebral circulation. Brain Res. 122: 170–176, 1977.
530. PICKARD, J. D. AND MACKENZIE, E. T.: Inhibition of prostaglandin synthesis and the response of baboon cerebral circulation to carbon dioxide. Nature, New Biol. 245: 187–188, 1973.
531. PICKEL, V. M., SEGAL, M. AND BLOOM, F. E.: A radioautographic study of the efferent pathways of the nucleus coeruleus. J. Comp. Neurol. 155: 15–71, 1974.
532. POLITOFF, A. AND MACRI, F.: Pharmacologic differences between isolated, perfused arteries of the choroid plexus and of the brain parenchyma. Int. J. Neuropharmacol. 5: 155–162, 1966.
533. POLLAY, M.: Effect of hypertonic solutions on the blood-brain barrier. Neurology 25: 852–856, 1975.
534. POLLAY, M. AND KAPLAN, R. J.: Diffusion of nonelectrolytes in brain tissue. Brain Res. 17: 407–416, 1970.
535. PONTE, J. AND PURVES, M. J.: The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels. J. Physiol. (London) 237: 315–340, 1974.
536. POSNER, J. B.: Newer techniques of cerebral blood flow measurement. Stroke 3: 227–237, 1972.
537. PUJOLD, J. F., MOURET, J., JOUVET, M. AND GLOWINSKI, J.: Increased turnover of cerebral norepinephrine during rebound of paradoxical sleep in the rat. Science 159: 112–117, 1968.
538. PURPURA, D. P.: A neurohumoral mechanism of reticulocortical activation. Amer. J. Physiol. 186: 250–254, 1956.
539. PURVES, M. J.: The Physiology of the Cerebral Circulation, Cambridge University Press, Cambridge, 1972.
540. PURVES, M. J. AND JAMES, I. M.: Observations on the control of cerebral blood flow in the sheep fetus and newborn lamb. Circ. Res. 25: 651–667, 1969.
541. QUADBECK, G.: Drug influence on the barrier. Prog. Brain Res. 29: 349–355, 1968.
542. RAEVSKII, K. S. AND TOLMACHEVA, N. S.: Effect of morphine on permeability of the blood-brain barrier in rats to noradrenaline-H^3. Byull. Eksp. Biol. Med. 77: 56–58, 1974.
543. RAICHLE, M. E., EICHLING, J. O. AND GRUBB, R. L.: Brain permeability of water. Arch. Neurol. 30: 319–321, 1974.
544. RAICHLE, M. E., EICHLING, J. O., STRAATMANN, M. G., WELCH, M. J., LARSON, K. B. AND TER-POGOSSIAN, M. M.: Blood-brain barrier permeability of ^{11}C-labeled alcohols and ^{15}O-labeled water. Amer. J. Physiol. 230: 543–552, 1976.
545. RAICHLE, M. E., HARTMAN, B. K. EICHLING, J. O. AND SHARPE, L. G.: Central noradrenergic regulation of cerebral blood flow and vascular permeability. Proc. Nat. Acad. Sci. U.S.A. 72: 3726–3730, 1975.
546. RAISIS, J. E., KINDT, G. W. AND MCGILLICUDDY, J. E.: The effects of elevated cerebral venous pressure on cerebral blood flow and intracranial pressure. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 6.17–6.18, Churchill Livingstone, Edinburgh, 1975.
547. RALL, D. P., OPELT, W. W. AND PATLAK, C. S.: Extracellular space of brain as determined by diffusion of inulin from the ventricular system. Life Sci. 2: 43–48, 1962.
548. RALL, T. W.: Role of adenosine 3′,5′-monophosphate (cyclic AMP) in actions of catecholamines. Pharmacol. Rev. 24: 399–409, 1972.
549. RAPELA, C. E. AND GREEN, H. D.: Autoregulation of canine cerebral blood flow. Circ. Res. 14 and 15: suppl. 1, 205–212, 1964.
550. RAPELA, C. E., GREEN, H. D. AND DENISON, A. B., JR.: Baroreceptor reflexes and autoregulation of cerebral blood flow in the dog. Circ. Res. 21: 559–568, 1967.
551. RAPELA, C. E. AND MARTIN, J. B.: Reactivity of cerebral extra and intraparenchymal vasculature to serotonin and vasodilator agents. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 4.5–4.9, Churchill Livingstone, Edinburgh, 1975.
552. RAPER, A. J., KONTOS, H. A. AND PATTERSON, J. L., JR.: Response of pial precapillary vessels to changes in arterial carbon dioxide tension. Circ. Res. 28: 518–523, 1971.
553. RAPER, A. J., KONTOS, H. A. AND PATTERSON, J. L., JR.: Effect of hypoxia on pial precapillary vessels. Fed. Proc. 33: 401, 1974.
554. RAPOPORT, S. I.: Effect of concentrated solutions on blood-brain barrier. Amer. J. Physiol. 219: 270–274, 1970.
555. RAPOPORT, S. I.: Reversible opening of the blood-brain barrier by osmotic shrinkage of the cerebrovascular endothelium: opening of the tight junctions as related to carotid arteriography. *In* Small Vessel Angiography, ed. by S. K. Hilal, pp. 137–151, C. V. Mosby, St. Louis, 1973.
556. RAPOPORT, S. I., BACHMAN, D. S. AND THOMPSON, H. K.: Chronic effects of osmotic opening of the blood-brain barrier in the monkey. Science 176: 1243–1244, 1972.
557. RAPOPORT, S. I., HORI, M. AND KLATZO, I.: Testing of a hypothesis for osmotic opening of the blood-brain barrier. Amer. J. Physiol. 223: 323–331, 1972.
558. RAPOPORT, S. I. AND LEVITAN, H.: Neurotoxicity of X-ray contrast media. Amer. J. Roentgenol. Radium Ther. Nucl. Med. 122: 186–193, 1974.
559. RAPOPORT, S. I. AND THOMPSON, H. K.: Osmotic opening of the blood-brain barrier in the monkey without associated neurological deficits. Science 180: 971, 1973.
560. RAPOPORT, S. I. AND THOMPSON, H. K.: Opening of the blood-brain barrier (BBB) by a pulse of hydrostatic pressure (abstr). Biophys. J. 15: 326, 1975.
561. RAPOPORT, S. I., THOMPSON, H. K. AND BIDINGER, J. M.: Equi-osmolal opening of the blood-brain barrier in the rabbit by different contrast media. Acta Radiol. Diag. 15: 21–32, 1974.
562. RAYNOR, R. B. AND MCMURTY, J. G.: Prevention of

serotonin-produced cerebral vasospasm. Neurology 13: 94–96, 1963.
563. RAYNOR, R. B., MCMURTY, J. G. AND POOL, J. L.: Cerebrovascular effects of topically applied serotonin in the cat. Neurology 11: 190–195, 1961.
564. REESE, T. S. AND KARNOVSKY, M. J.: Fine structural localization of a blood-brain barrier to exogenous peroxidase. J. Cell Biol. 34: 207–217, 1967.
565. REIVICH, M., ISAACS, G., EVART, E. AND KETY, S. S.: The effect of slow wave sleep and REM sleep on regional cerebral blood flow in cats. J. Neurochem. 15: 301–306, 1968.
566. REIVICH, M., JEHLE, J., SOKOLOFF, L. AND KETY, S. S.: Measurement of regional cerebral blood flow with antipyrine-^{14}C in awake cats. J. Appl. Physiol. 27: 296–300, 1969.
567. RENNELS, M. L. AND NELSON, E.: Capillary innervation in the mammalian central nervous system. An electron microscopic demonstration. Amer. J. Anat. 144: 233–241, 1975.
568. REYNERS, H., GIANFELICI DE REYNERS, E., JADIN, M. AND MAISIN, J. R.: An ultrastructural quantitative method for the evaluation of the permeability to horseradish peroxidase of cerebral cortical endothelial cells of the rat. Cell Tissue Res. 157: 93–99, 1975.
569. RICHARDS, J. G., LOREZ, H. P. AND TRANZER, J. P.: Indole-alkylamine nerve terminals in cerebral ventricles: Identification by electron microscopy and fluorescence histochemistry. Brain Res. 57: 277–288, 1973.
570. RISBERG, J., ANCRI, D. AND INGVAR, D. H.: Correlation between cerebral blood volume and cerebral blood flow in the cat. Exp. Brain Res. 8: 321–326, 1969.
571. RISBERG, J., HALSEY, J. H., WILLS, E. L. AND WILSON, E. M.: Hemispheric specialization in normal man studied by bilateral measurements of the regional cerebral blood flow—a study with the 133-Xe inhalation technique. Brain 98: 511–524, 1975.
572. RISBERG, J. AND INGVAR, D. H.: Patterns of activation in the grey matter of the dominant hemisphere during memorizing and reasoning. Brain 96: 737–756, 1973.
573. ROBERTS, V. S.: Haematocrit variations and electromagnetic flowmeter sensitivity. Biomed. Eng. 4: 408–412, 1969.
574. ROBISON, G. A., BUTCHER, R. W. AND SUTHERLAND, E. W.: Adenyl cyclase as an adrenergic receptor. Ann. N.Y. Acad. Sci. 139: 703–723, 1967.
575. ROCH, P. AND KALIX, P.: Effects of biogenic amines on the concentration of adenosine 3',5'-monophosphate in bovine superior cervical ganglion. Neuropharmacology 14: 21–29, 1975.
576. ROGERS, M., DISMUKES, K. AND DALY, J. W.: Histamine-elicited accumulations of cyclic adenosine 3',5'-monophosphate in guinea-pig brain slices: Effect of H_1- and H_2-antagonists. J. Neurochem. 25: 531–534, 1975.
577. RÖNNBERG, A. L., EDVINSSON, L., LARSSON, L. I., NIELSEN, K. C. AND OWMAN, CH.: Regional variation in the presence of mast cells in the mammalian brain. Agents Actions 3: 191–192, 1973.
578. ROSENBLATT, S., CHANLEY, J. D., SOBOTKA, H. AND KAUFMAN, M. R.: Interrelationships between electroshock, the blood-brain barrier and catecholamines. J. Neurochem. 5: 172–176, 1960.
579. ROSENBLUM, W. I.: Constriction of pial arterioles produced by prostaglandin $F_{2\alpha}$. Stroke 6: 293–297, 1975.
580. ROSENBLUM, W. I.: Effects of prostaglandins on cerebral blood vessels: Interaction with vasoactive amines. Neurology 25: 1169–1171, 1975.
581. ROSENDORFF, C.: The measurement of local cerebral blood flow and the effect of amines. Progr. Brain Res. 35: 115–156, 1972.
582. ROSENDORFF, C. AND CRANSTON, W. I.: Effects of intrahypothalamic and intraventricular norepinephrine and 5-hydroxytryptamine on hypothalamic blood flow in the conscious rabbit. Circ. Res. 28: 492–502, 1971.
583. ROSENDORFF, C., MITCHELL, G., SCRIVEN, D. R. L. AND SHAPIRO, C.: Evidence for a dual innervation affecting local blood flow in the hypothalamus of the conscious rabbit. Circ. Res. 38: 140–145, 1976.
584. ROVERE, A. A., SCREMIN, O. U., BERESI, M. R., RAYNALD, A. C. AND GIARDINI, A. A.: Cholinergic mechanism in the cerebrovascular action of carbon dioxide. Stroke 4: 969–972, 1973.
585. ROWAN, J. O., CROSS, J. N., TEDESCHI, G. M. AND JENNETT, W. B.: Limitations of circulation time in the diagnosis of intracranial disease. J. Neurol. Neurosurg. Psychiat. 33: 739–744, 1970.
586. ROWAN, J. O., HARPER, A. M., MILLER, J. D., TEDESCHI, G. M. AND JENNETT, W. B.: Relationship between volume flow and velocity in the cerebral circulation. J. Neurol. Neurosurg. Psychiat. 33: 733–738, 1970.
587. ROY, S., HIRANO, A., KOCHEN, J. A. AND ZIMMERMAN, H. M.: The fine structure of cerebral blood vessel in chick embryo. Acta Neuropathol. 30: 277–285, 1974.
588. ROY, S., HIRANO, A., KOCHEN, J. A. AND ZIMMERMAN, H. M.: Ultrastructure of cerebral vessels in chick embryo in lead intoxication. Acta Neuropathol. 30: 287–294, 1974.
589. RUBIO, R., BERNE, R. M., BOCKMAN, E. L. AND CURNISH, R. R.: Relationship between adenosine concentration and oxygen supply in the rat brain. Amer. J. Physiol. 228: 1896–1902, 1975.
590. SAGAWA, K. AND GUYTON, A. C.: Pressure flow relationships in isolated canine cerebral circulation. Amer. J. Physiol. 200: 711–714, 1961.
591. SALANGA, V. D. AND WALTZ, A. G.: Regional cerebral blood flow during stimulation of seventh cranial nerve. Stroke 4: 213–217, 1973.
592. SAMARASINGHE, D. D.: The innervation of the cerebral arteries in the rat: An electron microscope study. J. Anat. 99: 815–828, 1965.
593. SAMORAJSKI, T. AND MARKS, B. H.: Localization of tritiated norepinephrine in mouse brain. J. Histochem. Cytochem. 10: 392–399, 1962.
594. SAMORAJSKI, T., MARKS, B. H. AND WEBSTER, E. J.: An autoradiographic study of the uptake and storage of norepinephrine-H^3 in tissues of mice located with reserpine and cocaine. J. Pharmacol. Exp. Ther. 143: 82–89, 1964.
595. SAPIRSTEIN, L. A.: Measurement of the cephalic and cerebral blood flow fractions of the cardiac output in man. J. Clin. Invest. 41: 1429–1435, 1962.
596. SATO, S.: An electron microscopic study on the innervation of the intracranial artery in the rat. Amer. J. Anat. 118: 873–890, 1966.
597. SATTIN, A. AND RALL, T. W.: The effect of adenosine and adenine nucleotides on the cyclic adenosine 3',5'-phosphate content of guinea pig cerebral cortex slices. Mol. Pharmacol. 6: 13–23, 1970.
598. SATTIN, A., RALL, T. W. AND ZANELLA, J.: Regulation of cyclic adenosine 3',5'-monophosphate levels in guinea-pig cerebral cortex by interaction of *alpha* adrenergic and adenosine receptor activity. J. Pharmacol. Exp. Ther. 192: 22–32, 1975.
599. SAXENA, P. E. AND DE VLAAM-SCHLUTER, G. M.: Role of some biogenic substances in migraine and relevant mechanisms in antimigraine action of ergotamine—studies in experimental model for migraine. Headache 13: 142–163, 1974.
600. SCHILD, H. O.: The use of drug antagonists for the identification and classification of drugs. Brit. J. Pharmacol. 2: 251–258, 1947.
601. SCHILDKRAUT, J. J.: The catecholamine hypothesis of affective disorders: a review of supporting evidence. Amer. J. Psychiat. 122: 509–522, 1965.
602. SCHILDKRAUT, J. J. AND KETY, S. S.: Biogenic amines

and emotion. Science 156: 21–30, 1967.
603. SCHMIDT, C. F., KETY, S. S. AND PENNES, H. H.: The gaseous metabolism of the brain of the monkey. Amer. J. Physiol. 143: 33–52, 1945.
604. SCHUBERTH, J. AND JENDEN, D. J.: Transport of choline from plasma to cerebrospinal fluid in the rabbit with reference to the origin of choline and acetylcholine metabolism in brain. Brain Res. 84: 245–256, 1975.
605. SCHUBERTH, J., SUNDWALL, A., SÖRBO, B. AND LINDELL, J.-O.: Uptake of choline by mouse brain slices. J. Neurochem. 13: 347–352, 1966.
606. SCHULTZ, J. AND DALY, J. W.: Accumulation of cyclic adenosine 3′,5′-monophosphate in cerebral cortical slices from rat and mouse: stimulatory effects of α- and β-adrenergic agents and adenosine. J. Neurochem. 21: 1319–1326 1973.
607. SCHULTZ, J. AND DALY, J. W.: Adenosine 3′,5′-monophosphate in guinea pig cerebral cortical slices: effects of α- and β-adrenergic agents, histamine, serotonin and adenosine. J. Neurochem. 21: 573–579, 1973.
608. SCHWARTZ, J.-C.: Histamine as a transmitter in brain. Life Sci. 17: 503–518, 1975.
609. SCHWARZ, G. A.: The orthostatic hypotension syndrome of Shy-Drager. Arch. Neurol. 16: 123–139, 1967.
610. SCOTT, D. E., KOZLOWSKI, G. P. AND KROBISCH-DUDLEY, G.: A comparative ultrastructural analysis of the third cerebral ventricle of the North American mink (Musteia vison). Anat. Rec. 175: 155–168, 1973.
611. SCREMIN, O. U., ROVERE, A. A., RAYNALD, A. C. AND GIARDINI, A.: Cholinergic control of blood flow in the cerebral cortex of the rat. Stroke 4: 232–239, 1973.
612. SENGUPTA, D., HARPER, M. AND JENNETT, B.: Effect of carotid ligation on cerebral blood flow in baboons: 2. Response to hypoxia and haemorrhagic hypotension. J. Neurol. Neurosurg. Psychiat. 37: 578–584, 1974.
613. SENSENBACH, W., MADISON, J. AND OCHS, L.: A comparison of the effects of *l*-nor-epinephrine, synthetic *l*-epinephrine and U.S.P. epinephrine upon cerebral blood flow and metabolism in man. J. Clin. Invest. 32: 226–232, 1953.
614. SERCOMBE, R., AUBINEAU, P., EDVINSSON, L., GRIVAS, C., MAMO, H., OWMAN, CH., PINARD, E. AND SEYLAZ, J.: CBF changes by sympathetic nerve stimulation and denervation: correlation with the degree of sympathetic innervation of cerebral arterioles. *In* Blood Flow and Metabolism in the Brain, ed. by A. M. Harper, W. B. Jennett, J. D. Miller and J. O. Rowan, pp. 2.25–2.29, Churchill Livingstone, Edinburgh, 1975.
615. SERCOMBE, R., AUBINEAU, P., EDVINSSON, L., MAMO, H., OWMAN, CH., PINARD, E. AND SEYLAZ, J.: Neurogenic influence on local cerebral blood flow: effect of catecholamines or sympathetic stimulation as correlated with the sympathetic innervation. Neurology 25: 954–963, 1975.
616. SERCOMBE, R., AUBINEAU, P., EDVINSSON L., MAMO, H., OWMAN, CH. AND SEYLAZ, J.: Pharmacological evidence *in vitro* and *in vivo* for functional *beta* receptors in the cerebral circulation. Pflügers Arch., in press, 1977.
617. SEVERINGHAUS, J. W. AND LASSEN, N. A.: Step hypocapnia to separate arterial from tissue PCO_2 in the regulation of cerebral blood flow. Circ. Res. 20: 272–278, 1967.
618. SEYLAZ, J.: Développement d'une méthode de mesure instantée, localisée et semi-quantitative du débit sanguin *in vivo*. Biophysik 2: 330–339, 1965.
619. SEYLAZ, J., AUBINEAU, P. F., CORREZE, J.-L. AND MAMO, H.: Techniques for continuous measurement of local cerebral blood flow, P_aO_2, P_aCO_2 and blood pressure in the non-anesthetized animal. Pflügers Arch. 340: 175–180, 1973.
620. SEYLAZ, J., MAMO, H., GOAS, J. Y. AND HOUDART, R.: Human CBF regulation and physiological sleep. *In* Brain and Blood Flow, ed. by R. W. Ross Russell, pp. 143–149, Pitman, London, 1971.
621. SHACKLEFORD, R. T. AND HEGEDUS, S. A.: Bilateral superior cervical sympathectomy. Effect on cerebral blood flow of normal dogs. Arch. Surg. 82: 308–313, 1961.
622. SHAKIB, M. AND CUNHA-VAZ, J. G.: Studies on the permeability of the blood-retinal barrier. IV. Junctional complexes of the retinal vessels and their role in the permeability of the blood-retinal barrier. Exp. Eye Res. 5: 229–234, 1966.
623. SHALIT, M. N., REINMÜTH, O. M., SHINMOJYO, S. AND SCHEINBERG, P.: Carbon dioxide and cerebral circulatory control. III. The effects of brain stem lesions. Arch. Neurol. 17: 342–353, 1967.
624. SHARPE, J., MARQUEZ-JULIO, A. AND ASHBY, P.: Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. Can. Med. Ass. J. 107: 296–300, 1972.
625. SHENKIN, H. A.: Effects of various drugs upon cerebral circulation and metabolism in man. J. Appl. Physiol. 3: 465–471, 1951.
626. SHIMIZU, H., CREVELING, C. R. AND DALY, J. W.: The effect of histamines and other compounds on the formation of adenosine 3′,5′-monophosphate in slices from cerebral cortex. J. Neurochem. 17: 441–444, 1970.
627. SHINOHARA, Y., MEYER, J. S., KITAMURA, A., TOYIDA, M. AND RYU, T.: Measurement of cerebral hemispheric blood flow by intracarotid injection of hydrogen gas. (Validation of the method in the monkey.) Circ. Res. 25: 735–745, 1969.
628. SHY, G. M. AND DRAGER, G. A.: A neurological syndrome associated with orthostatic hypotension. Arch. Neurol. 2: 511–527, 1960.
629. SICUTERI, F., ANSELMI, B. AND DEL BIANCO, P. L.: 5-Hydroxytryptamine supersensitivity as a new theory of headache and central pain: A clinical pharmacological approach with *p*-chlorophenylalanine. Psychopharmacologia 29: 347–356, 1973.
630. SIVERTSSON, R.: The hemodynamic importance of structural vascular changes in essential hypertension. Acta Physiol. Scand., Suppl. 343: 1–56, 1970.
631. SKINHØJ, E.: Sympathetic nervous system and the regulation of cerebral blood flow in man. Stroke 3: 711–716, 1972.
632. SKINHØJ, E., HØEDT-RASMUSSEN, K., PAULSON, O. B. AND LASSEN, N. A.: Regional cerebral blood flow and its autoregulation in patients with transient focal cerebral ischemic attacks. Neurology 20: 485–493, 1970.
633. SKINHØJ, E., AND LASSEN, N. A.: Cerebral blood flow (letter). Lancet ii: 717, 1972.
634. SKINHØJ. E., OLESEN, J. AND PAULSON, B.: Influence of smoking and nicotine on cerebral blood flow and metabolic rate of oxygen in man. J. Appl. Physiol. 35: 820–822, 1973.
635. SKINHØJ, E., OLESEN, J. AND STRANDGAARD, S.: Autoregulation and the sympathetic nervous system: A study in a patient with idiopathic orthostatic hypotension. *In* Brain and Blood Flow, ed. by R. W. Ross Russell, pp. 351–353, Pitman, London, 1970.
636. SKINHØJ, E. AND PAULSON, O. B.: Carbon dioxide and cerebral circulatory control. Arch. Neurol. 20: 249–252, 1969.
637. SKINHØJ, E. AND STRANDGAARD, S.: Pathogenesis of hypertensive encephalopathy. Lancet i: 461–462, 1973.
638. SKOLNICK, P. AND DALY, J. W.: Functional compartments of adenine nucleotides serving as precursors of adenosine 3′,5′-monophosphate in mouse cerebral cortex. J. Neurochem. 24: 451–456, 1975.

639. SKOLNICK, P. AND DALY, J. W.: Stimulation of adenosine 3',5'-monophosphate formation by *alpha* and *beta* adrenergic agonists in rat cerebral cortical slices: effects of clonidine. Mol. Pharmacol. 11: 545–551, 1975.
640. SNYDER, S. H. AND TAYLOR, K. M.: Histamine in the brain. A neurotransmitter? *In* Perspectives in Neuropharmacology, ed. by S. H. Snyder, pp. 43–73, Oxford University Press, London, 1973.
641. SOKOLOFF, L.: The action of drugs on the cerebral circulation. Pharmacol. Rev. 11: 1–85, 1959.
642. SOKOLOFF, L., MANGOLD, R., WECHSLER, R. L. AND KETY, S. S.: The effect of mental arithmetic on cerebral circulation and metabolism. J. Clin. Invest. 34: 1101–1108, 1955.
643. SOLOMON, L. S.: Failure of buffered 5-hydroxytryptamine to increase brain capillary permeability to albumin in the monkey. J. Neurosurg. 40: 717–725, 1974.
644. SPATZ, M., RAP, Z. M., RAPOPORT, S. I. AND KLATZO, I.: The effects of hypertonic urea on the blood brain barrier and on the glucose transport in the brain. *In* Steroids and Brain Edema, ed. by J. W. F. Beks, I. Klatzo, D. M. Long, H. M. Pappius and J. Ransohoff, pp. 19–27, Springer-Verlag, Berlin, 1972.
645. SPOENDLIN, H. AND LICHTENSTEIGER, W.: The sympathetic nerve supply to the inner ear. Arch. Ohren-Nasen- Kehlkopfh. 189: 346–359, 1967.
646. STEINWALL, O.: Transport inhibition phenomena in unilateral chemical injury of the blood-brain barrier. Progr. Brain Res. 29: 357–364, 1967.
647. STEINWALL, O.: Brain uptake of selenomethionine after damage to blood-brain barrier by mercuric ions. Acta Neurol. Scand. 45: 362–368, 1969.
648. STEINWALL, O, AND OLSSON, Y.: Impairment of the blood-brain barrier in mercury poisoning. Acta Neurol. Scand. 45: 351–361, 1969.
649. STERRETT, P. R., THOMPSON, A. M., CHAPMAN, A. L. AND MATZKE, H. A.: The effects of hyperosmolarity on the blood-brain barrier. A morphological and physiological correlation. Brain Res. 77: 281–295, 1974.
650. STOICA, E., MEYER, J. S., KAWAMURA, Y., HIROMOTO, H., HASHI, K., AOYAGI, M. AND PASCU, I.: Central neurogenic control of cerebral circulation. Neurology 23: 687–698, 1973.
651. STONE, H. L., RAICHLE, M. E. AND HERNANDEZ, M.: The effect of sympathetic denervation on cerebral CO_2 sensitivity. Stroke 5: 13–18, 1974.
652. STRANDGAARD, S., JONES, J. V., MACKENZIE, E. T. AND HARPER, A. M.: Upper limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. Circ. Res. 37: 164–167, 1975.
653. STRANDGAARD, S., MACKENZIE, E. T., JONES, J. V. AND HARPER, A. M.: Studies on the cerebral circulation of the baboon in acutely induced hypertension. Stroke 7: 287–290, 1976.
654. STRANDGAARD, S., MACKENZIE, E. T., SENGUPTA, D., ROWAN, J. O., LASSEN, N. A. AND HARPER, A. M.: Upper limit of autoregulation of cerebral blood flow in the baboon. Circ. Res. 34: 435–440, 1974.
655. STRANDGAARD, S., OLESEN, J., SKINHØJ, E. AND LASSEN, N. A.: Autoregulation of brain circulation in severe arterial hypertension. Brit. Med. J. 1: 507–510, 1973.
656. STUDER, R. K., WELCH, D. M. AND SIEGEL, B. A.: Transient alteration of the blood-brain barrier: Effect of hypertonic solutions administered via carotid artery injection. Exp. Neurol 44: 266–273, 1974.
657. SULSER, F., OWENS, M. L., STRADA, S. J. AND DINGELL, J. V.: Modification by desipramine (DMI) of the availability of norepinephrine released by reserpine in the hypothalamus of the rat *in vivo*. J. Pharmacol. Exp. Ther. 168: 272–282, 1969.
658. SUNDT, T. M., JR. AND MICHENFELDER, J. D.: Focal transient cerebral ischemia in the squirrel monkey: Effect on brain adenosine triphosphate and lactate levels with electrocorticographic and pathologic correlation. Circ. Res. 30: 703–712, 1972.
659. SUNDT, T. M., JR. AND WALTZ, A. G.: Cerebral ischemia and reactive hyperemia: Studies of cortical blood flow and microcirculation before, during and after temporary occlusion of the middle cerebral artery of squirrel monkeys. Circ. Res. 28: 426–433, 1971.
660. SUNDT, T. M., JR. AND WINKELMANN, R. K.: Humoral responses of smooth muscle from rabbit subarachnoid artery compared to kidney, mesentery, lung, heart and skin vascular smooth muscle. Stroke 3: 717–725, 1972.
661. SWANK, R. L. AND HISSEN, W.: Influence of serotonin on cerebral circulation. Arch. Neurol. 10: 468–472, 1964.
662. SWANSON, L. W. AND HARTMAN, B. K.: The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. J. Comp. Neurol. 163: 467–506, 1975.
663. SYMON, L., PASZTOR, E., DORSCH, N. W. C. AND BRANSTON, N. M.: Physiological responses of local areas of the cerebral circulation in experimental primates determined by the method of hydrogen clearance. Stroke 4: 632–642, 1973.
664. THORNER, M. O.: Dopamine is an important neurotransmitter in the autonomic nervous system. Lancet i: 662–665, 1975.
665. TINDALL, G. AND GREENFIELD, J. C.: The effect of intra-arterial histamine on blood flow in the internal and external carotid artery of man. Stroke 4: 46–49, 1973.
666. TODA, N.: The action of vasodilating drugs on isolated basilar, coronary and mesenteric arteries of the dog. J. Pharmacol. Exp. Ther. 191: 139–146, 1974.
667. TODA, N.: Nicotine-induced relaxation in isolated canine cerebral arteries. J. Pharmacol. Exp. Ther. 193: 376–384, 1975.
668. TODA, N. AND FUJITA, Y.: Responsiveness of isolated cerebral and peripheral arteries to serotonin, norepinephrine, and transmural electrical stimulation. Circ. Res. 33: 98–104, 1973.
669. TODA, N. AND GOLDBERG, L.: Effects of dopamine on isolated canine coronary arteries. Cardiovas. Res. 9: 384–389, 1975.
670. DE LA TORRE, J. C.: Localization of dopamine in brain following administration of L-dopa and decarboxylase inhibitor. Advan. Neurol. 2: 59–77, 1973.
671. TOWNSEND, R. E., PRINZ, P. N. AND OBRIST, W. D.: Human cerebral blood flow during sleep and waking. J. Appl. Physiol. 35: 620–625, 1973.
672. TRAYSTMAN, R. J.: Effects of chemodenervation on cerebral circulatory responses to hypoxia. Fed. Proc. 34: 384, 1975.
673. TRAYSTMAN, R. J. AND RAPELA, C. E.: Effect of sympathetic nerve stimulation on cerebral and cephalic blood flow in dogs. Circ. Res. 36: 620–630, 1975.
673a. TRENDELENBURG, U.: Modification of the effect of tyramine by various agents and procedures. J. Pharmacol. Exp. Ther. 134: 8–17, 1961.
674. UENO, H., YAMASHITA, Y. AND CAVENESS, W. F.: Regional cerebral blood flow pattern in focal epileptiform seizures in the monkey. Exp. Neurol. 47: 81–96, 1975.
675. UNGERSTEDT, U.: Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand., Suppl. 367: 1–78, 1971.
676. URQUILLA, P. R., MARCO, E. J., BALFAGON, G. AND LLUCH, S.: Adrenergic mechanisms in cerebral blood vessels: Effect of tyramine on the isolated middle cerebral artery of the goat. Stroke 5: 447–452, 1974.
677. URQUILLA, P. R., MARCO, E. J. AND LLUCH, S.: Pharmacological receptors of the cerebral arteries of the

goat. Blood Vessels 12: 53–67, 1975.
678. VANDERHAEGHEN, J. J., PÉRIER, O. AND STERNON, J. E.: Pathological findings in idiopathic orthostatic hypotension: its relationship with Parkinson's disease. Arch. Neurol. 22: 207–214, 1970.
679. VAN ORDEN, L. S., BENSCH, K. G., LANGER, S. Z. AND TRENDELENBURG, U.: Histochemical and fine structural aspects of the onset of denervation supersensitivity in the nictitating membrane of the spinal cat. J. Pharmacol. Exp. Ther. 157: 274–283, 1967.
680. VEALL, N. AND MALLETT, B. L.: Regional cerebral blood flow determination by ^{133}Xe inhalation and external recording: the effect of arterial recirculation. Clin. Sci. (London) 30: 353–369, 1966.
681. VERITY, M. A.: Morphologic studies of the vascular neuroeffector apparatus. *In* Physiology and Pharmacology of Vascular Neuroeffector Systems, ed. by J. A. Bevan, R. F. Furchgott, R. A. Maxwell and A. P. Somlyo, pp. 2–12, S. Karger, Basel, 1971.
682. WADE, L. A. AND KATZMAN, R.: 3-O-Methyldopa uptake and inhibition of L-Dopa at the blood-brain barrier. Life Sci. 17: 131–136, 1975.
683. WADE, L. A. AND KATZMAN, R.: Rat brain regional uptake and decarboxylation of L-Dopa following carotid injection. Amer. J. Physiol. 228: 352–359, 1975.
684. WAGNER, H.-J., PILGRIM, CH. AND BRANDL, J.: Penetration and removal of horseradish peroxidase injected into the cerebrospinal fluid: role of cerebral perivascular spaces, endothelium and microglia. Acta Neuropathol. 27: 299–315, 1974.
685. WAHL, M., DEETJEN, P., THURAU, K., INGVAR, D. H. AND LASSEN, N. A.: Micropuncture evaluation of the importance of perivascular pH for the arteriolar diameter on the brain surface. Pflügers Arch. 316: 152–163, 1970.
686. WAHL, M. AND KUSCHINSKY, W.: The dilatatory action of adenosine on pial arteries of cats and its inhibition by theophylline. Pflügers Arch. 362: 55–59, 1976.
687. WAHL, M., KUSCHINSKY, W., BOSSE, O. AND NEISS, A.: Micropuncture evaluation of β-receptors in pial arteries of cats. Pflügers Arch. 348: 293–303, 1974.
688. WAHL, M., KUSCHINSKY, W., BOSSE, O., OLESEN, J., LASSEN, N. A., INGVAR, D. H., MICHAELIS, J. AND THURAU, K.: Effect of L-norepinephrine on the diameter of pial arterioles and arteries in the cat. Circ. Res. 31: 248–256, 1972.
689. WAHL, M., KUSCHINSKY, W., BOSSE, O. AND THURAU, K.: Dependency of pial arterial and arteriolar diameter on perivascular osmolarity in the cat. Circ. Res. 32: 162–169, 1973.
690. WALTER, D. S. AND ECCLESTON, D.: Increase of noradrenaline metabolism following electrical stimulation of the locus coeruleus in the rat. J. Neurochem. 21: 281–289, 1973.
691. WALTZ, A. G., YAMAGUSHI, T. AND REGLI, F.: Regulatory responses of cerebral vasculature after sympathetic denervation. Amer. J. Physiol. 221: 298–302, 1971.
692. DE WARDENER, H. E. AND MILES, B. E.: The effect of haemorrhage on the circulatory autoregulation of the dog's kidney perfused in situ. Clin. Sci. (London) 11: 267–272, 1971.
693. WARE, R. A., CHANG, L. W. AND BURKHOLDER, P. M.: An ultrastructural study on the blood-brain barrier dysfunction following mercury intoxication. Acta Neuropathol. 30: 211–224, 1974.
694. WATTERS, J. W.: The effects of bradykinin and histamine on cerebral arteries of monkeys. Radiology 98: 229–304, 1971.
695. WECHSLER, R. L.: Effects of cigarette smoking and intravenous nicotine on the human brain. Fed. Proc. 17: 169, 1958.
696. WEIL-MALHERBE, H., AXELROD, J. AND TOMCHICK, R.: Blood-brain barrier for adrenaline. Science 129: 1226–1227, 1959.
697. WEIL-MALHERBE, H., WHITBY, L. G. AND AXELROD, J.: The blood-brain barrier for catecholamines in different regions of the brain. *In* Regional Neurochemistry, ed. by S. S. Kety and J. Eldes, pp. 284–292, Pergamon, Oxford, 1961.
698. WEINSTEIN, J. D., LANGFITT, T. W. AND KASSELL, N. F.: Vasopressor response to increased intracranial pressure. Neurology 14: 1118–1131, 1964.
699. WEISS, S. AND LENNOX, W. G.: The cerebral circulation. XVII. Cerebral blood flow and the vasomotor response of the minute vessels of the human brain to histamine. Arch. Neurol. Psychiat. 26: 737–744, 1931.
700. WELCH, K. M. A., HASHI, K. AND MEYER, J. S.: Cerebrovascular response to intracarotid injection of serotonin before and after middle cerebral artery occlusion. J. Neurol. Neurosurg. Psychiat. 36: 724–735, 1973.
701. WELCH, K. M. A., MEYER, J. S., TERAURA, T., HASHI, K. AND SHINMARU, S.: Ischemic anoxia and cerebral serotonin levels. J. Neurol. Sci. 16: 85–92, 1972.
702. WELCH, K. M. A., SPIRA, P. J., KNOWLES, L. AND LANCE, J. W.: Simultaneous measurement of internal and external carotid blood flow in the monkey. Neurology 24: 450–457, 1974.
703. WELLENS, D. L. F., WOUTERS, L. J. M. R., DE REESE, R. J. J., BEIRNAERT, P. AND RENEMAN, R. S.: The cerebral blood distribution in dogs and cats. An anatomical and functional study. Brain Res. 86: 429–438, 1975.
704. WESTERGAARD, E.: The fine structure of nerve fibres and endings in the lateral cerebral ventricles of the rat. J. Comp. Neurol. 144: 345–354, 1972.
705. WESTERGAARD, E.: Enhanced vesicular transport of exogenous peroxidase across cerebral vessels, induced by serotonin. Acta Neuropathol. 32: 27–42, 1975.
706. WESTERGAARD, E.: The effect of serotonin, norepinephrine and cyclic AMP on the blood-brain barrier. J. Ultrastruct. Res. 50: 383, 1975.
707. WESTERGAARD, E. AND BRIGHTMAN, M. W.: Transport of proteins across normal cerebral arterioles. J. Comp. Neurol. 152: 17–44, 1973.
708. WESTERMANN, E.: Effects of catecholamines and prostaglandins on cyclic AMP levels in brain *in vivo*. *In* Frontiers in Catecholamine Research, ed. by P. Usdin and S. H. Snyder, pp. 339–343, Pergamon, New York, 1973.
709. WHALEN, W. J., GANFIELD, R. AND NAIR, P.: Effects of breathing O_2 or O_2 + CO_2 and of the injection of neurohumors on the PO_2 of cat cerebral cortex. Stroke 1: 194–200, 1970.
710. WHETSELL, W. O., JR. AND LOCKARD, I.: Responses to intracarotid hypaque in rabbits with and without low molecular weight dextran. J. Neuropath. Exp. Neurol. 25: 283–295, 1966.
711. WHITE, R. P., HAGEN, A. AND ROBERTSON, J. T.: Experimental evaluation of the spasmogenicity of dopamine on the basilar artery. J. Neurosurg. 44: 45–49, 1976.
712. WILLIS, T.: Cerebri anatome. Martin & Allestry, London, 1664.
713. WILSON, E. M. AND HALSEY, J. H.: An improved thermal dilution method for measuring jugular venous flow. Stroke 2: 128–138, 1971.
714. WOLFF, J. R., SCHIEWECK, CH., EMMENEGGER, H. AND MEIER-RUGE, W.: Cerebrovascular ultrastructural alterations after intra-arterial infusions of ouabain, scilla-glycosides, heparin and histamine. Acta Neuropathol. 31: 45–58, 1975.
715. WYPER, D. J., LENNOX, G. A. AND ROWAN, J. O.: Two-minute slope inhalation technique for cerebral blood flow measurement in man. I. Method. J. Neurol. Neurosurg. Psychiat. 39: 141–146, 1976.
716. WYPER, D. J., LENNOX, G. A. AND ROWAN, J. O.: Two-

minute slope inhalation technique for cerebral blood flow measurement in man. II. Clinical appraisal. J. Neurol. Neurosurg. Psychiat. 39: 147–151, 1976.

717. XANALATOS, C. AND JAMES, I. M.: Effect of arterial CO_2 pressure on the response of cerebral and hind-limb blood flow and metabolism to isoprenaline infusion in the dog. Clin. Sci. (London) 42: 63–68, 1972.
718. YAMAGUCHI, T. AND WALTZ, A. G.: Hyperemia and ischemia in experimental cerebral infarction: Correlation of histopathology and regional blood flow. Neurology 21: 565–578, 1971.
719. YAMAGUCHI, T. AND WALTZ, A. G.: Non-uniform response of regional cerebral blood flow to stimulation of cervical sympathetic nerve. J. Neurol. Neurosurg. Psychiat. 34: 602–606, 1971.
720. YASHON, D., BLOCKER, D., BROWN, R. J. AND HUNT, W. E.: Quantitative *in vitro* vasoactivity of 5-hydroxytryptamine on the human basilar artery. Surg. Neurol. 3: 295–300, 1975.
721. YUDILEVICH, D. L. AND DE ROSE, N.: Blood-brain transfer of glucose and other molecules measured by rapid indicator dilution. Amer. J. Physiol. 220: 841–846, 1971.
722. YUDILEVICH, D. L., DE ROSE, N. AND SEPULVEDA, F. V.: Facilitated transport of amino acids through the blood-brain barrier of the dog, studied in a single capillary circulation. Brain Res. 44: 569–578, 1972.
723. ZERVAS, N. T., LAVYNE, M. H. AND NEGORO, M.: Neurotransmitters and the normal and the ischemic cerebral circulation. N. Engl. J. Med. 293: 812–816, 1975.
724. ZIMMER, R., LANG, R. AND OBERDÖRSTER, G.: Post-ischemic reactive hyperemia of the isolated perfused brain of the dog. Pflügers Arch. 328: 332–343, 1971.
725. ZIMMER, R., LANG, R. AND OBERDÖRSTER, G.: Effects of catecholamine infusions on cerebral blood flow and oxygen consumption of the isolated perfused dog brain. Stroke 5: 397–405, 1974.
726. ZWETNOW, N. N.: Effects of increased cerebrospinal fluid pressure on the blood flow and on the energy metabolism of the brain. Acta Physiol. Scand., Suppl. 339: 1–31, 1970.