SPECIAL ARTICLE

Vascular Mechanisms Pertaining to the Intrinsic Regulation of the Cerebral Circulation *

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IN normal and pathologic physiology, there has long been an accumulation of experimental evidence that the function and the regulation of the intraorganic blood circulation differ from those of the large vessels. The function of providing an adequate supply of blood to all tissues and organs is carried out only by the intraorganic vessels that regulate the local or regional circulation. On the other hand, the function of the heart and the large arteries as a whole consists in the maintenance of the constant level of systemic arterial pressure at an optimal condition to ensure the delivery of the necessary amount of blood to every organ at all times. The systemic circulation possesses its own regulatory mechanisms (the buffer reflexes, emanating largely from the receptors of the aortic arch and carotid sinuses), which do not have an immediate importance for the intrinsic regulation of the blood perfusion of the organs.

The Role of “Extrinsic” and “Intrinsic” Mechanisms in the Regulation of the Brain’s Blood Supply

Although it is generally recognized nowadays that the regulation of the circulation in all organs of the body is achieved by the vessels of these organs, that is, by “intrinsic mechanisms,” a contrary view had been long and firmly held regarding the cerebral circulation. It was maintained previously that the decisive role in its regulation was played by changes in the level of the systemic arterial pressure, that is, by “extrinsic” mechanisms, since in physiologic experiments the cerebral vessels usually react weakly to stimulation of the corresponding nerves and also to the action of physiologically active and pharmacologic substances.1 If this were true, it would appear that whenever a deficit in the blood supply arose in one part of the brain or another, there would be an elevation of the systemic arterial pressure, resulting in an increase in the cerebral circulation. Aside from the irrationality of such a principle of regulation (with simultaneous changes in the blood supply of other organs), there is no experimental evidence to support this view. The role of the systemic arterial pressure in the regulation of the brain’s blood supply was initially demonstrated by the fact that its level is elevated when ischemia develops in the brain. It is found, however, that when a cuff is placed on the animal’s neck,2 with occlusion of the carotid arteries, a pressor reflex is elicited from the carotid sinus receptor zone; while with compression of the brain there is an increase in the intracranial pressure,3–5 this elevation of systemic arterial pressure is apparently dependent on the ischemization of specific structures that regulate blood pressure, particularly those in the medulla oblongata,6,7 on the stimulation of the baroreceptors within the cranium; and

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on the secretion of a pressor substance into the blood. If, however, the above secondary factors are excluded and an ischemic focus in the cortex is created by occlusion of appropriate vessels, the systemic arterial pressure does not change and the circulatory deficit is compensated for only by the pial arterial system.

In general, there is no evidence that a regional circulatory insufficiency, even in as highly differentiated a tissue as the cerebral cortex, gives rise to an elevation of the systemic arterial pressure or that the latter takes part in the regulation of the blood supply to any tissues whatsoever. It follows from this that in the brain (as also in other organs) the regulation of the circulation, from the viewpoint of adequacy of blood supply to the tissue, is achieved only by intrinsic mechanisms, i.e., by the vessels of the organ, and not by extrinsic factors, such as a change in the level of the systemic arterial pressure.

**Basic Aims in the Study of the Intrinsic Vascular Mechanisms of Regulation of the Cerebral Circulation**

In the majority of studies devoted to the cerebral circulation, the methods used yield findings that do not enable us to analyze the vascular mechanisms of the brain (i.e., the behavior of different components of the cerebral vascular bed). Among such studies are the investigations of the blood volume changes of the brain by determination of its hemoglobin content; electroplethysmography; and the study of total resistance in the cerebral vessels by the use of resistography. The nitrous oxide method suffers from the limitation that it only measures the average blood flow of the brain and that it does not yield information about the variations in the blood flow in different parts of the brain. It is also evident that the mechanisms of the intrinsic regulation of the cerebral circulation cannot be studied by merely measuring the blood flow through the individual arteries that supply blood to the brain. Several workers have designed methods to study the relative changes of the regional cerebral blood flow. Most of these methods are based upon thermolectric principles, or simply on measurements of the venous outflow. They do not, however, yield information as to how the circulatory changes observed are brought about: how the different parts of the cerebral vascular system react in a given situation.

In view of the fact that the methods enumerated do not provide an opportunity to clarify the behavior of the individual vessels of the brain and their role in hemodynamic changes, the authors have been compelled to speak of the cerebral vessels in general. There is, however, reason to assume that the different parts of the vascular system of the brain—its arteries of various diameters, capillaries and veins—as in all other organs, have different kinds of innervation and react differently to various stimuli; have different functions; and play a different role in the regulation and alteration of the cerebral circulation.

Not having any direct experimental data for the analysis of the vascular mechanisms taking part in changes of the cerebral circulation, the majority of investigators assert that the fundamental locus of resistance in the circulatory system of the brain is the arterioles. As we know, this concept is based on Poiseuille's law, which was established for water flowing through narrow glass tubes. It was later shown, however, that the blood flow in the small blood vessels does not obey this law, and that an essentially opposite phenomenon occurs here; that is, the sigmoid effect.

At the present stage of the investigations of the intrinsic mechanisms that regulate the blood supply to the brain, it was thought necessary, first of all, to analyze more thoroughly the vascular mechanisms in the brain, and in particular to clarify the following: (1) the role of various parts of the circulatory system of the brain in the changes in, and regulation of, the circulation of the blood in them; (2) the direct and reflex action of neurohumoral factors on certain vascular areas of the brain, with due consideration of possible changes in their general he-
modynamics and in the capillary circulation in particular; (3) the physiologic mechanisms of correlation of the blood circulation (with the analysis of their details as a necessary condition) with brain function and metabolism. Secondly, it was necessary to investigate individual segments of vessels and their effects on hemodynamics. It was impossible, however, to limit the study to the analysis of the peripheral circulatory processes of the brain, for example, by studying only some one segment of a blood vessel; it was found necessary also to know its interaction with other parts of the peripheral vascular bed and its role in circulatory changes.

It would appear that it is only by this route that we can achieve clarification of those problems that according to Kety remain unstudied but are of particular importance: the nature and mechanism of the intrinsic control, the functions of the nervous supply to cerebral vessels, the question of vascular spasms in the brain, the relationship between regional circulation, metabolism, and function in the nervous system.

Some Methods Used by the Author to Ascertained the Functional State Various Parts of the Cerebral Vascular System

There are several problems in the study of different parts of the vascular system of the brain. One of them pertains to the major arteries of the brain: the internal carotid and vertebral arteries, which in part are situated inside the bony canals (especially their active parts) and are inaccessible to direct observation. Studies in mammals are facilitated somewhat by the fact that the major arteries of the brain, joined in the region of the circle of Willis by broad arterial anastomoses, operate as a single functional system. The following methods can be used for the continuous recording of the functional state of this system of arteries. One of the carotid arteries is usually tied off (but this does not affect the blood supply of the brain). 1. By recording the rate of blood flow out of the circle of Willis through the internal carotid artery, for example, by the use of a drop counter, it is possible, under conditions of stable aortic pressure, to determine the changes of the resistance in a vascular segment, which includes the aorta, the three functioning major arteries of the brain, the circle of Willis, and the isolated internal carotid artery. 2. By simultaneously measuring the pressure in the aorta and in the circle of Willis (with due consideration of the actual hemodynamic conditions), one can judge the magnitude of the resistance along the course of the major arteries of the brain. It has been claimed that by recording, through one of the internal carotid arteries, the velocity of propagation of a pulse wave from the aorta to the circle of Willis, “tonus” of the functioning major arteries of the brain can be judged. 4. Finally, by simultaneously recording the blood flow in the two internal carotid arteries with the aid of a photohemotachometer or any other kind of flowmeter, the change in the lumen of each of them can be estimated when one of these arteries is subjected to the action of some external factor.

Although in all the cases enumerated the total resistance (or “tonus”) is recorded along the course from the aorta to the circle of Willis, it is found that in both the common and the internal carotid artery, the tonic changes in the lumen should most likely be ascribed to what has been called the “closing mechanisms” of the internal carotid and vertebral arteries. The reason for this view was that it is these segments of the arteries that have the smallest lumina (and, consequently, also the greatest resistance), and, in addition, they can change the lumen actively within broad limits.

The width of the lumen in the major arteries of the brain can also be studied morphologically, but in doing so it is essential to take the shrinkage by the histologic treatment into account. For example, supravital fixation of these vessels in situ can be used for this purpose.

The condition of the pial arteries and veins

* Recently a new method has been elaborated for estimation of the resistance in “isolated” internal carotid arteries by means of a perfusion pump.
is best recorded by taking serial photomicrographs of them or a motion-picture film through a "window" in the skull and then using a micrometer ocular of the microscope to measure the diameters of various vessels on the individual frames of the film (consecutively at fixed time intervals).36-38

The ratio of the amounts of erythrocytes and plasma in the blood that flowed through the pial vessels in various physiologic and pathologic states was studied in total preparations of pia mater fixed intravitaly in situ at various times.39, 40

Under ordinary conditions, it is impossible to measure the blood flow in the pial arteries and veins in terms of the movement of the formed elements of the blood; but when the blood flow is slowed down under pathologic conditions this becomes possible.41 Another technic has also been used: under steady-state conditions, the cerebral vessels were filled briefly from the circle of Willis with a colorless liquid and the time taken for a particular vessel on the surface of the brain to become refilled with blood was determined.10

In order to determine the functional state of the capillaries of the cerebral cortex, it is best first to subject the tissue to supravital fixation in situ and then make microscopic preparations and stain the erythrocytes in them selectively.42 This method allows detection of certain features of the capillary circulation of the cerebral cortex in the rabbit. In order to determine the degree of intracapillary aggregation of erythrocytes in the blood flowing in the brain, a simultaneous study was made of the erythrocyte sedimentation rate in blood taken from the venous sinuses of the brain and from the femoral vein (control).43, 44

The functional state of the drainage veins that carry blood from the cranium was evaluated on the basis of their pressure gradient, the latter being measured simultaneously in the cerebral sinuses and in the cranial (superior) vena cava.37, 45

In view of the fact that blood pressure fluctuations in the aorta (and also in the cranial vena cava) can themselves be reflect-

ed in the results of studies of the cerebral circulation and even distort such results, it was found necessary, in a number of cases, to stabilize the systemic arterial (or venous) pressure either by the use of an ordinary compensator31 or by performing experiments on a "chest-head" preparation.46

**Nature of the Intrinsic Mechanisms of the Regulation of the Cerebral Circulation**

Despite many investigations of the cerebral circulation over the past hundred years, the question of the nature of the intrinsic mechanisms of its regulation, i.e., which vascular segments regulate the circulation, has still remained almost entirely unclarified. Meanwhile, before undertaking a study of the neurohumoral control over the cerebral circulation, it is important to clarify the functional significance of the various parts of the cerebral vascular bed.

Here, a departure is made from the postulate that the cerebral circulation is regulated to provide an adequate blood supply for the functional demands of the brain tissue; therefore, the behavior of various vessels of the brain were studied either during normal alterations of the functional activity of the brain, or during "compensatory" events taking place in disturbances of the cerebral circulation. To begin with, the studies under pathologic conditions appeared more promising, not only because there is a much greater diversity of conditions here and, consequently, a large number of ways in which the regulatory potentialities of the cerebral circulation can manifest themselves, but also because in this case the changes may be much more clearly manifested in a quantitative sense and hence more readily ascertained than under physiologic conditions.47

With use of a combination of methods to observe various parts of the cerebral circulation (see above), a detailed study was made of the circulation in the brain under the following conditions: when the large venous trunks at the neck of the animal were occluded,30 in terminal states,37 when the vital functions of the organism were restored,38 in
cases of traumatic cerebral edema,43, 44, 48 with occlusion of the cranial (superior) vena cava,45 with ischemization of the cortex of the cerebral hemispheres,10 in asphyxia,46, 49 and in some other disturbances of the cerebral circulation. It was found that under these conditions the role of the various segments of the cerebral vascular bed in the regulation of the blood supply is not uniform.

The functional significance of the system of internal carotid and vertebral arteries (which are termed the major arteries of the brain) in the regulation of cerebral circulation has not been given significant attention by other workers.* This is explained not only by the fact that these vessels are relatively inaccessible to direct observations (in view of their location within the bony canals) but also by the fact that the importance of the arterioles has been overemphasized and that the role of the larger arteries for the peripheral resistance has not been sufficiently analyzed. Recent studies have shown, however, that the major arteries of the brain represent a single functional system. During disturbances in the cerebral circulation, they constrict when a venous stagnation arises in the brain30 and when edema of various origins develops in the brain,36, 48, 49 In terminal states they may occlude their lumina entirely and shut off the arterial system of the brain from the other arteries of the organism.37 It was concluded that these events tend to eliminate or alleviate the circulatory disturbances in the brain. A diminution of the blood flow in the internal carotid artery due to vasoc- striction of this artery was also shown in extreme hypotension following bleeding,30 this phenomenon was considered a protective mechanism preventing cerebral edema. Active changes of the diameter of the major arteries of the brain during fluctuations of the systemic arterial pressure have also been demonstrated.31, 32 Consequently, the major arteries of the brain can change their lumina within broad limits, can give rise to changes in the blood flow, and thus participate in the regulation of the cerebral circulation. Morphologic studies of these arteries after intravital fixation of their walls in situ revealed that the "closing mechanisms" of these vessels are localized in certain sections and not along their entire length.35

The pial arteries can also actively change their lumina within broad limits. They show particularly pronounced dilatation in asphyxia (this was noted by Donders 51 as early as 1851 and later also observed by other investigators 25, 26), when the vestibular receptors are stimulated,52 during the arousal reaction,53 when there is an inadequate supply of blood to the cerebral cortex,38, 40 and when the activity of the cortical neurons is increased as a result of local application of strychnine.49, 65, 77 It is interesting to note that under certain conditions a dilation of the pial arteries is observed simultaneously with a constriction of the major arteries of the brain, i.e., the internal carotid and vertebral arteries. It is known that the pial arteries are capable of constricting actively when the intravascular pressure is elevated,54 and also after direct mechanical and electrical stimulation of the arterial wall, when the lumen of the vessel may close entirely.55 This indicates that the walls of the pial arteries can actively change their lumina within broad limits, to the point of complete closing.

With the intravital tissue-fixation method, it was found that when there are changes in the cerebral circulation, the breadth of the lumina of functioning active capillaries changes relatively little in physiologic conditions: their diameter when both carotid arteries were occluded was 8 per cent less, and their diameter when breathing 10 per cent carbon dioxide was about 6 per cent larger than the control values. In asphyxia, how-

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* The only exception is the suggestion that the major arteries of the brain, or rather, their curvature (siphon), play an important role in the damping of the pulsatile fluctuations of arterial pressure.6 The damping of the pulsatile, respiratory, and other fluctuations has since been confirmed, but this takes place even in animals in which there is no "siphon" (rabbits), and it was shown that this phenomenon can be attributed to the active changes in the tone of the major arteries of the brain.32
ever, it was found that the mean diameter was augmented by 28 per cent. The number of functioning active capillaries can be changed to a considerable extent; although in the brain, unlike other organs, the capillaries that are excluded from the circulation apparently do not close but remain open, they are transformed here into plasmatic capillaries. According to previous investigation of the mechanisms of microcirculation in blood capillaries, all these changes may depend only on changes in the intracapillary pressure and hemodynamics in the small vessels of the brain. Consequently, no experimental findings are yet known that indicate an active role of the capillary walls in changes in the cerebral circulation.

The venous system of the brain can play an active role in the regulation of the cerebral circulation, but unlike the cerebral arteries, it apparently does not participate in this regulation under ordinary conditions. It is only in extreme circumstances, when there are severe disturbances of the circulation of blood in the brain (for example, in terminal states, edema, and during occlusion of the aorta or the superior vena cava), conditions which cannot be eliminated by the compensatory mechanisms of the arterial system, that the venous system of the brain is also brought into the chain of protective reactions. Thus, an active constriction of the pial veins can set in even in spite of the presence of an elevated intravascular pressure in them (when there is occlusion of the cranial superior vena cava). It was also found that there can occur isolated constrictions of the drainage veins of the brain, which carry blood from the cerebral sinuses into the extracranial venous system, resulting in an elevation of the pressure in the cerebral veins and evidently also in the capillaries of the brain.

Thus, studies in recent years have shown that certain sections of the circulatory system of the brain can alter the size of their lumina actively and within broad limits, and consequently may be supposed to participate in the regulation of the cerebral circulation. This applies principally to the arterial system of the brain. The veins of the brain are less active, but, even so, they can participate in the regulation of the cerebral circulation. The capillaries are the least active part of the vascular system of the brain, but this does not exclude the possibility of a great diversity of changes in the capillary circulation, since it is now known that the decisive role in their genesis is played by the afferent arteries. It should be emphasized that in this case we are concerned only with the phenomena of the circulation of the blood in the strict sense and not with the importance of permeability of the capillary wall.

Functional Characteristics of Various Parts of the Arterial System of the Brain

Study of the cerebral circulation in various conditions has shown that different parts of the arterial system of the brain do not have the same function. Definite differences were found between the major arteries of the brain (the internal carotid and vertebral arteries), on the one hand, and the pial arteries, on the other.

When occlusion of the large venous trunks in the neck results in even temporary venous stagnation in the brain and an elevation of the venous pressure within its sinuses, a constriction of the major arteries of the brain ensues, as a result of which there is a temporary reduction of the flow of blood into the cerebral vessels. The same reaction of the system of internal carotid and vertebral arteries is observed in traumatic edema of the brain, when the constriction of the major arteries brings about a lowering of the blood pressure in the capillaries and veins of the entire brain. This may lead to a diminution of the filtration of liquid into the cerebral capillaries and an enhancement of the resorption of the cerebrospinal fluid. In view of the fact that under the conditions in question there does not seem to be any substantial deficit in the blood supply of the brain tissues, the pial arteries manifest the same kind.
of compensatory constrictor reaction.\textsuperscript{30, 43, 48}

The major arteries of the brain display a compensatory function not only when the pressure in the venous sinuses is elevated and the volume of the brain is enlarged in edema, but also when there are fluctuations of the systemic arterial pressure. Thus, when there were repeated elevations of the latter as a result of intravenous administration of epinephrine, the pressure in the circle of Willis first rose together with the systemic arterial pressure, but then this elevation gradually decreased and finally disappeared entirely, although the reaction of the systemic arterial pressure to epinephrine remained constant.

It was concluded that this effect was dependent on a compensatory constriction of the major arteries of the brain.\textsuperscript{31} Moreover, the respiratory fluctuations of the arterial pressure, and sometimes also the Hering-Breuer waves, are eliminated, completely or partially, from the circle of Willis and consequently also from other vessels of the brain by the active reactions of the major arteries of the brain.\textsuperscript{32} All these reactions of the major arteries of the brain seem to be directed toward the maintenance of the arterial pressure in the circle of Willis at a constant level.

A question arises as to which parts of the arterial system of the brain participate in those changes in the cerebral circulation that arise in connection with the deficit in the blood supply of the brain and the changes in the blood-supply requirements of its tissue components. When strychnine is applied to the surface of the brain cortex and corresponding changes occur in the electrical activity, the pial arteries dilate strongly and there is an increase in the blood supply to the same region of the cortex, as evidenced by the characteristic changes in the capillary circulation.\textsuperscript{42} The state of the major arteries of the brain remains unchanged here,

that is, they do not participate in the changes mentioned above in the cerebral circulation.\textsuperscript{49, 77}

When there is a deficit in the supply of blood to a large portion of the cerebral cortex, a manifest compensatory dilation of the pial arteries occurs, while the major arteries of the brain do not take part in these changes in the cerebral circulation.\textsuperscript{10} Here we have a characteristic nutritive function of the pial arteries: they are responsible for those changes in the cerebral circulation that are connected with changes in the blood-supply requirements of the brain tissue, while the major arteries of the brain do not participate in these changes.

The fact that the major arteries of the brain do not take part in the formation of the "nutritive" changes in the cerebral circulation above represents a functional characteristic of these arteries. It is not the result of some limitation of the distribution of these circulatory changes in the brain as when, for example, strychnine is applied locally. This is indicated by experiments when there is a blood deficit throughout the brain and cerebral edema develops (for example, during the restoration of vital functions after the subject has survived a terminal state): the major arteries of the brain then constrict, compensating for the edema \textsuperscript{*} while the pial arteries dilate considerably, compensating for the deficit in the blood supply.\textsuperscript{38} Such opposite reactions of the major arteries of the brain and the pial arteries are often encountered in cases of asphyxia \textsuperscript{49} and also under conditions of occlusion of the cranial (superior) vena cava.\textsuperscript{41}

Consequently, while the largest arteries that provide the blood supply of the brain (its major arteries) compensate largely for fluctuations of the systemic arterial pressure and also for circulatory disturbances in the entire brain, the smaller ones (the pial arteries) are found to have a different function,\textsuperscript{48}

\textsuperscript{*} The reduction of the blood circulation in the brain is usually so pronounced here that the restoration of the original oxygen tension is greatly delayed.\textsuperscript{58}
that is, a nutritive one: they are responsible for those changes in the cerebral circulation that are connected with the blood-supply requirements of the neural elements of the brain tissue.

It has been shown that there is a gradual transition from the characteristics of the larger arteries of the brain to those of the smaller ones. Thus, in the restoration of the vital functions of the organism after the latter has endured a terminal state, the small pial arteries dilate much more than the large ones, while the major arteries of the brain constrict.28 When the cranial vena cava of the dog is occluded, the largest pial arteries in some cases constrict somewhat (like the major ones), while the smaller ones only dilate: the smaller the diameter of the pial arteries, the greater is their "nutritive" dilation.41 Consequently, the smaller the diameter of the cerebral arteries, the more clearly manifest is their nutritive function.*

**Function of the Neural Elements within the Walls of the Cerebral Vessels; Neurohumoral Regulation of the Cerebral Circulation**

As is known, nerve fibers, individual cellular elements, and also receptors are found along the full length of the entire arterial system of the brain; they are connected both with the cervical sympathetic chain and with other craniocerebral nerves. Despite numerous attempts, however, it has not been possible to clarify the function of these neural elements. When, by analogy with studies of the vasomotor control in other organs, nerves connected with cerebral vessels were stimulated or cut or subjected to the action of various physiologically active substances (of the type of the mediators of neural excitation or their inhibitors), the cerebral vessels either did not react at all or gave a very inconstant reaction.25, 59 For this reason, it was concluded that the vessels of the brain are entirely devoid of any neural control, or else that this control is very weak.1, 26 According to this view, the regulation of the cerebral circulation is accomplished mainly by humoral factors, the chief role being attributable to the carbon dioxide, which strongly dilates certain vessels of the brain.25, 59, 60

Several years ago, the author came to the conclusion that the difficulty of demonstrating a neural control of the cerebral vessels is not explained by its absence but rather by the fact that the cerebral circulation is extremely well controlled by several factors. It is known that all the aforesaid experimental procedures (stimulation and sectioning of the vascular nerves, action of neurohumoral factors) usually interfere with the normal circulation. In the majority of other organs (in which this is not as dangerous for their vital activities as in the case of the brain) an effect is regularly produced in response to the action of the aforesaid factors (for example, vasoconstriction with stimulation of the sympathetic nerves), and later a "counterregulation" may set in (for example, constriction is replaced by vasodilatation). The effects that have been recorded enable one to make a conclusion as to the character of the action of the nerve in question on the local circulation. In the brain, however (perhaps in view of the danger of any disturbances of the blood circulation and as a result of the very exact regulation), the experimental factors in question do not have any effect, or the effect is variable, depending on the functional state of the tissue and vascular system of the brain. In all probability we also have here the cause of the lack of definite results from the study of the neurohumoral control over the cerebral circulation in the majority of experimental investigations.47

In recent years there have been studies of the neurohumoral control and neural regulation of the cerebral circulation in which consideration was given not only to the aforesaid circumstance but also to the functional characteristics of various parts of the cerebral vascular system. The study of the neurohumoral control of the major arteries of the brain was facilitated by the fact that any changes

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* Since no methods are available, nothing is yet known about the function of the radial arteries that carry blood from the surface of the brain to the capillaries of the cortex.
in the lumen of one of them, even to the point of total occlusion, has no effect upon the cerebral blood supply.\textsuperscript{29} It has been found that the internal carotid arteries are approximately as sensitive to the local action of neurohumoral agents, in terms of the threshold doses and the magnitude of the effect (epinephrine, acetylcholine, and histamine), as are the branches of the external carotid artery.\textsuperscript{33, 34} When the upper cervical sympathetic ganglion was stimulated with weak electrical current there was a definite constriction of the ipsilateral internal carotid artery, while when the stimulating current was slightly stronger, it was closed entirely.\textsuperscript{61} These experiments indicated that there is a distinct neural control of the major arteries of the brain.

The neural regulation of the cerebral circulation, achieved by reflex through the mediation of the system of internal carotid and vertebral arteries, was also established. Thus, after it had been observed that there is a compensatory constriction of these arteries that prevents stagnation of the blood in the brain,\textsuperscript{30} it was shown that there is a reflex from the baroreceptors of the venous sinuses of the brain (when the pressure was raised within them) to its major arteries, by means of which this compensatory reaction appears.\textsuperscript{63} It was later demonstrated that there are direct reflex impulses from the receptors of the carotid sinus to the major arteries of the brain; in addition to the direct effect, there are also regular changes in the sensitivity of these arteries to the local action of physiologically active substances.\textsuperscript{64}

The pial arteries can react even to very small doses of humoral transmitter substances, for example, to 0.1 \( \mu g \), per cent solution of acetylcholine (Mchedlishvili, unpublished observations). This indicates that their walls contain specialized receptors for this neurohumoral agent. So far as the direction of the reactions of the pial arteries to one and the same factor is concerned, it has been found that they are often not only different in magnitude but also opposite in character.

This constantly changing reactivity is dependent, in all probability, on the differences in the initial functional state of the corresponding parts of the cerebral cortex and vascular walls. Recently the author was able to show that when there is some deficiency of blood supply to the brain cortex, the dilating reactions to locally applied acetylcholine of the corresponding pial arteries become much higher.\textsuperscript{65}

Analysis of one of the nutritive reactions of the pial arteries (dilatation resulting in a rapid collateral influx of blood and inclusion of previously nonfunctioning arterial anastomoses in response to the occlusion of a relatively large trunk of the pial arteries) showed that under certain experimental conditions the dilatation observed is due to an active neurogenic reaction independent of the so-called Bayliss effect (the myogenic dilatation of the vascular wall to lowering of the intravascular pressure).\textsuperscript{49}

Recently experiments with use of a microsurgical technic indicate that the “nutritive” dilating reactions of the pial arteries that arise during the increased neuronal activity of the brain cortex or with developed blood-supply deficiency, can be neural in nature.\textsuperscript{65}

Consequently, there has been a gradual accumulation of experimental data regarding the neural mechanism of the regulation of the caliber not only of the major arteries of the brain, internal carotid, and vertebral arteries, but also of the pial arteries, providing for an adequate flow of blood into the cerebral cortex.

**Problem of the Physiologic Mechanisms of Correlation of Blood Supply and Brain Function**

Monro and Kellie advanced the well-known theory of the constancy and invariability of the cerebral circulation. Later numerous unsuccessful attempts were made to discover definite changes in the circulation of the

\textsuperscript{*} Similar effects were obtained in the experiments of Shimizu,\textsuperscript{92} but the method used did not give any quantitative data and hence the magnitude of the action remained unclear.

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brain. This supported the general notion that the brain circulation remains constant and that it is not influenced by changes of the brain function. Gradually, however, studies began to appear which indicated that the circulation of the blood in the brain changed with its function, just as in other organs. The activation of individual parts of the brain was found to be accompanied by an increase in the brain blood circulation.\textsuperscript{53, 66-69} These studies have, however, been concerned with net effects, that is, variations in blood flow, and the mechanisms underlying the local circulatory phenomena observed remain largely unknown.

Recently in our laboratory, studies of the cortical circulation under conditions of intensified activation of the parietal cortex by local application of strychnine were carried out. This gives rise to a marked increase of its electrical activity, and convulsive discharges appeared, accompanied by dilatation of the pial arteries. Studies of the capillaries in the cerebral cortex after they had been subjected to vital fixation in situ revealed an augmentation of the number of active capillaries by about one third. Their diameters showed an increase by about 7 per cent (statistically significant) on the average, as compared with the contralateral (control) region of the cerebral cortex.\textsuperscript{62} The increase in the number of active capillaries (in this case, the transformation of plasmatic capillaries into functioning ones) was undoubtedly to be ascribed, to a considerable extent, to an increase in the erythrocyte content in the blood, which flows from the dilated pial arteries into the corresponding capillary network: changes in the ratio of erythrocytes and plasma in the pial arteries were discovered in vital fixation of the pia mater at a time when strychnine was acting on the corresponding region of the brain.\textsuperscript{59} A slight dilatation of the functioning capillaries could have been the result of an elevation of the intracapillary pressure due to a dilatation of the pial arteries. Thus, the increase in the local circulation in the region of action of the strychnine must have been due to a dilatation of the pial arteries, and this is made all the more probable by the fact that the condition of the major arteries of the brain (internal carotid and vertebral) and the level of the systemic arterial pressure remained unchanged.\textsuperscript{49}

A question arises whether, in this case, there is an actual correlation between the functional state of the cerebral cortex and its blood supply, or whether the dilatation of the pial arteries is dependent on the direct action of strychnine on them. Experiments have made it possible to exclude this latter supposition: when strychnine acts directly on the pial arteries, the latter do not dilate but may even constrict somewhat. Consequently, the vascular reactions that we have described are the result of primary changes in the activity of the cerebral cortex, which in turn have a dilating effect on the pial arteries, giving rise to an increase in the circulation in the corresponding region of the cortex.\textsuperscript{77} This is also indicated by the fact that when the heightened activity of the cortex resulting from strychnine treatment was reduced substantially by the use of tetraethylammoniumbromide, the dilating reaction of the pial arteries was absent entirely or was considerably less pronounced.

The physiologic mechanism of this correlation between the blood-supply requirements of the cortical elements of the brain and the actual blood influx is being studied further, especially the possible role of neural mechanisms.

The widely accepted hypothesis that this form of regulation of the cerebral circulation is accomplished only as a result of an increase in the carbon dioxide content appears still to be lacking in direct experimental evidence. There is, for example, no direct proof that carbon dioxide, which is augmented in the cortical tissue during increased activity, may act upon the pial arteries. However, recent developments of technics for measurement of tissue tension of pCO\textsubscript{2} offer new possibilities for a further analysis of this question.
Some Mechanisms of Compensation in Disturbances of the Cerebral Circulation

Disturbances of the cerebral circulation can result (a) from "extrinsic" causes, such as changes in the systemic arterial or venous pressure, and consequently, from changes in the influx of blood into the brain or its outflow from the cranium, and also (b) from "intrinsic" causes (local changes in the circulation of the blood in the cerebral vessels *). In each of these pathologic states, the inherent compensatory mechanisms of the cerebral circulation make their appearance within certain limits. They attenuate and in some cases even eliminate completely the circulatory disturbances that have arisen. Recent studies have shown that the cerebral circulation possesses a considerable capacity for compensation: here we find such compensatory mechanisms as have not been discovered in any other organs of the body, including the heart.

When there is a lowering of the systemic arterial pressure, both the major arteries of the brain and the pial arteries are dilated, as a result of which the resistance in the vascular system of the brain is reduced and its blood supply tends to remain normal. Thus it was found that the cerebral circulation in the cat does not drop until the systemic arterial pressure falls below 30 mm. Hg. When the systemic arterial pressure rises, there is an opposite reaction in the arteries of the brain: a constriction of both the major arteries of the brain and the pial arteries, so that their resistance is increased to such an extent that even under conditions of arterial hypotension the cerebral circulation remains unchanged.

When the systemic arterial pressure drops to zero (terminal states, occlusion of the aorta), the vascular mechanisms in the brain begin to function, so that the circulation of the blood is maintained in the cerebral capillaries for several minutes, while in the other organs it ceases entirely. In terminal states, total occlusion of the major arteries of the brain is seen, and thus a total isolation of its arterial system from the other arteries of the organism, so that in the large arteries of the base of the brain the blood pressure is maintained at a certain level; simultaneously, the pial arteries exhibit peristalsis-like contractions, which promote the continuation of the orthograde current of arterial blood in the cerebral capillaries. At the same time the constriction of the drainage veins of the brain causes an elevation of the venous (and evidently also of the capillary) pressure, and this must promote a more complete utilization of nutrient substances from the blood.

When the outflow of blood from the cranium is impaired by occlusion of the large venous trunks in the neck and the first signs of stagnation of the blood appear in the brain, a compensatory constriction develops both in the major arteries of the brain and in the pial arteries, as a result of which the influx of blood into the brain is reduced somewhat and the appearance of stagnation of the blood is prevented. When the cranial (superior) vena cava is occluded, the stagnation of the blood that develops is accompanied simultaneously by the appearance of a deficit in the blood supply to the brain tissues, and the pial arteries dilate, manifesting their primarily nutritive function.

The system of the major arteries of the brain may also be the cause of disturbances of the circulation of blood in the brain. In deteriorated preparations it was sometimes observed that a simultaneous constriction of the entire carotid-vertebral arterial system took place which led to a diminution of the cerebral blood supply, and sometimes to the death of the organism. The cause of such a general constriction is not clear, but hypoxia may play a role in it.

When individual branches of the cerebral arteries, which are situated peripherally to the circle of Willis, are occluded there are active reactions of the pial arteries that result in a rapid collateral influx of blood into the region in which there is a reduced cerebral

* This study will deal with the functional and not the morphologic aspects of the disorders of the cerebral circulation.
circulation. If the branches of the middle cerebral artery are occluded, we find in the corresponding area of the brain surface a considerable number of previously nonfunctioning arterial anastomoses with the branches of anterior and posterior brain arteries (under normal conditions, the majority of these anastomoses are not closed but serve as plasmatic vessels). 40

The development of traumatic edema of the brain is accompanied by compensatory constriction of both the major arteries of the brain and the pial arteries, and as a result the pressure drops in the veins, and probably also within the capillaries, of the brain. At the same time, there is a decrease in the surface area of the walls of the cerebral capillaries. All of this creates the conditions for a decrease in the filtration of liquid out of the vessels into the brain tissues and also for a heightened resorption of cerebrospinal fluid and a lowering of its pressure. 43, 44, 48

True capillary stasis in the brain with edema apparently arises as a result of the same process as stasis in other organs, that is, an increased intravascular aggregation of erythrocytes. 28, 77 Such an aggregation is in fact discovered in the brain in cases of traumatic edema. 43, 44

Despite the highly controlled regulation and high compensatory capacity of the cerebral circulation, it is often not possible to eliminate disturbances of this system, and the death of the organism results. This is explained by the fact that under many conditions (for instance, after recovery from severe ischemia, when the aorta is blocked, or when the superior vena cava is occluded) two types of disturbances take place in the brain: a deficit in the blood supply, on the one hand, and a cerebral edema, on the other. Here the vascular mechanisms of the brain that compensate for the deficit in the blood supply aggravate the cerebral edema, and vice versa. 28, 41, 45 This interferes with the natural protective adaptations of the organism to overcome disturbances of the cerebral circulation.

Summary

A review is given of recent work on the vascular mechanisms that participate in the intrinsic control of the cerebral circulation. The main emphasis is given to studies carried out at the Department of Pathophysiology, Institute of Physiology of the Georgian Academy of Sciences in Tbilisi (USSR). Physiologic as well as pathophysiologic mechanisms are considered. Emphasis is given to the important role of the large arteries carrying blood to the brain—the internal carotid and the vertebral arteries (major arteries of the brain)—in the regulation of cerebral circulation. These vessels differ in several respects from the smaller cerebral (pial) arteries in their functional and vasomotor behavior. The pial arteries have mainly a "nutritive" role as demonstrated during, for example, changing demands of blood supply for the cerebral tissue. Some recent data are presented that stress the important role played by the vasomotor innervation and by humoral factors for different parts of the cerebral vascular system during normal and pathologic events. A survey is also given of mechanisms pertaining to the cerebral venous system in the various compensatory vascular reactions during pathologic states of the brain.

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References *


* Because of unusual circumstances the form of the bibliographic references does not conform to our usual editorial style.
REFERENCES


Timelessness of Learning

Very late in life, when he was studying geometry, someone said to Lacydes, "Is it then a time for you to be learning now?" "If it is not," he replied, "when will it be?"—Diogenes Laertius, in The Lives and Opinions of Eminent Philosophers.
Vascular Mechanisms Pertaining to the Intrinsic Regulation of the Cerebral Circulation
GEORGE I. MCHEDISHVILI

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