Factors Influencing Cerebral Blood Flow and Metabolism

A Review

By Peritz Scheinberg, M.D., and Harold W. Jayne, M.D.

The results of studies utilizing the nitrous oxide technic for measuring cerebral blood flow have been reviewed and divided into three groups: (1) those in which cerebral blood flow and metabolism were normal, (2) those in which cerebral blood flow was increased, and (3) those in which cerebral blood flow and metabolism were decreased. The factors which apparently regulate and control cerebral blood flow and metabolism are reviewed and discussed.

The development of the nitrous oxide technic for the determination of cerebral blood flow by Kety and Schmidt in 1945 has resulted in considerable clarification of many problems related to the circulation and metabolism of the brain; simultaneously these studies have raised many new questions and opened new vistas for speculation and investigation into the problems of cerebral circulation and metabolism. Prior to the use of this technic, numerous indirect methods of estimating changes in cerebral blood flow had been in use. None was entirely satisfactory, though each made some definite contribution to our knowledge. Direct observations of pial blood vessels through a glass window in the skull had the disadvantages of using animals rather than man, and inferences concerning changes in intracerebral vessels had to be made from observing pial vessels, which may not react similarly to vessels within the brain substance. Measurement of arterial-cerebral venous oxygen differences is useful in some instances in estimating changes in cerebral blood flow, but no quantitative values can be obtained, and certain alterations in cerebral metabolism will obviate even these estimations. The dye injection method and rate of displacement of spinal fluid are useful procedures; the latter is complicated by the fact that changes in circulation in the skin of the face may directly affect the measurement.

The nitrous oxide procedure is an application of the Fick principle, which states, in effect, that the amount of a substance deposited in an organ in a given period of time is equal to the amount of that substance brought to the organ by the arterial blood minus the amount removed by the venous blood. Cerebral venous blood is obtained from a needle placed in either internal jugular bulb, for the composition of blood in both is essentially the same. Arterial blood is obtained from any convenient artery. Blood is drawn from both these sources as the patient breathes a nonanesthetic mixture of nitrous oxide. The final nitrous oxide concentration in the brain is obtained by inference from the cerebral venous nitrous oxide concentration after equilibrium between venous blood and brain has occurred. Cerebral oxygen and glucose consumption are the products of cerebral blood flow and arterial-cerebral venous oxygen and glucose differences respectively. Cerebral vascular resistance is the quotient of mean arterial pressure divided by cerebral blood flow. Cerebral venous oxygen tension can be computed from the per cent oxygen saturation of cerebral venous blood by means of a standard oxyhemoglobin dissociation curve drawn for pH 7.4.

It should be pointed out that the nitrous
oxide procedure for measuring cerebral blood flow is different from most physiologic applications of the Fick principle in that it measures blood flow per unit weight of brain tissue, and therefore is not dependent upon a knowledge of the weight of the organ. This has certain advantages and disadvantages. One advantage is that determination of brain weight in any given individual would obviously be difficult and unquantitative. A disadvantage is that normal values for cerebral blood flow and metabolism could theoretically be obtained even if a portion of the brain were completely removed, provided that the circulation to and metabolism of the remainder of the brain were still normal.

There has been some discrepancy in the reported normal values for cerebral blood flow. Using a modification of the original nitrous oxide procedure, in which the mean arteriovenous nitrous oxide difference was measured by drawing simultaneous continuous samples from the artery and vein, rather than five separate samples from each, Scheinberg and Stead found a normal mean cerebral blood flow value of 65 ml. per minute per 100 Gm. brain. The reasons for this difference from Kety's reported normal mean value of 54 are not entirely clear, and may be due to differences in the technics.

The normal cerebral blood flow represents about 14 per cent of the total cardiac output. The brain extracts considerably more oxygen from the blood flowing through it than does either the liver or the kidney, so that the normal cerebral oxygen consumption is 3.8 ml. oxygen per minute per 100 Gm. brain, or about 53 ml. oxygen per minute for the whole brain. Thus the brain, an organ of only 1400 Gm., accounts for about 22 per cent of the total oxygen consumption of the body. The importance of the brain in the metabolic scheme of the body is even further emphasized by the finding that normal cerebral glucose consumption is 6.2 mg. glucose per minute per 100 Gm. brain, or about 87 mg. glucose per minute for the whole brain. This represents about 70 per cent of the total glucose output of the normal liver. Numerous studies have established that the cerebral respiratory quotient is practically unity, indicating that carbohydrate is the almost exclusive foodstuff of the brain. Although all the oxygen consumed by the brain is apparently utilized in the oxidation of glucose, this oxidation is not complete, and a portion of the glucose is converted to intermediary products, such as lactate and pyruvic acids. Stoichiometrically, the total utilization of 6.0 cc. of oxygen (the normal arterial-cerebral venous oxygen difference) would be accomplished by 8 mg. of glucose. Thus 8 mg. of the 9.9 mg. of glucose (the normal arterial-cerebral venous glucose difference) utilized by the brain can be accounted for by oxidation. The 1.2 mg. of lactic acid and 0.22 mg. pyruvic acid freed by the brain may be considered as representing the anaerobic breakdown of equivalent amounts of glucose. Added to 8 mg. (aerobic consumption), this gives a total of 9.4 mg. of glucose metabolized, which corresponds fairly closely with the measured value of 9.9 mg. Since the brain appears to be incapable of maintaining normal function by energy from the anaerobic breakdown of glucose, a constant supply of oxygen is essential. A constant supply of glucose is also necessary for cerebral cells are apparently able to use only carbohydrates for energy purposes.

The great dependence of brain cells upon a constant and prosperous oxygen environment is well known clinically and cerebral symptoms are prominent in extensive pulmonary disease, at high altitude, or during asphyxia or carbon monoxide poisoning. Apparently certain portions of the brain are able to withstand anoxia better than others, and it appears that the newest areas phylogenetically are most rapidly injured, so that the higher central nervous system functions, such as speaking, thinking, and remembering, are most likely to be permanently impaired by anoxia of short duration. As a matter of fact, unconsciousness usually results in five to seven seconds after complete cessation of cerebral blood flow and anoxia persisting for more than four to five minutes usually results in death, although higher functions may be impaired by much shorter periods of anoxia.

The arterial anatomy of the cerebral circulation is of considerable interest and clinical importance. It consists exclusively of the two internal carotid and vertebral arteries, and
those sources communicate with each other at their entrance into the brain substance in the circle of Willis. It is generally thought that under ordinary circumstances there is little or no exchange of blood among the various sources.\textsuperscript{19} Studies have shown that when one of the internal carotids is occluded, the circle of Willis acts as an anastomotic channel, and the blood flow and oxygen consumption on the two sides of the brain remain essentially equal but may both be reduced from normal.\textsuperscript{20} The rather high incidence of hemiplegias and other complications following unilateral carotid ligation may be explained by failure of the circle of Willis to function as an anastomotic channel.

Although we are still unable to draw final conclusions concerning all the factors responsible for the regulation of cerebral blood flow and metabolism, we are much farther along in our thinking as a result of studies by the nitrous oxide technic. In addition to gaining specific information about the mechanisms which may regulate cerebral circulation, these studies have granted us further insight into the pathologic physiology of the various disease states studied. For greater clarity these conditions may be divided into three groups: (1) those in which cerebral blood flow and metabolism are unchanged, (2) those in which cerebral blood flow is increased, and (3) those in which cerebral blood flow and metabolism are decreased.

**Group I. Cerebral Blood Flow and Metabolism Normal (Table 1)**

*Apprehension, Artificial Fever, Hyperthyroidism.* These will be discussed together, for they all represent states in which cardiac output and total body metabolism are increased. Loose usage of the term *apprehension* in relation to cardiovascular dynamics has resulted in unnecessary confusion. The effects of apprehension on the cardiovascular apparatus will be entirely dependent on the individual's reaction, and general statements, without specific accompanying data, may have no significance. The psychiatric state of acute emotional disturbance defined as apprehension may result in any or all of the following circulatory changes: (1) Tachycardia and increased pulse pressure, with decreased peripheral resistance; this results in an increase in cardiac output of some 40 to 50 per cent and a similar increase in total oxygen consumption.\textsuperscript{21} (2) Bradycardia, increased sweating, constriction of skin vessels as characterized by paleness, followed by hypotension, and occasionally, fainting; in this group cardiac output may be below normal.\textsuperscript{21} (3) Hyperventilation, associated with changes in the circulation which can no longer be attributed to apprehension per se. Cerebral blood flow studies in a group of normal young men who fell into the first part of the above classification revealed normal values for cerebral blood flow and cerebral oxygen consumption.\textsuperscript{24} Under these circumstances, at least, the brain does not share in the increased cardiac output and total oxygen consumption.

In a group of patients with hyperthyroidism, in whom the mean basal metabolic rate was +54, the average increase in cardiac output was 35 per cent.\textsuperscript{22} A similar group of patients showed normal values for cerebral blood flow.

<table>
<thead>
<tr>
<th></th>
<th>CMRO\textsuperscript{*}</th>
<th>CVR\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apprehension</td>
<td>Normal</td>
<td>Slightly Increased</td>
</tr>
<tr>
<td>Induced Fever</td>
<td>Normal</td>
<td>Slightly Increased</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Essential Hypertension</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Stellate Block</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Intravenous Procaine</td>
<td>Normal</td>
<td>Slightly Increased</td>
</tr>
<tr>
<td>Histamine</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Insulin Hypoglycemia</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Uremia</td>
<td>Deceased</td>
<td>Normal</td>
</tr>
<tr>
<td>Desoxycorticosterone</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Glucose</td>
<td>Normal</td>
<td>Normal or Increased</td>
</tr>
<tr>
<td>Toxemia of Pregnancy</td>
<td>Normal or or De-</td>
<td>Normal or Increased</td>
</tr>
<tr>
<td>20° Head-up Tilt</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

\textsuperscript{*} CMRO\textsubscript{2} = Cerebral oxygen consumption

\textsuperscript{†} CVR = Cerebral vascular resistance
and metabolism. This rather surprising finding indicates that the previously accepted belief that cardiac output in hyperthyroidism is increased secondarily to a generalized increased demand of the tissues for blood is probably much too simple. Neither the brain nor the splanchnic area have a low peripheral resistance to act as a stimulus for an increased cardiac output. The finding of a normal cerebral blood flow and metabolism in hyperthyroidism, however, does not further very much our understanding of the psychic manifestations which occur in this disease. Perhaps a series of observations on patients with true psychoses of hyperthyroidism will clarify the issue.

Cardiac output and total body metabolism are greatly increased during induced fever, but cerebral blood flow and metabolism are unchanged in patients with asymptomatic neurosyphilis, and probably normal individuals, during induced fever. It is possible, though no absolute evidence exists to confirm it, that this inability of the brain to increase its metabolism may indicate a relative cerebral metabolic deficiency, and may conceivably account for the delirium which frequently accompanies fever, and even for the aberrant mental behavior seen in some patients with hyperthyroidism. This, however, is at best a conjecture. Until recently, existing evidence indicated that cerebral metabolism normally goes on at its optimal and maximal rate, for those circumstances which increased cardiac output or general body metabolism seemed to have no effect on cerebral circulation and metabolism; however, preliminary studies by Kety and his associates indicate that cerebral metabolism may be increased by injections of epinephrine or muscular exercise.

Essential Hypertension. There is a great increase in cerebral vascular resistance in hypertension uncomplicated by evident renal, cardiac, or peripheral vascular disease, although blood flow and oxygen consumption remain normal. There may be some discrepancy in the reported values for cerebral blood flow in hypertension, for recent observations show a value for cerebral blood flow greater than the value for normal subjects as obtained in that laboratory. This increase in cerebral vascular resistance would appear to be related specifically to an increase in the tone of the cerebral vessels, since none of the other factors known to alter cerebral vascular resistance appear to be operative in this disease. It appears to be rather a reflection of a uniform increase in vascular tone throughout the body. The mechanism for this increase in vascular tone is still unidentified, but studies have indicated that the increased tone can be at least partially relaxed by a drop in arterial pressure, whether such a reduction in pressure is produced by differential spinal sympathetic block, dihydroergocornine, head-up tilt, thoracolumbar sympathectomy. There is no satisfactory explanation for the observation that cerebral vascular relaxation is not sufficient to maintain normal blood flow following differential spinal block, whereas a normal blood flow is maintained during the reduction in blood pressure resulting from the administration of dihydroergocornine.

Stellate Ganglion Block, Intravenous Nicotinic Acid and Procaine. Unilateral or bilateral stellate ganglion block with procaine produces no alteration in cerebral blood flow, metabolism, or vascular resistance in normals, subjects with essential hypertension, with cerebral vascular disease, and most types of acute cerebral vascular accidents. Recent studies suggest that bilateral stellate ganglionectionomy may reduce cerebral vascular resistance in patients with parkinsonism. Interpretation of the statistical analyses of these last data, however, remains somewhat controversial. These studies throw some doubt on the concept that the sympathetic innervation of brain vessels plays a significant role in regulation of cerebral blood flow and also casts considerable doubt on the role of cerebral vascular spasm in the pathogenesis of most varieties of cerebral vascular accidents. Certainly these findings would indicate that stellate block has, at best, a questionable role in the treatment of most types of vascular accidents. It should be pointed out that young patients with cerebral embolisms have not been included in the above studies, and statements concerning the efficacy of stellate block in such subjects cannot be made. Nicotinic acid also produces no change in
cerebral blood flow, even when administered intravenously in large dosage. The intense facial blush produced by nicotinic acid is another reminder that an increase in skin circulation does not necessarily reflect an increase in cerebral circulation. Intravenous procaine in large doses produces no apparent change in cerebral blood flow and may actually increase cerebral vascular tone. Intravenous histamine results in a considerable decrease in cerebral vascular resistance with no change in cerebral blood flow or metabolism. This decrease in cerebral vascular tone may be a response to the fall in arterial pressure resulting from histamine. There is no evidence that this drug has any direct action on cerebral vessels.

Schizophrenia. The finding of normal values for cerebral blood flow and metabolism in schizophrenia does not shed light on the mechanisms regulating cerebral blood flow but does indicate that striking aberrations in mental function may coexist with normal cerebral metabolic values. This is a clinical confirmation of the negative pathologic findings in the brains of schizophrenics.

Insulin Hypoglycemia and Uremia. In both these circumstances cerebral metabolism is reduced even though cerebral blood flow remains normal. In insulin hypoglycemia the mechanism for the reduction in cerebral metabolism appears to be the deprivation of glucose, essential to normal function of cerebral cells. The decreased cerebral vascular resistance which accompanies this condition may be a compensatory effort by the body to provide the needed additional nourishment to the brain. It is not known how long cerebral blood flow would be maintained in a normal range under these circumstances, for the experiments were of an acute nature.

In those patients with uremia who do not have complicating vascular disease, cerebral blood flow and vascular resistance may be normal in association with reduced cerebral metabolism. The lack of correlation between cerebral metabolism and nonprotein nitrogen in these patients suggests that the defect in cerebral oxygen consumption is not due to the presence in the blood of nitrogenous wastes per se, but may be due to the widespread chemical and metabolic disturbances known to occur in uremia.

Desoxycorticosterone Glucoside. The failure of cerebral blood flow and oxygen consumption to change when the cerebral arteriovenous glucose difference and cerebral glucose consumption are greatly decreased following administration of desoxycorticosterone glucoside is of great interest and is difficult to explain. It would indicate that glucose can be "released" from the brain, perhaps from its glycogen stores. These observations lend support to clinical studies on the effects of steroidal hormones on cerebral functions of man.

Toxemia of Pregnancy. Cerebral blood flow remains normal, though there is a great increase in cerebral vascular tone in the toxemias of pregnancy. In the most severe cases, classified as true eclampsia, cerebral oxygen consumption is decreased, apparently due to inability of the cerebral cells to extract normal quantities of oxygen from the blood.

Twenty Degree Head-Up Tilt. The slight decrease in effective cerebral arterial pressure which occurs when a subject is tilted head up twenty degrees is sufficient to relax cerebral vascular tone so that cerebral blood flow remains normal. This differs from the changes resulting from a greater degree of tilting, as will be discussed later.

Group II. Cerebral Blood Flow Increased (Table 2)

Carbon Dioxide (5 to 7 per cent), Diabetic Coma, Anoxia (10 per cent Oxygen). Although only a few conditions exist in which cerebral blood flow has been shown to be increased, through them a great deal has been learned about the mechanisms regulating the flow of blood in the brain. It is not known in what manner the inhalation of 5 to 7 per cent carbon dioxide increases cerebral blood flow (averaging 75 per cent above normal); it may be a local effect of the carbon dioxide on the vessels themselves, but it is more likely the result of the acidosis (blood pH 7.3) which results. This latter theory is supported by the finding of an increased cerebral blood flow in severe diabetic acidosis, in which there is a decreased blood pH, and a markedly decreased carbon dioxide ten-
sion.\textsuperscript{45} There appears to be an excellent correlation between cerebral blood flow and arterial pH in both these circumstances, blood flow increasing as hydrogen ion concentration rises. The association of a decreased cerebral vascular resistance and decreased cerebral oxygen consumption in diabetic coma is further evidence that local brain metabolism has no consistent effect upon cerebral vascular tone. In moderate diabetic acidosis, cerebral blood flow is decreased and cerebral oxygen consumption decreased moderately, but as the acidosis progresses, cerebral blood flow increases even though the patient may be in coma. This seeming paradox is probably the result of the great increase in hydrogen ion concentration in the blood as acidosis progresses, even though carbon dioxide tension progressively decreases.

The increased cerebral blood flow resulting from administration of 5 to 7 per cent carbon dioxide should be remembered in the treatment of patients in whom it is desired to speed up the cerebral circulation. Apparently anoxia (administration of 10 per cent oxygen) also has a powerful dilator effect on cerebral vessels,\textsuperscript{44} indicating that oxygen tension may play a role in the regulation of cerebral vascular resistance. It is thought that this effect of anoxia upon cerebral vessels is of the greatest clinical importance in the subject’s adjustment to relatively acute changes in oxygen environment (such as high altitude); however, further studies at high altitude are necessary to confirm this impression. The administration of oxygen in concentrations above that of room air may actually cause a slight constriction of cerebral vessels.\textsuperscript{44}

\textbf{Anemia of Acute Blood Loss.} In the few cases studied, the anemia of acute blood loss appears to cause an increase in cerebral blood flow commensurate to the rise in cardiac output which occurs.\textsuperscript{46} This increase in circulation is a compensatory mechanism which maintains a normal state of oxygen delivery and is common to all tissues and organs and not exclusively a property of cerebral vessels. That this compensatory increase does not occur in all types of anemia will be demonstrated later. It is possible that decreased blood viscosity in anemia may account for some of the increase in circulatory rate.

\textbf{Cerebral Hemangioma.} The rapid blood flow in cerebral hemangioma is to be expected and is simply a reflection of the presence of arteriovenous shunting, so that the blood does not pass through cerebral capillaries.\textsuperscript{47} Its occurrence is of practical importance in that the measurement of cerebral blood flow may be a diagnostic aid in doubtful cases.

\textbf{Papaverine.} Papaverine, in large doses, apparently has a direct effect on cerebral vessels, resulting in cerebral vasodilatation.\textsuperscript{38, 39} The increased cerebral blood flow is an indication that the effect of papaverine is due to more than the fall in arterial pressure which follows its administration.

\textbf{Thiopental Anesthesia and Natural Sleep.} Anesthesia produced by Thiopental results in a 30 per cent decrease in cerebral oxygen consumption, probably indicating a direct depressant effect on the cerebral cells. The slight increase in cerebral blood flow and decrease in cerebrovascular resistance may be completely unrelated to the Thiopental, but due to the increased arterial carbon dioxide tension which occurs in such anesthetized patients.\textsuperscript{12} Natural sleep is accompanied by no such alteration in cerebral oxygen consumptions, which remains normal.\textsuperscript{48} The slight increase in cerebral blood flow in natural sleep is unexplained, but again may be related to decreased ventilatory exchange and accompanying elevation of arterial carbon dioxide tension.

\textbf{GROUP III. CEREBRAL BLOOD FLOW DECREASED (Table 3)}

As can be observed from table 3, a reduction in cerebral blood flow may be present with a
normal, increased, or decreased cerebral oxygen consumption, and may even occur in the presence of a decrease in cerebral vascular resistance. The inconsistency of the relationship among these various cerebral metabolic values lends credence to the belief that the rate of cerebral metabolism does not consistently influence cerebral vascular tone. There is little doubt that it plays a role in certain conditions, such as pernicious anemia and myxedema, but the mechanisms whereby changes in cerebral metabolism may influence cerebral vessel tone remain obscure. Hyperventilation and Administration of 85 to 100 per cent Oxygen. The reduction of cerebral blood flow in hyperventilation seems to be related to the alkalosis resulting from the over-breathing, again adding support to the belief that hydrogen ion concentration is an important factor in the regulation of cerebral circulation, blood flow decreasing as blood pH rises. The reason for the increased cerebral metabolism accompanying hyperventilation is not at all clear, particularly since such subjects usually show considerable depression in their level of awareness. The cerebral vascular constriction which accompanies the breathing of high oxygen content gas has been previously mentioned.

Polycythemia. The role of blood viscosity in cerebral circulation is exemplified by the increased vascular resistance accompanying poly-cythemia. The thicker blood apparently offers greater frictional resistance to its flow through small vessels, and clinical confirmation of this phenomenon is seen in numerous cerebral symptoms, such as vertigo, giddiness, headache, and vascular occlusions, which accompany this disease.

Motionless Standing. Although an increase in the arterial pressure head does not result in increased cerebral blood flow, a great decrease in cerebral arterial pressure is usually followed by a reduction in blood flow, as indicated by data collected in normal subjects in the upright posture. Under most circumstances the decreasing cerebral blood flow is compensated for by increased oxygen extraction by the brain so that cerebral metabolism remains normal. If this compensating mechanism is stretched too far, however, cerebral metabolism will probably fall and the subject will faint. This ability of the brain to maintain a stable rate of oxygen utilization during changes in blood flow when cellular function remains intact is also exemplified in heart failure, many patients with cerebral vascular disease, and following intravenous administration of aminophylline or caffeine. The fall in cerebral vascular resistance in the upright posture may represent true dilatation of cerebral vessels in response to a drop in arterial pressure, or it may be the result of a decrease in pressure on the venous side of the capillaries, thereby decreasing peripheral resistance. Recent investigations on the human centrifuge indicate that a fall in cerebral arterial pressure induced by gravitational stress may be compensated for by strikingly decreased cerebral venous pressure with fairly adequate maintenance of cerebral circulation.

Increased Intracranial Pressure. An increase in intracranial pressure results in an increase in cerebral vascular resistance, probably due to compression of cerebral vessels. Cerebral blood flow does not decrease, however, until intracranial pressure is three to four times its normal level, because the rising arterial pressure which accompanies a rising intracranial pressure partially compensates for the increased resistance. This compensatory mechanism soon

<table>
<thead>
<tr>
<th>Table 3.—Group III. Cerebral Blood Flow Decreased</th>
<th>CMRO₂</th>
<th>CVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>O₂ (85–103%)</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Motionless Standing</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Increased Intracranial Pressure</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cerebral Vascular Disease</td>
<td>Normal or Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Myxedema</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Pernicious Anemia</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Diabetic Acidosis</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Pentothal Narcosis</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>ACTH or Cortisone</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
</tbody>
</table>
fails, however, and cerebral hypoxia results in mental cloudiness and coma. The intimate communication of the cerebrospinal fluid with the veins of the body plays an important role in protecting the cerebral vessels from rapid changes in arterial or venous pressure (as in a sneeze or cough), for the increased pressure is thereby transmitted to the cerebrospinal fluid, thereby cushioning the cerebral vessels.

Cerebral Vascular Disease. Organic occlusion of cerebral vessels results in a progressive reduction in cerebral blood flow, which is at first compensated by increased oxygen extraction so that oxygen consumption remains normal despite a greatly increased cerebral vascular resistance.\textsuperscript{32} As the occlusive disease progresses, however, the decreased blood flow can no longer be compensated by widening of the cerebral arteriovenous oxygen difference and cerebral oxygen consumption falls. There is a striking correlation in these patients between oxygen consumption and mental status and these studies demonstrate the various stages in the progression of cerebral vascular disease. In the presence of an already decreased cerebral blood flow the occurrence of any unusual drop in arterial pressure or momentary decrease in cardiac output may be sufficient to result in cerebral circulatory stasis and thrombosis. This may be the explanation for certain types of cerebral vascular accidents. The nitrous oxide procedure may also be used clinically to distinguish between certain types of affective and organic psychoses, for, as already mentioned, schizophrenic patients show no alteration in cerebral blood flow or metabolism.

Heart Failure. Although cerebral blood flow is reduced some 40 per cent below normal in chronic low output heart failure, greatly increased cerebral oxygen extraction results in only a small (13 per cent) decrease in cerebral oxygen consumption.\textsuperscript{33} The mechanism for the increased cerebral vascular tone in heart failure is not yet known, but apparently the brain, like the liver, continues to receive its normal percentage share of the decreased cardiac output. The finding that cerebral blood flow and oxygen consumption are reduced in heart failure comes as somewhat of a surprise, for it has been felt that the disproportionate reduction in renal blood flow seen in heart failure was the result of the body's efforts to maintain a normal circulation in other organs. If such favored organs exist, the brain is not one of them. The great reduction in cerebral blood flow in heart failure is a physiologic explanation for the mental symptoms frequently seen in cardiac patients.

Aminophylline and Caffeine. The administration of aminophylline or caffeine apparently results in cerebral vascular constriction, even though normal cerebral metabolism is maintained.\textsuperscript{37, 38} The use of such a drug in the treatment of cerebral vascular disease is obviously contraindicated.

The importance of local tissue needs as a regulator of cerebral blood flow and vascular resistance is demonstrated in the group of conditions in which the reduction of cerebral metabolism may be the mechanism which initiates the changes in blood flow and vascular resistance.

Myxedema. In myxedema the reduction in cerebral metabolism and blood flow and increase in vascular resistance are reversible following thyroid therapy,\textsuperscript{55} suggesting that replacement of this metabolic substance permits the return of normal cellular metabolism and thereby increases the demand of the tissue for blood. It also appears that the reduction in cardiac output in myxedema is the result of the decreased tissue demands for blood. The abnormal mental symptoms of patients with myxedema, and even the syndrome of myxedematous madness, are probably due to the decreased cerebral metabolism, for there is an adequate correlation between the severity of mental status changes and degree of reduction of cerebral oxygen and glucose metabolism in myxedema. A similar type of situation may obtain in pentothal narcosis, paresis, and partially in diabetic coma.

Pernicious Anemia. Studies in pernicious anemia have served to emphasize the point that this disease cannot be considered as a simple anemia in its effects upon the cardiovascular apparatus.\textsuperscript{46} The patients studied fell into two groups, those with severe anemia and those with moderate or no anemia. In the first group, cerebral blood flow was increased and
cerebral vascular resistance decreased; in the second group, cerebral blood flow was decreased and vascular resistance increased. In both groups, cerebral oxygen and glucose consumption were decreased. There was a good correlation between the mental status defects and cerebral oxygen consumption. Specific therapy (with liver or B₁₂) resulted in a moderate increase in cerebral oxygen consumption and cerebral vascular resistance. In no instance did cerebral oxygen consumption become normal, despite the fact that many of the patients returned to normal clinically. The patients with pernicious anemia demonstrate the unusual disparity which may occur between mental status and physical activity on the one hand and cerebral oxygen consumption on the other, for many of them were able to remain ambulatory and active with greatly decreased rates of oxygen and glucose metabolism. The studies also demonstrated that pernicious anemia results in specific nervous system involvement not related to the anemia and that this damage is at least partly irreversible. The results emphasize the great importance of early and accurate diagnosis in pernicious anemia so that therapy can be instituted before irreversible changes occur.

Diabetic Acidosis. The reduction in cerebral oxygen consumption in diabetic acidosis may be partially attributable to a fundamental derangement in the cellular biochemical processes responsible for the normal utilization of oxygen, but the presence of large quantities of circulating ketone bodies in diabetic acidosis also probably plays an important role in the reduction of cerebral metabolism. Early in diabetic acidosis there is a fair correlation between cerebral oxygen consumption and cerebral blood flow, but as acidosis progresses the decreasing blood pH produces a high cerebral blood flow and low cerebral vascular resistance even in the face of a strikingly decreased cerebral oxygen consumption.

Pentothal Narcosis and Central Nervous System Syphilis. In Pentothal narcosis the primary mechanism responsible for the defects in cerebral metabolism and accompanying alterations of mental status and consciousness appears to be impaired cerebral cellular metabolic activity. This depressant effect upon the brain cells in Pentothal narcosis is acute, usually temporary, and unquestionably due to the drug itself; the precise way in which it interferes with cellular metabolism is unknown. Studies on patients with meningovascular syphilis and paresis indicate that at least two mechanisms may be responsible for the measured reduction in cerebral metabolism and for the changes in mental status which may occur in these conditions. Small vessel occlusion as a result of the syphilis may cause cerebral ischemia and reduction in cerebral blood flow and metabolism. The reduction in cerebral metabolism may also be due mainly to primary injury of the brain cells by the disease, rendering them incapable of utilizing oxygen properly, and resulting in diminished cerebral blood flow secondarily. The increase in cerebral blood flow and metabolism following specific therapy (fever and penicillin) supports, at least partially, this latter hypothesis.

In all these conditions cerebral vascular tone and cerebral blood flow appear to be regulated, in part, by cerebral metabolic demands. A reduction in cerebral metabolism, whether it is the result of a lack of an indispensible cellular metabolite or the presence of an injurious foreign agent, is apparently capable of stimulating an increased cerebral vascular resistance and decreased blood flow. That this is not inevitably true is demonstrated by the greatly reduced cerebral vascular resistance which may accompany a low cerebral metabolism in insulin shock or some phases of diabetic acidosis, and the normal cerebral vascular resistance which accompanies decreased cerebral metabolism in uremia. Even so, the importance of local tissue needs as a regulator of cerebral blood flow cannot be dismissed. The mechanisms whereby decreased cellular metabolism results in these changes have not yet been elucidated.

Adrenocorticotrophic Hormone (ACTH) and Cortisone. The administration of ACTH and cortisone results in a reduction in cerebral blood flow and cerebral metabolism and increased vascular resistance, findings which may explain the alterations in mental status frequently noted in patients being treated with these preparations. The mechanisms for these altera-
tions in cerebral metabolic functions are not clear; the metabolic alkalosis accompanying ACTH or cortisone administration may be partially responsible.19

In summary, it can be stated that the regulation of cerebral blood flow and metabolism is accomplished by a variety of complex mechanisms, all of which appear to operate interdependently. These factors include the arterial pressure head, blood viscosity, cerebral venous tone, intracranial pressure, degree of cerebral vascular occlusion, blood pH, blood oxygen and carbon dioxide content, and local cerebral tissue requirements. By investigating these mechanisms, we have enhanced our knowledge of many diseases affecting the brain and thereby are able to approach their therapy more rationally. Changes in mental status, if characterized by an alteration in the level of awareness of the patient, are usually accompanied by a decrease in cerebral metabolism; however, changes in mental function and great alterations in behavior pattern of a patient, such as in schizophrenia, are not necessarily related to abnormal cerebral metabolism. The causes for this type of mental aberration remain to be discovered. The great potentialities of any investigative procedure which permits inquiry into the intricacies of mental function are obvious, as is the eventual value of these investigations to the clinical physician in his handling of patients.

REFERENCES


6 Finessinger, J. E.: Cerebral circulation. XVIII.


21 Hickam, J. B., Cargill, W. H., AND Golden, A.: Cardiovascular reactions to emotional stimuli; effect on the cardiac output, arteriovenous oxy-
23 Scheinberg, P.: Cerebral circulation and metabol
26 Kety, S. S.: Personal communication.
27 —, Hafkenschiel, J. H., Jeffers, W. A., Leo
pold, I. H., and Shenkin, H. A.: The blood flow, vascular resistance and oxygen consump
28 Hafkenschiel, J. H., Crumpton, C. W., Shen
30 Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H., and Jeffers, W. A.: The effects of di
41 Bentinck, R. C., Gordon, G. S., Adams, J. E., Ar
42 McCall, M. L.: Cerebral blood flow and metabo
46 Scheinberg, P.: Unpublished data.
48 Mangold, R., Sokoloff, L., Therman, P. O., Con
ner, E. H., Kleinerman, J. S., and Kety, S. S.: Cerebral blood flow and oxygen consump
49 Kety, S. S., and Schmidt, C. F.: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, car-


Factors Influencing Cerebral Blood Flow and Metabolism: A Review
PERITZ SCHEINBERG and HAROLD W. JAYNE

Circulation. 1952;5:225-236
doi: 10.1161/01.CIR.5.2.225

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/5/2/225

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/