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Cerebral Blood Flow and Oxygen Consumption in Man

NIELS A. LASSEN¹

*Laboratory of Clinical Science, National Institute of Mental Health, National Institutes
of Health, Bethesda, Maryland*

THE BLOOD FLOW AND OXYGEN METABOLISM of the human brain has been studied intensively since Kety developed the inert gas method in 1945. More than 200 clinical studies employing this method have been published so far, and now the former terra incognita is well mapped out. The information gained from all these studies will form the subject of the present review. It will also include, however, the results obtained by an indicator injection technique which has been applied to the measurement of cerebral blood flow in man to a much more limited extent. The early results obtained in this particular field have been reviewed by Schmidt (292) and Kety (156-163) and by other authors (38, 61, 76, 216, 281, 307). The aim of the present review is to offer an up to date presentation of the subject, and, in particular, to discuss certain aspects in greater detail. The general field of cerebral circulation was reviewed by Wolff in 1936 (348), by many authors in a comprehensive study in 1938 (41), and extensive bibliographic compilations of original contributions from 1938 to 1952 have also been published (255, 256). The pharmacology of the cerebral circulation alone, which has recently been reviewed by Sokoloff (318), forms an overwhelming body of knowledge. In the present study great emphasis will be put on information regarding cerebral oxygen consumption in man, whereas only scant attention will be paid to the intermediary metabolism of the brain. Himwich in 1951 published an excellent review (142) of much of the pertinent literature in this rapidly expanding field. Reference is also made to the recent study by Sokoloff (319).

The first attempt to measure the cerebral blood flow in man was made in 1941 by observing the displacement of spinal fluid caused by compression of the

¹ Visiting Scientist. Present address: Department of Neuromedicine, Rigshospitalet, University of Copenhagen, Denmark.

two jugular veins (74). This method, however, was based upon assumptions whose validity must be seriously questioned (315). Better methods are now available: the inert gas method (170) and the indicator injection method (110). These two methods also permit measurement of the cerebral oxygen uptake. The inert gas method is presumably the most accurate, and it is at the same time technically the less complicated of the two methods. Therefore it is not surprising that it has won wide acceptance and that it has been the method of choice for the study of the cerebral circulation in man.

INERT GAS METHOD

The inert gas method is based on the Fick Principle (79). This principle represents a practical application of the law of conservation of matter to the problem of blood flow measurements. Regarding the inert gas method, the Fick Principle may be phrased: Blood flow to any organ or to the body as a whole may be obtained as the ratio between the uptake of inert gas per unit time and the arteriovenous inert gas difference across the organ in question. Kety and Schmidt developed the inert gas method and applied it to the study of cerebral circulation in man (155, 170, 173). Although the method has since been successfully adapted for the measurement of blood flow in other organs in man, as well as in various experimental animals, human cerebral blood flow measurements have remained the most important application of the inert gas method. The procedure may be briefly described as follows: An inert gas is introduced into the arterial blood supply of the brain via the lungs. During a suitable period of inhalation of a constant concentration of the gas, blood samples are taken from a peripheral artery—assumed to be representative of the cerebral arteries—and from the main venous drainage from the brain, the internal jugular vein. After a suitable experimental period ensuring a fair degree of saturation of all cerebral tissues, it is possible to estimate indirectly the inert gas uptake per unit weight of brain from the venous concentration. But it is not possible in this way to estimate the inert gas uptake in the total brain. For this reason the inert gas method does not measure total cerebral blood flow but the flow per unit weight of the brain. The unit of brain weight referred to is usually 100 gm. Therefore, in the following discussion, the abbreviation CBF will be taken to mean the cerebral blood flow per 100 gm of brain per minute. The CMRO₂ is the cerebral metabolic rate of oxygen calculated by multiplying the CBF and the corresponding arteriovenous oxygen difference. The unit of CMRO₂ is cc of O₂ consumed per 100 gm of brain per minute.

The original technique (173) employed 15% N₂O as the inert gas and a 10-minute inhalation period. During this period, five samples were taken from a peripheral artery and five from one of the internal jugular veins. Several minor modifications have been introduced: The continuous sampling technique of Scheinberg and Stead (284) reduced the number of blood samples necessary, but it probably also reduced the accuracy of the method; the volume of the blood samples has been reduced for the adaptation of the method for studies in children (11, 99, 152, 153); the use of Kr⁸⁵ (a β -emitting isotope of krypton) as the inert gas, increasing the number of blood samples, and sampling from both internal jugular

veins, have resulted in some gain in precision (188, 234). A more fundamental modification has recently been developed by Lewis and associates, using the γ -emitting Kr⁷⁹ as the inert gas (197, 198). By direct and continuous external measurement of the amount of inert gas in the whole brain and simultaneous blood sampling, it is possible to calculate the total cerebral blood flow and to follow any fairly rapid changes in this flow.

The inert gas method is based upon a number of assumptions. These will be discussed with special regard to the different modifications. It will become apparent that some of the assumptions are only approximately correct. For this reason it is of considerable importance that the validity of the method has been clearly demonstrated by Kety and Schmidt (170, 173). These authors found a good agreement between the inert gas method and direct blood flow measurements in nine monkey experiments covering a large span of perfusion values (CBF values from 17 to 76 cc/100gm/min.).

Choice of Inert Gas

It is assumed that the inert gas employed does not influence the CBF and CMRO₂. In nearly all clinical studies 15% N₂O has been used as described by Kety and Schmidt (170, 173). Usually the subjects feel a slight tingling in the hands and feet, and often they become somewhat drowsy. It thus appears that even in as low a concentration as 15% nitrous oxide is not completely devoid of cerebral effects. When radioactive isotopes are employed, the concentration of the inert tracer is infinitesimally small and there is no evidence of cerebral effects. The normal values determined by the original N₂O method (173) are almost identical with those obtained much later by the Kr⁸⁵ modification (188). This demonstrates that 15% N₂O does not significantly affect the CBF and CMRO₂. The choice of inert gas depends on the analytical problems and on the nature of the physiological situation which is to be studied. The 15% N₂O is easy to administer and analyze, and for many kinds of studies the accuracy obtained is sufficient. Employment of radioisotopes allows a highly specific, accurate and rapid analysis, which can readily be adapted for handling a large number of samples per study (188, 197, 198). Such techniques permit the reduction of random experimental errors (234). Gamma-emitting inert gases allow, as already stated, the study of rapid changes in total cerebral blood flow (197, 198).

Solubility of Inert Gases in Brain and Blood

The ratio of the solubility of the inert gas in brain and whole blood is a factor necessary for calculating cerebral blood flow. Both N₂O and Kr⁸⁵ are somewhat more soluble in red cells than in plasma (167, 188). Hence it follows that the whole blood solubility and, therefore, also the above mentioned ratio, varies to some extent with the hematocrit value. In pronounced cases, variations of about 10 per cent can be calculated (167, 188). When comparing groups of subjects with different hematocrit levels, omission of correction for this factor may thus be expected to cause a moderate systematical error of CBF and CMRO₂. No correction for the influence of variations of the hematocrit has been used in studies

employing the N_2O technique, whereas such a correction has been applied by Lassen and Munck when developing the Kr^{85} modification (188).

Individual variations in the solubility of inert gases in the brain are presumably quite small. N_2O studies demonstrated the same solubility in pathological brain tissue as in normal human and canine brain (167). The absolute value of the brain-blood partition coefficient is of much less importance for the method than its constancy. The experimental procedures employed in determining this coefficient for N_2O and Kr^{85} have inherent technical difficulties which could tend to give somewhat low values (167, 188). For N_2O the coefficient was found to be 1.00 (167) and for Kr^{85} , 1.06 for a hematocrit of 50% (188). Simultaneous N_2O and Kr^{70} studies have confirmed that the ratio of the coefficients is close to 1.00/1.06 (197). When γ -emitting inert gases are used, the calculation of the total cerebral blood flow and oxygen uptake is independent of the solubility in brain and blood (197).

Effect of Heterogeneous Cerebral Perfusion²

When calculating the CBF according to the equation of Kety and Schmidt (173), it is assumed that at the end of the experiment the average inert gas tension of the brain is the same as the tension of the mixed cerebral venous blood. For each separate cerebral tissue and its corresponding venous blood this relation holds true, as diffusion equilibrium is almost instantaneous according to theoretical calculations by Copperman, cited by Kety (159). However, as the various cerebral tissues have different perfusion rates (95, 164), this obviously does not apply for the brain as a whole before all cerebral tissues are in diffusion equilibrium with the arterial inert gas tension. Thus, ideally, the experiment should be carried on until all cerebral tissues are completely saturated, as recently reemphasized by Sapirstein and Ogden (269). In practice, however, it is only important that the assumption is approximately fulfilled. Like Kety and Schmidt (170, 173), nearly all investigators have used an experimental duration of 10 minutes. The choice of 10 minutes was based on theoretical considerations (170) and on animal experiments where direct comparison was made between the N_2O concentrations of the whole brain and the mixed cerebral venous blood (167). External γ -ray measurement of the cerebral uptake of radioactive inert gases in man gave confirmatory evidence (157).

When the CBF is calculated serially for each minute, as recommended by Kety and Schmidt (173), it becomes apparent that the CBF value does not reach a constant minimal value at 10 minutes. The calculated CBF continues to decrease beyond 10 minutes, although a marked leveling-off of values is usually noted. This observation indicates that the effect of heterogeneous perfusion is also present to a small degree at 10 minutes. Kety and Schmidt were originally of the opinion that the cerebral perfusion was so rapid that even the areas of slowest perfusion

² Strictly speaking the term, heterogeneous cerebral clearance rate of gases, should be used, as the proper exponential coefficients are ratios of both perfusion and relative solubility (159). The relative solubility of inert gases in different areas of the brain varies much less than the perfusion rates (95), and for this reason it was felt justified to use the term, heterogeneous cerebral perfusion, as it is much easier to conceptualize.

were in equilibrium with the mixed cerebral venous blood after 10 minutes. For this reason they attributed the continued decrease of the calculated CBF to extracerebral contamination (173). Lassen and Munck interpreted the same phenomenon differently (188). They held the opinion that some intracerebral tissue might have a relatively slow perfusion rate. The slow saturation of inert gas in such a tissue could cause the observed phenomenon. An attempt was made to take into account this slow component of supposedly cerebral origin. The duration of the experiment was extended to about 14 minutes, and a procedure of extrapolation to infinite time employed.

Recent animal experiments by Kety and associates (164) have tended to resolve this question. These studies show that the white matter of the brain has a rather slow uptake rate of inert gases—so slow that it may well account for the fraction of the jugular blood which only slowly reaches the arterial inert gas concentration. Inserting the perfusion rates determined experimentally in normal unanesthetized cats (164) in the equations of Kety (159), it can be calculated that the inert gas tension of the whole brain reaches, in 10 minutes, about 90 per cent of the simultaneous inert gas tension of the mixed cerebral venous blood. In normal man the CBF value calculated at 10 minutes is thus at most about 10 per cent higher than the true value.

The discussion in the present section is confined to the average case in which no significant extracerebral contamination of the cerebral venous blood sampled occurs (see below). It is concluded that due to heterogeneous cerebral perfusion, the 10-minute CBF value is always moderately higher than the true value. In subjects with high perfusion rates of all cerebral tissues the error is relatively small. A somewhat greater error is to be expected in subjects with subnormal CBF, with intracranial arteriovenous shunts or with an arterial inert gas curve which continues to rise at an unusual rate. Inserting fairly extreme values in the proper equations (159), it becomes apparent that the error in such cases is not likely to exceed 25 per cent. Thus, the effect of heterogeneous cerebral perfusion would not seriously invalidate the inert gas method. Apparently, no major conclusion on the blood flow and oxygen uptake of the human brain has been in error for this reason.

Constancy of CBF

When calculating the CBF, it is assumed that the cerebral perfusion does not change during the experiment. In order to obtain constant experimental conditions, the study is usually not started until about 15 minutes have elapsed after the vessels have been punctured. Repeated examinations of CBF under essentially unchanged conditions and with an interval of 30–40 minutes have been reported by many investigators (21, 128, 188, 199, 217; see also 20, 62, 146, 173, 270, 272, 282, 310, 321). These many reports, comprising over 100 studies, have shown that in the majority of cases no significant change of CBF occurs. Thus there is ample support for the conclusion that under supposedly steady state conditions the CBF does not usually vary materially within the 10–15 minute sampling period.

It will become apparent in the section on the regulation of CBF, that minor changes in the pulmonary ventilation and the ensuing changes in the arterial carbon dioxide tension must be considered the most likely cause of CBF variations in supposedly steady state conditions. It has been demonstrated experimentally that the cerebral arteriovenous oxygen difference, $(A-V)O_2$, varies inversely with CBF in hyper- and hypocapnia, so that the CMRO₂ is unchanged (171, 174). This implies that the demonstration of constancy of $(A-V)O_2$ during an individual experiment would, under many conditions, constitute strong evidence of the constancy of CBF. The CBF is proportional to the area between the cerebral arterial and venous inert gas saturation curves. As the main part of this area is determined during the first few minutes of the experiment, it is preferable to calculate the CMRO₂ from an $(A-V)O_2$ obtained during the first few minutes. In case minor variations of CBF and $(A-V)O_2$ should occur, this procedure would tend to minimize the effect on the CMRO₂. The use of gamma-emitting inert gases makes it possible to measure fairly rapid changes in total cerebral blood flow continuously over a period of about 5 minutes (197).

Cerebral Arterial Blood

Peripheral arterial blood is usually assumed to be representative of cerebral arterial blood, and only a few investigators use blood samples from the carotid artery (27). Superimposable saturation curves were found in a few experiments where blood was sampled simultaneously from the carotid and femoral arteries (150, 178). In special cases, such as congenital heart diseases, peripheral arterial blood might differ from cerebral arterial blood.

Extracerebral Contamination of Internal Jugular Blood

Blood supposedly sampled from the superior bulb of the internal jugular vein is assumed to be cerebral venous blood essentially free from extracerebral contamination. The technique for puncturing the vein at this high level is well described (106, 236), and in actual practice it is not unusual that the base of the skull is encountered by the needle before the correct position is found. Fazekas and associates found that by inserting the needle a little further spinal fluid could be withdrawn (6, 32). Clearly in these cases the needle must have penetrated the jugular foramen and entered the cranial cavity. Thus it seems unlikely that blood from the facial vein contaminates the venous samples in the average case when the standard technique is employed. This conclusion is also supported by the result of dye injection studies by Shenkin, Harmel and Kety (306), who found that the blood in the superior bulb of the internal jugular vein contains very little blood derived from the external carotid artery. Comparing the dye concentration in the internal jugular to that in the external jugular, a value for extracerebral admixture was calculated. The maximal value of this admixture was 6.6 per cent and the average value 2.7 per cent. These low values may, however, be somewhat too high. By the method of calculation employed, the authors cautiously made two assumptions, both of which tended to exaggerate the calculated value of the contamination. Thus, it was assumed that no branches of the external carotid

artery supplied blood to cerebral tissue and, also, that the extracerebral admixture was caused by blood as diluted with respect to dye as the external jugular blood. An admixture of the calculated value of a few percentages cannot affect the CBF seriously. Thus it is to be concluded that in the average case no gross extracerebral contamination of the internal jugular blood occurs, and thus the CBF refers essentially to the intracranial tissues, i.e., mainly the brain.

The above mentioned conclusion from the dye injection studies of Shenkin, and Harmel and Kety is based on only eight observations in eight subjects. It cannot therefore be ruled out that gross contamination, and hence gross errors, may occur in occasional cases. Various observations have been interpreted to indicate such contamination in a small percentage of cases. Kety and Schmidt found, in 2 out of 100 studies using the original nitrous oxide method, that the venous curve failed to approach the arterial curve in the usual fashion (173). By applying the equation for CBF for each minute it became apparent that in these two cases the calculated value continued to decrease quite unusually even at the end of the experiment at 10 minutes' inhalation of nitrous oxide. These authors recommended that such studies should be rejected as being presumably grossly contaminated.

Scheinberg observed a marked increase in CBF in 2 out of 19 subjects to whom nicotinic acid was administered (270). The drug was found to increase the perfusion of the facial tissues, and it was concluded that in the two cases mentioned gross extracerebral contamination had caused the rise in CBF. Using the simplified, continuous sampling modification of the nitrous oxide method, Scheinberg was unable to apply the minute-to-minute calculations proposed by Kety and Schmidt (173). This is unfortunate, since such data might have revealed gross extracerebral contamination even in the control studies of the two subjects who subsequently reacted abnormally to nicotinic acid. From the data presented by Scheinberg, the possibility cannot be excluded that an increase of the cerebral perfusion rate had actually occurred in these two subjects. In order to evaluate this possibility, it would have been of importance if the arterial carbon dioxide tension and the respiratory quotient of the tissue had been reported.

Hyperventilation studies have been interpreted to indicate gross extracerebral contamination in 9 out of 69 determinations (75, 200). In these nine cases, hyperventilation failed to decrease the oxygen saturation of the internal jugular blood. Variations in the exact site of sampling of internal jugular blood might be implicated, in view of the fact that other investigators have not reported similar cases of non-responsiveness in any out of 33 cases (106, 171, 192). Such variations in sampling site may also explain the observations of Kety and Schmidt (173) and of Scheinberg (270) mentioned above.

From the discussion in this section it may be surmised that there are reasons to believe that the blood in the internal jugular vein at its exit from the skull is derived predominantly from the intracranial tissues. Failure to puncture the vein correctly may well be the cause of gross contamination which is found occasionally. Such studies should be rejected. It would be desirable if more data were available regarding the criteria for rejecting such studies. In the experience of the author,

it is usually not too difficult to recognize gross contamination, since such cases will fall quite out of line with other studies in comparable cases studied under comparable conditions. When an intermittent sampling method is employed, application of the CBF equations from minute to minute affords a valuable criterion. In addition, unusually low values for the CBF and the arteriovenous oxygen difference are found. Thus, exceedingly low CMRO₂ values are found in grossly contaminated cases, while the oxygen saturation of the internal jugular vein may be unusually high. Low values for the respiratory quotient may also be found. If bilateral sampling of the internal jugular veins has been performed and only one side is grossly contaminated, then unusually large side-to-side differences of CBF and CMRO₂ may be found. Perhaps a brief period of hyperventilation might constitute an additional criterion for the origin of the venous blood sampled.

It must be emphasized that gross contamination is rare, that it is usually easily recognized, and that it can possibly be kept to a minimum by using a meticulous technique in puncturing the internal jugular vein. The detailed description of the technique by Gibbs, Lennox and Gibbs (106) is very useful, and it is important to strive to place the needle as high as possible. When unusual difficulty in placing the needle is encountered or when it is felt that the final position of the needle is unusual, then, in the experience of the present author, gross contamination is more likely to occur.

Unilateral and Bilateral Cerebral Blood Flow

The calculated CBF is only representative of the whole brain if it can be assumed that the venous blood sampled is representative of mixed cerebral venous blood. It is quite likely that the bulk of the cerebral venous blood drains normally via the internal jugular veins in the human subject. Anatomical observations (117) and the rapid and marked rise in cerebrospinal fluid pressure following sudden compression of both internal jugular veins, favor this conclusion. For this reason it may be stated, without gross oversimplification, that if the blood in the two internal jugular veins always is identical, then a unilateral study gives CBF and CMRO₂ values representative of the whole brain. But if different CBF and CMRO₂ values occur on the two sides, then a unilateral study cannot with certainty be representative of the whole brain. In cases where significant side-to-side differences exist, a unilateral study refers only to that unknown part of the brain draining to the vein actually punctured. Sampling from both internal jugular veins simultaneously, i.e. bilateral studies, becomes in this situation the only possible method of obtaining values representative of the whole brain. Several bilateral studies have been reported (11, 61, 145, 173, 234, 271, 303). It is now established that side-to-side differences which are not due to random technical errors do occur in a high proportion of both normal subjects and subjects with various pathological conditions (234). In many cases these differences are quite small, but in some cases they are more pronounced.

The standard deviation of the difference between the unilateral CBF and the bilateral value can be calculated to be about 10 per cent of CBF (234). Kety and Schmidt presented evidence to show that this source of variation was not

materially greater than that due to random experimental errors of the N_2O technique (173). It was concluded that "... in the great majority of individuals, blood from one internal jugular at the superior bulb is fairly representative of mixed cerebral venous blood..." (173). Munck and Lassen found that the Kr^{85} method was more accurate. Therefore, using this method, the very same side-to-side differences became a major source of variation (234). It was concluded, that "... bilateral values reflect the blood flow and oxygen consumption of the whole brain much more reliably than unilateral values."

A final evaluation of the physiological significance of the side-to-side differences is not possible at present. The position of the jugular needles relative to the blood stream could be of importance if pronounced streaming was present. But then, reinserting a needle during a study would be expected occasionally to give rise to an abrupt discontinuity of the venous inert gas saturation curve. Such a phenomenon has never been observed as far as we know. It is unlikely that side-to-side differences found are caused only by varying amounts of extracerebral contamination. In the average case such contamination is, according to dye injection studies (306), presumably in the order of a few percentages, whereas the average side-to-side difference of CBF has been found to be about 15 per cent (234). It can be calculated that variations of a contamination of this magnitude alone can hardly be expected to account for the whole side-to-side variation observed.

Thus it appears likely that the side-to-side differences represent, to some extent at least, true differences between the cerebral venous blood draining via the right and left internal jugular veins. According to this explanation, the side with the higher CBF drains proportionally more venous blood from highly perfused brain tissues than the side with the lower CBF. Accepting this explanation, one further assumption is necessary in order to calculate a representative CBF value. It is necessary to know the ratio of the total blood flow of the two internal jugular veins. No information on this ratio is available. The assumption has been made that both jugulars drain the same amount of blood (234), but more complicated calculations have also been proposed (189). As the side-to-side differences are usually not excessive, moderate variations of this ratio, e.g. between 0.5 and 2.0, will not affect the result markedly.

Only few series of bilateral studies have been published so far (145, 173, 234, 271, 303). The largest series was reported by Munck and Lassen (234) using Kr^{85} as the inert gas, and a multiple sample technique. On the basis of their observations, it may be concluded that the bilateral approach, using an accurate technique, seems to increase the accuracy of the individual observation, to reduce the standard deviation (especially of the calculated cerebral oxygen uptake value) in homogeneous clinical groups, and to increase the coefficients of correlation. It should be emphasized, however, that no systematic side-to-side predominance has been found in normal man or in a number of clinical conditions (11, 61, 145, 173, 234, 271). Therefore, in a series of cases, the mean of unilateral measurements would be as representative of the whole brain as bilateral measurements; only the standard deviation would be greater. Almost all conclusions drawn from studies

using unilateral techniques have been based on measurements of fairly large series of subjects. It appears very unlikely that any positive conclusion from such unilateral studies is in error because of side-to-side differences of CBF and CMRO₂.

Systematic side-to-side differences have been found only in some cases of intracranial arteriovenous aneurysms (26, 28, 33, 189, 286, 312) and immediately following surgical obliteration of one carotid artery in one elderly subject (303). In diffuse chronic cerebral disease, findings suggestive of a consistent difference of the cerebral oxygen uptake values of the right and left internal jugular have recently been obtained in a bilateral study by Lassen, Lane and Feinberg (unpublished observations). Studying a series of aged mental hospital patients with signs suggestive of organic brain damage, it was found that the bilateral and the left side values for cerebral oxygen uptake correlated much more closely than the corresponding right side values to the degree of mental deterioration assessed from clinical data and psychological test results. This finding may be interpreted to indicate that disease of the left side of the brain is of more direct importance for the development of mental deterioration than a comparable right-sided cerebral process. As mentioned, no previous study has shown a consistent side-to-side predominance. It seems that further experimental evidence is necessary in order to determine whether or not left-sided unilateral values do actually show a closer agreement with mental function than the corresponding right-sided values.

Additional Comments

By the very nature of the method, the CBF refers to all tissues exchanging inert gas with blood subsequently draining via the superior bulb of the internal jugular. For this reason the unit of reference, '100 gm brain', must be thought of as 100 grams of all tissues taken approximately in their actual proportion by weight.

Non-cerebral tissues, exchanging inert gases and/or oxygen and contributing to the venous blood sampled, do not necessarily have the same partition coefficient as the brain. This means that tissues such as the cerebrospinal fluid (188) and the orbital fat (191) are represented in '100 gm brain' in proportion to the ratio of their weight and their relative inert gas solubility (the tissue inert gas solubility is, in this connection, taken relative to that of the whole brain). Furthermore, if any of the contributing tissues have a very slow clearance rate of inert gas, then they will be represented less in the '100 gm brain' than in proportion to their weight. When extrapolating to infinity, it is likely that all cerebral tissues—even slowly perfused areas such as the white matter of the brain—are adequately taken into account. (See the discussion in the section on the effect of heterogeneous cerebral perfusion.) Very slow inert gas uptake, however, is likely to occur in non-cerebral tissues such as the liquor cerebrospinalis (6, 32, 199), the meninges, the orbital adipose tissue, and part of any contribution from the facial tissues. The supposedly already small contribution of such tissues to the calculated cerebral blood flow is thus further minimized.

Thus the unit, '100 gm brain,' includes the cerebral tissue proper, the blood in the cerebral vessels (159), the liquor (6, 32, 199), and presumably also part of

the meninges and the orbital contents. A correction for the blood content of the cerebral vessels has been attempted by Lassen and Munck (188). The correlation was based on crude estimates of the mean circulation time over the brain, and is of doubtful value. Variations of the intracranial blood volume do apparently occur (260, 308, 346), but are presumably too small to be of any real importance. Undoubtedly the CBF reflects predominantly the perfusion of the hemispheres, as they form the bulk of the brain.

As the unit of reference is 100 gm. of perfused tissue, the CBF is not influenced by the absolute size of the brain or by localized complete infarction of the brain. This aspect of the method is of some importance for evaluating the results obtained in clinical conditions such as microcephaly (78) or acute cerebrovascular accidents (199). In many conditions it may be considered an advantage, however, that the results do not reflect individual variations in brain weight.

The accuracy of the inert gas method has never been established in man, as no suitable independent method without error is available. Kety and Schmidt's monkey studies did, however, demonstrate that the error of the method is likely to be quite small (173). The influence of side-to-side variations has been discussed, and it was pointed out that the difference between a unilateral CBF and the corresponding value has a standard deviation of about 10 per cent of CBF. Random errors of a technical nature also influence the measurements. The magnitude of these errors and of biological variants with time has been determined by analyzing the results obtained in series of paired unilateral studies repeated on the same individual and under the same experimental conditions within a time interval of about 30 minutes. Regarding unilateral CMRO₂, a standard deviation of 0.19 cc per 100gm per minute, or about 6 per cent of the average CMRO₂, was found using the original N₂O method (173). Using Scheinberg and Stead's modification of the N₂O method, a greater random error of unilateral values must be expected. This modification also gives systematically higher values than the original method (173, 284), presumably due to timing and dilution errors (333). The Kr⁸⁵ technique appears to be the most accurate modification thus far developed. The variation of unilateral CMRO₂ calculated from repeated unilateral studies was 0.13 cc per 100gm per minute (188). This variation is about 4 per cent of the average CMRO₂ of the cases studied. Theoretical (234) and experimental (188) attempts have been made to determine more rigorously the effect of random analytical errors on unilateral CBF and CMRO₂. As it is possible that these approaches did not include all random errors, the error estimates arrived at will not be discussed further. No experimental evidence is available for the evaluation of the accuracy of the direct method of measuring total cerebral blood flow using γ -emitting inert gases (197, 198). Presumably the continuous measurement of the amount of radioactivity in the brain alone—excluding all other sources of radiation—is subject to quite a considerable error.

INDICATOR INJECTION METHOD

Gibbs, Maxwell and Gibbs (110) have applied the Stewart-Hamilton techniques (132, 133, 326-330) to the study of cerebral circulation in man. A known

amount of a biologically inert indicator, such as Evans blue dye (T-1824), is injected into one of the internal carotid arteries, and the dilution of indicator is followed by sampling from one or both internal jugular veins. By this method the total cerebral blood flow can be calculated. By simultaneously determining the arteriovenous difference of oxygen or other metabolites the metabolic rate of the whole brain of such compounds can also be calculated³. A continuous injection of indicator over a period of at least 2 minutes was employed in the original method of Gibbs, Maxwell and Gibbs (110). Instantaneous injection was employed by another group, a modification which reduced the duration of the experiment to less than 1 minute (306). Mylin and Blömer have further modified the method by using multiple venous samples instead of integrated samples (242, 243). Thus it became possible to calculate in addition the cerebral mean circulation time and vascular volume of the brain. The method is based on several assumptions, some of which have already been discussed in connection with the inert gas diffusion method. Thus it is superfluous to repeat the arguments in favor of the conclusion that the internal jugulars carry the bulk of the cerebral venous blood without significant extracerebral contamination. Also, the assumption of constancy of total cerebral blood flow during an experiment lasting a few minutes, or even less, would seem to be valid in the majority of conditions. Undoubtedly the requirement of physiological inertness is adequately fulfilled when using small amounts of T-1824 or thorium B-labeled red cells (242, 243) as the indicator. Moreover, these indicators can be assumed not to be retained or metabolized in the brain. The injection of a known amount of indicator into an internal carotid artery poses a major technical problem. Most investigators have used percutaneous carotid puncture, and presumably errors of injection may occur occasionally.

The problem of recirculation of indicator is not very great, due to the large dilution in the central blood volume. This error can be reduced by subtracting the recirculating arterial indicator concentration from the cerebral venous concentration (110, 306). The use of highly diffusible indicators would reduce recirculation, but would also increase the time needed for washout from the brain. Radioactive potassium might offer some advantage, as it remains largely intravascular during the first transit through the brain but leaves the blood stream rapidly in other tissues (47, 268).

The indicator is usually injected into only one of the internal carotid arteries. Thus it is not surprising that pronounced side-to-side differences often occur between the indicator dilution curves of the two internal jugular veins (242-244, 306). The side-to-side differences are of much greater magnitude than those observed with the inert gas method, in which the gas reaches the brain in the same

³ Sapirstein has recently proposed a new indicator injection method for the measurement of total cerebral blood flow in man (267). The technique involves external counting of radioactivity over the head following serial i.v. injections of the radioactive compounds I¹³¹-antipyrine and K⁴². Simultaneously the cardiac output must be measured. The method is based on the difference between two determinations, neither of which can be expected to give a completely reliable value for the physiological parameter it is supposed to measure. It does not permit measurement of the cerebral metabolic rate of oxygen or other compounds.

concentration via all arteries. The side-to-side differences of injected indicator are also very variable. Usually the ipsilateral jugular has a higher concentration than the contralateral, but in some instances the opposite is found. This means that unilateral measurements cannot be assumed to be representative of the whole brain (155). Only if the opposite jugular is occluded can a unilateral study be reasonably accurate. It is uncertain, however, whether in this situation the bulk of the cerebral venous blood actually drains via the patent jugular. Compression of the contralateral jugular was used by Gibbs, Maxwell and Gibbs in an isolated study. In this case the total outflow of one internal jugular measured directly compared favorably to the results obtained by the indicator injection method (110). This unique experiment is the only case in which a direct measurement of the cerebral blood flow in man has been attempted. Bilateral studies seem to offer a more reliable approach to avoid the influence of side-to-side differences without disturbing the venous outflow. The magnitude of these differences implies, however, that variations in the ratio of total flow of the two jugulars have a greater influence on the accuracy of the results than when using the inert gas method.

The indicator injection method has so far only been used in a single clinical study (104). In the following discussion, when reference is made to studies of cerebral blood flow and metabolism, the inert gas method has been used unless otherwise stated. It is to be hoped, however, that bilateral studies using the indicator injection method will be employed more extensively in the future. In many clinical studies, such as degenerative cerebral diseases, it would be of interest to study the total flow and oxygen uptake of the brain. These values cannot be obtained by the inert gas method unless the modification using γ -emitting isotopes is employed, a modification which is technically quite involved and presumably less accurate. Unilateral or bilateral studies employing the injection of several indicators simultaneously seem to be a promising approach for the study of the transcapillary exchange of a variety of compounds. Thus far such dynamic studies of the blood-brain barrier have been made only in a small number of animal experiments by Chinard and associates (47).

REGULATION OF CEREBRAL BLOOD FLOW

In healthy young adults studied in the supine position, the cerebral blood flow is about 50–55 cc per 100 gm per minute, or approximately 750 cc per minute for a brain of average weight (173). Thus, the brain receives about 15 per cent of the total cardiac output of a resting subject. The cerebral perfusion is controlled very efficiently by homeostatic regulation of the perfusion pressure and the so called cerebral vascular resistance.

Perfusion Pressure of the Brain

The pressure difference between the cerebral arteries and veins is the driving force of the cerebral circulation. The pressure in the cerebral veins is usually only a few mm Hg above the atmospheric pressure. For this reason the arterial blood pressure at the level of the head will in most situations adequately represent the cerebral perfusion pressure. Only in positive gravitational stress is the cerebral

venous pressure the decisive factor in maintaining an adequate pressure difference. Studies during acute acceleration to 4–5 g have shown that the arterial pressure at brain level is reduced to a few mm Hg, while simultaneously the pressure in the cranial part of the internal jugular veins drops to as low as –60 mm Hg (136). In the erect posture, and on exposure to normal gravitational forces, the driving pressure of the human brain is only slightly reduced. This very moderate pressure decrease can hardly be the cause of the reported reduction of cerebral blood flow to about 80 per cent of the values in the supine position (247, 252, 284, 310). This reduction most likely results from a decrease in the arterial pCO_2 (147). The effect of a primary increase of the jugular pressure to a moderately elevated level of 235 mm H_2O was studied by Moyer and associates (225). The cerebral blood flow was not significantly influenced by the pressure rise.

The prime importance of the arterial blood pressure for sustaining cerebral circulation was well recognized by early investigators. Until quite recently it was generally believed that this factor alone determined the cerebral blood flow, i.e. that the cerebral vessels did not possess any significant capacity for intrinsic control of the vascular tone, so that the perfusion passively followed changes of the arterial blood pressure (141, 348). Maintenance of a relatively constant cerebral blood flow was thought to be solely the result of the homeostatic regulation of the arterial blood pressure. The location of the pressure-sensitive zones in the cranial part of the arterial tree (10) could be taken to support this concept. Recent quantitative studies in man, however, have demonstrated that—within a wide pressure range—the cerebral blood flow is independent of changes of the arterial blood pressure (fig. 1). A moderate reduction of blood pressure does not influence cerebral blood flow (58, 124–126, 206). Only in marked hypotension with pressures of half the normal value or less is cerebral vasodilatation inadequate, the cerebral blood flow falling to a critically low value of about 60 per cent of the control level, and clinical signs of cerebral hypoxia becoming apparent (81). Hypotension induced by tilting (81) or spinal anesthesia (168, 184, 185) has the same effect as a similar degree of hypotension induced by various antihypertensive drugs (24, 29, 31, 223, 224, 229, 230). Also, in hypertension cerebral blood flow remains fairly normal irrespective of the cause of the pressure rise (cf. essential hypertension, refs. 122, 131, 166, 172, 228, 229; hypertensive toxemia of pregnancy, refs. 203–212; vasopressin infusion, ref. 323; and *l*-norepinephrine infusion, refs. 177, 230, 298). It may be pointed out, however, that in these various hypertensive states the possibility cannot be excluded that the cerebral vasoconstriction noted might be secondary to circulating vasoconstrictor substances. For this reason, the relative constancy of CBF in hypertension cannot be taken as definite proof of intrinsic autoregulation of cerebral vascular tone in this condition.

The above mentioned clinical studies are thus in agreement with the earlier observations in animals by Fog (82–85), and by Forbes and associates (92), demonstrating that when the systemic blood pressure increased, the pial arterioles contracted; when the pressure decreased, the vessels dilated. Fog also found that the reactions of the pial arteries were qualitatively and quantitatively independent of

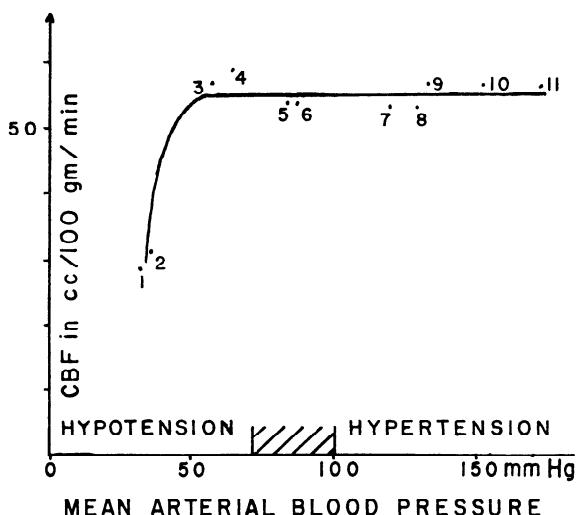


FIG. 1. Cerebral blood flow and blood pressure. Mean values of 11 groups of subjects reported in 7 studies have been plotted. Various acute and chronic conditions have been selected, characterized by a change in blood pressure. In all, this figure is based on 376 individual determinations.

1 and 2, Drug-induced severe hypotension (81). 3 and 4, Drug-induced moderate hypotension (206). 5 and 6, Normal pregnant women and normal young men (206, 173). 7, Drug-induced hypertension (230). 8, Hypertensive toxemic pregnancy (206). 9, 10, 11, Essential hypertension (229, 131, 228).

the method used for producing the blood pressure variations (82, 85). In addition, it was demonstrated that the vascular reactivity to pressure changes was unaffected by sectioning the vagus, cervical sympathetic, sinus and aortic nerves. Subsequent studies showed that the pial arteries are fairly insensitive to the local application of sympathicomimetic drugs in doses insufficient to elevate the systemic blood pressure (84, 202). On the basis of these studies, Fog concluded that the active regulation of the cerebrovascular tone in face of variations of the blood pressure was a kind of autoregulation, possibly due to a direct effect of the pressure changes on the inherent smooth muscle tone; i.e., contraction being an automatic response of the arteries to an increase of the distending pressure and vice versa. The general principle of such a direct or so called mechanical control of the myogenic tonus of the arteries was first proposed by Biedl and Reiner (35) and by Bayliss (16, 17), and is supported by many experimental observations (see 86-88).

Adjustment of local cerebral blood flow following cerebrovascular occlusion seems to be, on the local level, a situation similar to that of maintaining total cerebral blood flow in hypotension. In a recent study by Meyer and Denny-Brown, the effect of occlusion of the pial arteries was studied in monkeys by means of a variety of experimental techniques (220). Chemical factors were considered to be of minor importance for the local vasodilatation observed, since this dilatation occurred in a far wider area than that rendered hypoxic by the arterial occlusion. The authors concluded that the collateral vasodilatation was predomi-

nantly due to the mechanism described by Fog, i.e., it was caused by the reduction in the local intraarterial pressure distal to the occlusion. These observations are of importance, as they seem to permit the described separate evaluation of the effect of chemical and mechanical regulatory factors on cerebral vascular tone. They form a substantial support for the theory of the existence of a mechanical control of the above mentioned type. This is noteworthy, since the many data on the intact human organism do not permit exclusion of the possibility that the autoregulation of CBF in response to blood pressure variations could be explained by chemical control of the type described in the following section.

Studies in man have showed that CBF is completely normal in mild hypotension as well as in essential hypertension without encephalopathy. The cerebral oxygen uptake is also normal in both conditions. The cerebral perfusion is apparently regulated in such a way as to maintain scrupulously the normal chemical milieu of the brain. This observation suggests the influence of a regulatory mechanism governed by the metabolic demands of the cerebral tissues, i.e., chemical control. It is more difficult to imagine that a local mechanical regulation from the wall of the vessels could permit the perfusion to remain so completely adequate relative to the metabolic demands. For this reason it seems likely that both mechanical and chemical factors are of importance for the autoregulation of CBF, the latter factor, however, having the final regulatory effect.

Cerebral Vascular Resistance

At any level of perfusion pressure the cerebral blood flow depends solely on the interplay of this systemic force and local impeding factors. These impeding factors form collectively the cerebrovascular resistance, which is defined as the ratio of perfusion pressure to the cerebral blood flow. (It should be pointed out that this ratio does not imply a linear relationship between pressure and flow and it is not a constant for any given subject.) The cerebrovascular resistance depends on the viscosity of the blood and on the nature of the intracranial vascular bed.

Significant changes in the viscosity of the blood are achieved by fairly marked alterations in the erythrocyte concentration or the temperature of the blood. In severe anemia a marked decrease in cerebrovascular resistance is observed (137, 261, 275), whereas in polycythemia (238, 292) and hypothermia (181) it is increased. There is no doubt that changes in physical viscosity must play a role in these conditions. It is quite possible, however, that chemical control of the diameter of the cerebral vascular bed is of decisive importance, since in all three conditions the cerebral perfusion is adjusted quite accurately to the metabolic requirements of the brain as judged from the normal level of the oxygen and carbon dioxide tensions of the cerebral venous blood.

The nature of the intracranial vascular bed is of major importance to cerebrovascular resistance. In this respect it is convenient to discuss three aspects of this vascular bed separately: 1) the vascularity of the intracranial tissues, 2) the passive changes of vascular diameter due to changes of the intracranial pressure, and 3) the active changes of the diameter and/or tone of the vessels due to changes of the vasomotor activity of the smooth muscle cells of the vessel walls.

Intracranial vascularity may be taken to embrace all morphological or anatomi-

cal features of the intracranial vascular bed. Thus it comprises the number of vessels, their diameter, their length, and their mutual interconnection. In intracranial arteriovenous aneurysms the cerebrovascular resistance is markedly decreased because of an abnormally increased intracranial vascularity (312). In chronic degenerative cerebral diseases the cerebral vascular resistance is increased (96). Decreased vascularity of the brain is presumably implicated, reducing the number of vessels as well as their size, a process in which arteriosclerotic vascular disease may or may not play a role.

Intracranial pressure is presumably nearly the same in all conditions as the pressure in the thin-walled pial veins. Thus, even marked variations in absolute pressure in the veins, e.g. those produced by changes of posture, result in little change in the actual distending pressure of these vessels. By this mechanism the cerebral veins and capillaries are protected against collapse as well as against extreme distention. Hence the variations in intracranial pressure constitute a highly efficient 'permanent anti-g-suit' for the brain. In the resting recumbent position, the intracranial pressure usually varies only moderately. These variations parallel variations in cerebral blood flow, presumably because increased flow tends to cause an increased pressure in the cerebral vessels and an increased intracranial blood content, and vice versa (260, 304, 308, 346). The intracranial pressure is presumably also of importance for the circulation in the cerebral arteries. The intracranial pressure may be taken to reflect the external pressure upon the walls of the cerebral arteries, and it is thus the one of the two pressures which determine the distending pressure of the arteries. This means that with regard to the influence on the cerebral arteries an increase of intracranial pressure equals a decrease of arterial blood pressure, and vice versa. In accordance with the previous discussion, it follows that mechanical and chemical factors may both be of importance for the dilatation of the pial arteries which follows an increase of intracranial pressure (82). Changes of posture induce variation of the intracranial pressure, but also cause similar variations in the intra-arterial pressure. Hence the distending pressure of the arteries remains essentially unchanged, just as is the case with the distending pressure of the veins. A primary rise in the intracranial pressure constricts the outflow from the cerebral venous channels. At the same time the increased pressure tends to cause arterial vasodilatation, as just mentioned. However, if a rise in arterial blood pressure occurs this latter effect is presumably counteracted. The net effect of a moderate induced rise of intracranial pressure on cerebrovascular resistance is probably small. No experimental studies of the effect of a primary rise of the intracranial pressure on CBF and CMRO₂ have been reported. Indirect evidence, however, suggests that the cerebral circulation remains adequate when the intracranial pressure is increased for 5–10 minutes to about 500 mm H₂O (349). The cerebral circulation of patients with increased intracranial pressure associated with brain tumor will be discussed later in this review.

The *vasomotor activity* of the intracranial vessels constitutes the decisive intrinsic regulator of the cerebrovascular resistance. One important type of vasomotor activity has already been discussed, i.e., the variations in diameter of the cerebral arteries due to pressure changes. Equally important for the regulation of

cerebrovascular resistance are chemical or humoral factors, whereas the role of neurogenic regulatory mechanisms remains, as we shall see, more dubious. The chemical and neurogenic control mechanisms will be discussed in the remainder of this section.

Carbon Dioxide

CO_2 causes pronounced dilatation of the cerebral arterioles. This has been demonstrated repeatedly in animal studies employing a variety of techniques (350; see also 292, 318).

Quantitative data. In normal man, an increase of the alveolar and thus the arterial carbon dioxide tensions (pCO_2) causes a striking increase in cerebral blood flow. Thus, hypercapnia induced by the inhalation of 5% CO_2 increases cerebral perfusion by about 50 per cent, while 7% CO_2 causes an increase of about 100 per cent (174, 197, 198, 249, 289). Using the indicator method, Gibbs, Maxwell and Gibbs found that 10% CO_2 also caused a comparable increase (110). No quantitative studies have been reported on the effect of higher CO_2 concentrations. Conversely, subnormal alveolar and arterial pCO_2 values cause a pronounced cerebral vasoconstriction. Hypocapnia produced by marked hyperventilation has been found to decrease cerebral blood flow to about 60 per cent of the resting value (171). It is interesting that this is the same low critical level of cerebral perfusion as was found in severe hypotension associated with clinical signs of cerebral hypoxia (81). This indicates that the cerebral symptoms produced by severe hyperventilation may be partially caused by cerebral hypoxia in addition to the more direct effect of the low arterial pCO_2 on cerebral cells. A recent study by Patterson and associates suggests that the cerebral vasodilatation produced by hypercapnia is a threshold phenomenon occurring only when the inspired CO_2 concentrations exceed 2.5% (249). This threshold corresponds to a rise in arterial pCO_2 of about 4.5 mm Hg. In anesthetized dogs, however, Noel and Schneider found that changes of arterial pCO_2 of 2 mm Hg caused variations of the arteriovenous oxygen difference indicative of changes of 8 to 10 per cent in cerebral blood flow (239). During inhalation of up to 7% CO_2 , as well as during marked hyperventilation, the cerebral arteriovenous oxygen difference varies inversely with the changes of cerebral blood flow, and the cerebral oxygen uptake remains essentially unchanged (46, 63, 66, 104, 110, 116, 127, 171, 174, 197, 198, 241, 249).⁴

Mechanism of action. It is generally believed that the concentration of carbon dioxide—the pCO_2 —is in itself the decisive factor, and that concomitant changes of pH or the bicarbonate concentration play a secondary role or no role at all. Schieve and Wilson have clearly demonstrated in clinical experiments that CO_2 acts independently of moderate changes of pH (288). No clearcut data are available to distinguish the action of pCO_2 from that of associated changes of the bicarbonate concentration.

⁴ Kety and Schmidt (171) found a tendency to an increase in CMRO_2 during hyperventilation. A possible explanation of this finding is given in the section on cerebral blood flow and oxygen uptake in disease states.

Increased arterial CO₂ concentration results in relaxation of the intrinsic myogenic tone of the smooth muscle cells of the walls of the cerebral vessels. The fact that subnormal pCO₂ values cause cerebral vasoconstriction may be taken as evidence for a kind of tonic relaxing influence exerted by the normal pCO₂ level. There is little doubt that CO₂ causes cerebral vasodilatation by some local action. This conclusion was reached by Wolff on the basis of animal experiments demonstrating that the dilatation by CO₂ was unaffected by interrupting all the known nervous pathways which could possibly affect the cerebro-vascular resistance, i.e., sectioning of the cervical sympathetic nerve, the cranial nerves VI, VII and VIII, the spinal cord or the brain stem (348). The mechanism of this local action is not known. The above mentioned animal studies do not rule out the possibility that CO₂ acts via local perivascular nervous structures. The observation that CO₂ will relax isolated strips of the wall of the carotid artery favors the hypothesis that CO₂ acts directly on the smooth muscle cells of the vessel walls (53). It is probable that CO₂ reaches the smooth muscle cells by diffusion either from the blood or directly from the surrounding tissues.

Physiological importance. The obvious net effect of CO₂ is that of cushioning the sensitive cerebral tissues against the harmful effects of marked variations of the arterial pCO₂. Arterial hypercapnia, by increasing cerebral perfusion, facilitates the disposal of CO₂ produced by the brain, and thus the cerebral venous pCO₂ is raised less above its normal level than the arterial pCO₂. Conversely, in arterial hypocapnia the decrease of cerebral perfusion restricts the CO₂ loss from the brain, and for this reason the cerebral venous pCO₂ is less decreased than the arterial. This damping of the excursions of the cerebral venous pCO₂ probably reflects a similar damping of the pCO₂ of the cerebral tissues. The beneficial effect of such a homeostatic control of the tissue pCO₂ is illustrated by the fact that both high and low tissue pCO₂ values have a noxious effect on the brain. High tissue pCO₂ values cause depression of mental functions, as exemplified by the coma resulting from the inhalation of 30% CO₂ in normal man (219), and the confusion or coma due to CO₂ retention which may be caused by a reduction of pulmonary ventilation by oxygen inhalation in patients with severe pulmonary insufficiency (250). Low values of pCO₂ in the cerebral tissues have presumably also a depressant effect on the cerebral functions, according to studies by Gibbs and co-workers, which showed that hypocapnia per se may cause derangement of the mental and electrical activities of the cerebral cortex (108).

CO₂ is a more powerful cerebral vasodilator than any other substance yet studied. Also, CO₂ is the main product of cerebral metabolism. These facts, combined with the local site of action of CO₂, form the basis for a widely accepted theory concerning the physiological role of CO₂ in the homeostatic regulation of cerebral perfusion according to the metabolic needs of the tissues: An increase of function in a local nervous center causes an increase of oxidative metabolism, and hence an increased CO₂ production; this causes a local rise of tissue pCO₂ and local vasodilatation; the increased perfusion of the area tends to sustain the increased metabolism and to maintain the chemical milieu of the tissue. The opposite chain of events may follow a decrease of function and metabolism (50,

90, 158, 292, 296, 348). Various proponents of this theory have stressed that the local adjustment of perfusion to metabolism may be due not only to CO₂, but also to other vasodilator products of metabolism (see e.g. 292).

Clinical implications. The cerebral circulatory response to CO₂ has been studied in a variety of clinical conditions. In diabetic coma (169) and arterial hypoxia (105, 174, 192) cerebral vasodilatation occurs in spite of hypocapnia. This indicates that in these extreme conditions the vasoconstriction of low pCO₂ is overpowered by strong vasodilatory effects, probably acidosis and hypoxia in the two conditions respectively. In anesthesia and cerebrovascular disease the absolute increase in cerebral blood flow caused by CO₂ inhalation is somewhat less than that in normal man (289). However, relative to the reduced cerebral blood flow in both conditions the reaction to CO₂ may be considered normal, since the induced increase of cerebral venous oxygen tension reaches the same level as in normal man. For this reason, and because of the great variability reported in literature, CO₂ responsiveness does not seem to be applicable as a test for disclosing fixed organic pathology of the walls of the cerebral vessels in the average case of cerebrovascular disease (63, 66, 190, 241, 289; see also the discussion of cerebral circulation in cerebral arteriosclerosis).

In clinical conditions where marked hyperventilation is causing cerebral symptoms, the inhalation of CO₂ in moderate concentrations would be expected to have an immediate beneficial effect. Stimulation of the cerebral circulation by CO₂ inhalation is also of value in hastening recovery from general anesthesia with volatile anesthetics. Moreover, it increases the tolerance to low oxygen tensions (108) and to positive radial acceleration (42, 43, 101, 218, 265, 340). The use of CO₂ inhalation in chronic cerebral vascular disease is impracticable, and presumably without use. In certain cases of acute cerebral vascular disease, however, CO₂ may be of some benefit. CO₂ has been widely used in resuscitation from asphyxia. But in this condition the cerebral vessels are already maximally dilated, and the brain pCO₂ is elevated. The addition of CO₂ to the inspired air in this situation is therefore not indicated, unless actual hypocapnia has been produced by prolonged hyperventilation. Conceivably, it might even have a noxious effect by raising the pCO₂ in the brain to a depressant level.

Oxygen

Inhalation of air mixtures of low oxygen tensions causes dilation of the pial arteries, whereas high oxygen tensions cause a moderate vasoconstriction (350). Thus, the effect of O₂ is in the opposite direction to that of CO₂. In man, inhalation of 8–10% O₂ at atmospheric pressure causes a distinct increase in cerebral blood flow to about 40 per cent above the resting value. No change occurs in cerebral oxygen consumption, but the arterial pCO₂ decreases as a result of a secondary hyperpnea (137, 174, 186). This hypocapnia was shown by Turner and associates to have no power to constrict the cerebral vessels in face of the anoxic stimulus (339). These investigators found that the increase in cerebral blood flow due to hypoxia was not further increased by artificially maintaining the arterial pCO₂ at about the control level. Moderate variations of oxygen tensions below and above the normal level do not affect the cerebral blood flow or metabolism (138, 246,

339). This is presumably due to the fact that the dissociation curve for oxyhemoglobin is nearly horizontal at normal arterial oxygen tensions. Thus, such variations of oxygen tensions cause little change of the oxygen content of the arterial blood and of cerebral oxygen delivery. Oxygen tensions in inspired air mixtures of 0.8–1.0 atmosphere cause a small but significant decrease of cerebral perfusion without changing the cerebral oxygen uptake (63, 137, 174, 186). Patients with cerebrovascular disease show less variation of CBF following changes of the inspired oxygen tension than normal subjects (63, 138). However, this response may be considered adequate relative to the reduced cerebral blood flow in such patients, since the observations suggest that the induced changes of cerebral venous oxygen tension were of the same magnitude as in normal man (cf. the similar findings regarding the reactivity to CO₂ in cerebrovascular disease).

On the basis of all these observations and of similar results in animal studies, it appears that oxygen is of especial importance for the homeostatic regulation of cerebral perfusion in the emergency situation of severe anoxia of the brain (105, 292, 319). The pronounced vasodilatory response to oxygen lack means that a greater degree of arterial oxygen unsaturation can be tolerated than would be the case if this response did not occur. Consciousness is lost when the oxygen tension of the cerebral venous blood reaches 15–20 mm Hg, and at this level abnormal cortical electrical activity also starts abruptly (193, 194). It is interesting that the same critical level of cerebral venous oxygen tension has been found to limit the vasoconstriction of hypocapnia in animal experiments (239). Oxygen is generally thought to act on the cerebral vessels via local mechanisms just as does carbon dioxide (292). However, experimental evidence does not rule out the possible role of reflexes involving chemoreceptors (36).

Low arterial oxygen tensions cause mental symptoms before unconsciousness is reached, and such early symptoms are not associated with a measurable reduction of cerebral oxygen uptake (174). Possibly anoxia initially causes hypo-function only in small areas of the brain; but the contributory role of the secondary hypocapnia must also be considered (108).

Inhalation of 100% O₂ under a pressure of 3–4 atmospheres decreases cerebral blood flow moderately, does not change cerebral oxygen uptake, and causes only a slight increase in the pCO₂ of cerebral venous blood (186). These observations indicate that the cerebral symptoms of oxygen toxicity are not caused by insufficient cerebral circulation or hypercapnia, but rather by a noxious effect of high oxygen tensions locally in the cerebral tissues. The inhalation of 100% O₂ at a pressure of 1 atmosphere or less has been found useful in a variety of conditions. In a few instances, however, oxygen inhalation may have serious side effects. In premature infants it may lead to blindness, and in severe pulmonary failure it may cause a deleterious rise in pCO₂ associated with a further rise in the already increased cerebral blood flow (250).

Hydrogen Ion Concentration and Glucose

The effect of variation of pH on the cerebral circulation in animals is not clear, although weak vasodilation by acidosis and mild vasoconstriction by alkalosis have been most commonly reported (292, 319). Schieve and Wilson studied

moderate changes of pH in man and failed to demonstrate any effect beyond that which may be attributed to the concomitant changes of the carbon dioxide concentration (288). They found that mild acidosis caused by ammonium chloride infusion reduced arterial pCO_2 and the cerebral blood flow, while mild alkalosis produced by bicarbonate infusion caused an increase of cerebral perfusion. In the latter studies the arterial pCO_2 was not reported, but it is likely that it was increased (317). Observations by Kety and associates, however, have been interpreted to indicate that acidosis may cause cerebral vasodilation in man (169). These authors studied patients in diabetic coma with marked acidosis and low arterial pCO_2 . The cerebral oxygen uptake was much reduced, while the cerebral blood flow was higher than normal. In these studies, the arterial pH was much lower than in the above mentioned studies of the effect of ammonium chloride. For this reason, it is entirely possible that the vasodilation in diabetic coma is caused by the severe acidosis. It cannot be ruled out, however, that other biochemical abnormalities may be of importance.

Glucose lack is presumably directly or indirectly a vasodilatory stimulus in hypoglycemic coma. In this condition, the arterial concentrations of carbon dioxide, oxygen and hydrogen ion are essentially unchanged, but the cerebral oxygen uptake is markedly reduced (176). As will be described in the following section, under such conditions the cerebral blood flow would be expected to be reduced pari passu with the decrease in oxygen uptake of the brain. Thus it is remarkable that the cerebral perfusion has been found to remain at the normal level (176), an observation suggesting the presence of a vasodilating influence.

Cerebral Metabolism

In 1914 Barcroft formulated the principle that increased activity of an organ results in enhanced oxidative metabolism and blood flow, while decreased activity reduces both factors (12). The brain of primates seems to conform to this principle, according to the studies on monkeys of Schmidt, Kety and Pennes (294). During induced convulsions the cerebral oxygen consumption and the cerebral blood flow increased in parallel fashion, while during anesthesia both values decreased proportionately. The tensions of carbon dioxide and oxygen in the cerebral venous blood remained fairly unchanged, indicating that the perfusion changes adequately compensated for the metabolic changes. As artificial ventilation was used in these monkey experiments, they cannot be taken to reflect directly the situation in spontaneous seizures in man, where marked arterial hypoxia develops. No adequate human studies made during convulsions have been reported. In an isolated observation of a spontaneous eclamptic seizure in a toxemic patient, McCall and Taylor found that the cerebral arteriovenous oxygen difference dropped to half the resting value (210). Unless the cerebral blood flow had actually quadrupled, the oxygen metabolism cannot have doubled during the seizure, as was the case in the monkey studies. Such a tremendous increase of cerebral perfusion is unlikely, and the observation, however isolated, suggests that the cerebral oxygen delivery may be insufficient to sustain a 100 per cent increase in cerebral oxygen metabolism during spontaneous seizure in man.

High values of cerebral metabolism and cerebral blood flow have been found in normal children (152) and during infusion of synthetic epinephrine (177). Numerous clinical studies have confirmed that decreased cerebral activity is accompanied by reduced cerebral oxygen uptake and, other factors being equal, a perfusion reduction which is proportionate to the reduction in oxygen uptake. This has been found in all studies of severe chronic brain disease and of acute cerebral disorders characterized by reduced consciousness. These studies will be discussed in detail later.

The regulation of cerebral perfusion according to the metabolic demand signifies that the chemical environment of the cerebral cells tends to remain unchanged. This important regulation of cerebrovascular resistance is presumably effected by a continuous interplay between chemical control mechanisms and the inherent tendency of the vessels to contract (292). Indirect evidence, already presented, strongly suggests that carbon dioxide and, in some conditions, oxygen are of prime importance in this control, although the possible role of other metabolites also must be kept in mind.

Neurogenic Control

Anatomical studies have demonstrated perivascular nerve fibers accompanying the cerebral vessels both in man and in animals (214, 253, 334). The unmyelinated fibers are believed to mediate the neurogenic control of the cerebrovascular resistance, whereas the myelinated fibers are believed to be sensory afferents. These fibers are abundant in the adventitia of the major cerebral arteries, and Chorobski and Penfield have found nerve fibers even on intracerebral arterioles with a diameter of only 30–25 μ (48).

Sympathetic innervation. Arising mainly from the stellate and superior cervical ganglion, postganglionic sympathetic fibers form a continuous nervous plexus accompanying the internal carotid and vertebral arteries and their branches (48). In animal studies, Forbes and co-workers observed a feeble ipsilateral constriction of the pial arteries when the cervical sympathetic nerve was stimulated electrically, whereas stimulation of the stellate ganglion had no measurable effect (91, 94). Fog made similar observations, stressing that only the larger vessels showed any reactivity (82). Studies of local cerebral perfusion in animals during stimulation of the cervical sympathetic nerve have shown a decrease in perfusion in some areas of the brain, and no effect in other areas (201, 290, 291, 293, 295). Animal studies have also shown that when the cervical sympathetic nerve was cut, no vasodilatation or increase of perfusion occurred, not even in areas which responded to stimulation (82, 91, 94, 221, 293). Compared to the peripheral sympathetic innervation, that of the cerebral vessels may be characterized as being weak, inconsistent, and without tonic effect. As the cerebral vessels are highly reactive to other stimuli (chemical or pressure-induced), Schmidt has concluded that the sympathetic cerebral vasomotor innervation is probably without physiological importance (292). In man, no studies have been reported of the influence on cerebral blood flow of stimulations of the cervical sympathetic nerve. As will be discussed below, blocking or extirpation of the stellate ganglion does not change

cerebral blood flow significantly in patients with or without acute cerebrovascular disease.

Parasympathetic innervation. Chorobski and Penfield have traced unmyelinated nerve fibers from the facial nerve through the geniculate ganglion via the great superficial petrosal nerve to the pericarotid nerve plexus (48). Animal experiments have demonstrated a weak, ipsilateral cerebral vasodilation during faradic stimulation of the facial nerve (48, 92, 93). The physiological role of this parasympathetic vasodilator pathway is unknown, and no pertinent studies in man have been reported.

Influence of vagus, aortic and sinus nerves. Observations of the diameter of the pial arteries have shown weak and inconsistent cerebral vasodilatation following stimulation of the vagus, aortic and sinus nerves (92). Studies by Fog, however, strongly suggest that a decrease of arterial blood pressure may have been implicated (82). Also, Schmidt and co-workers were unable to find changes of local cerebral perfusion during stimulation or following the cutting of these nerves (290, 291, 293, 295). No studies have been reported concerning the influence of these various nerves on the cerebral circulation in man.

Stellate block in apoplexy. Animal studies showed, as has been mentioned, that while stimulation of the cervical sympathetic nerve did produce moderate vasoconstriction in some cerebral areas, then stimulation of the stellate ganglion was without any effect, and cutting of the sympathetic nerve did not cause cerebral vasodilatation. In man, several groups of investigators have studied the cerebral circulatory effect of stellate block or stellectomy, particularly in patients with acute cerebrovascular accidents (9, 135, 199, 237, 272, 302, 307). In none of these studies, with a total of 91 subjects, was a significant change in cerebral blood flow found. Shenkin and co-workers found a reduction in cerebrovascular resistance when restudying 11 subjects a few days after bilateral stellectomy (302, 307). A similar reduction of resistance, however, was found by Lassen and Munck, who reexamined 10 subjects at an interval of days without any operative intervention or other attempt to change the clinical conditions (188). Thus it appears likely that changes of arterial pCO_2 , blood pressure, and the concentration of hemoglobin, can wholly account for the observations of Shenkin and co-workers. In two studies it was noted that subjects with low initial values for cerebral blood flow showed an increase following stellectomy or stellate block (199, 302). This cannot be taken to indicate a cerebral vasodilation caused by the therapeutic measure. In effect, the results may be explained solely by regression towards the mean, as described by Sir Francis Galton in 1886 (98).

Meyer, Fang and Denny-Brown have recently reported an interesting study on the oxygen tension in the cerebral cortex of monkeys subjected to occlusion of the middle cerebral artery (221). It was found that cutting the cervical sympathetic nerve did not decrease the area of tissue anoxia, whereas such an effect was found following the inhalation of 100% O_2 (or oxygen without carbon dioxide). This study would indicate that oxygen inhalation might be of value in apoplexy. However, studying the effect of inhalation of 50–100% O_2 in 17 patients with apoplexy, Heyman and co-workers found no rise of the subnormal

values for the oxygen uptake of the brain. The authors even felt that the inhalation of pure oxygen might be noxious in this condition, as the slight reduction of blood flow might favor propagation of local thrombotic processes.

The negative result of the many experimental attempts to find cerebral vasodilatation after stellate block in apoplexy is, of course, not decisive in evaluating the therapeutic results of the procedure. It does, however, stress the importance of objective clinical criteria. It would be of great value if future clinical studies of the therapeutic effect of stellate block would include untreated control series and also objective techniques of assessing the clinical improvement (196, 199, 335).

Concluding remarks. The role of neurogenic mechanisms in the physiological intrinsic control of cerebral circulation is still uncertain. The very fact that perivascular nerves are abundant in the brain favors the idea that they do also have a function. The many observations mentioned above have demonstrated that the cerebral vasomotor innervation via sympathetic or parasympathetic pathways is either absent or at least much less pronounced than the corresponding innervation of the peripheral circulation. Indeed, available data suggest that the cerebral circulation does not participate in the central control of peripheral resistance: induced hypotension and carbon dioxide inhalation cause a centrally induced constriction of the peripheral vessels (86-88, 259, 325); in both conditions cerebral vasodilatation occurs; peripheral vessels will when denervated remain unchanged or even dilate in these conditions.

The possibility of the involvement of the perivascular nerves in the local regulation of cerebral blood flow according to the perfusion pressure and variations in the metabolic activity of the tissues cannot be excluded. Such involvement, however, remains entirely speculative, as no relevant experimental data are available. Perhaps available techniques could be utilized in studying these problems. Thus it might be of interest to know if local cocaineization of the brain surface would block or alter the vascular adaptation to variations of blood pressure, to a local increase in metabolism, or to local tissue anoxia.

CEREBRAL OXYGEN UPTAKE IN NORMAL MAN

The normal brain consumes oxygen at an average rate of 3.5 cc per 100 gm per minute and has a total oxygen uptake of about 50 cc per minute (27, 61, 173, 188, 199, 262, 284). Thus, nearly 20 per cent of the oxygen taken up by the whole body at rest is utilized by the brain. Normal mental functions are uniquely dependent on an uninterrupted and ample oxygen supply. If cerebral oxygen delivery is arrested by stopping the cerebral circulation, consciousness is lost in a few seconds (264). It can be calculated that the amount of oxygen physically dissolved in the brain tissues would actually suffice to sustain the cerebral metabolism at its normal level for a similar short period of a few seconds (158). This agreement between physiological observations and theoretical calculations suggests that the aerobic metabolism of the brain must continue at its normal rate in order to preserve the mental functions. Quantitative studies in man lend substantial support to this suggestion. It has been repeatedly shown that when arterial hypoxia or

arterial hypotension are carried to such an extreme that mental symptoms of cerebral hypoxia begin to develop, then the cerebral oxygen uptake is still not measurably decreased (81, 174, 229, 230). In other words, during the actual situation of measurement in the average subject this uptake seems to be very close to, if not identical with the minimal value compatible with normal cerebral function. The observation that the cerebral oxygen uptake continues unabated at the waking level during natural sleep indirectly supports this general statement (217). It is also noteworthy in the present context that no condition is known in which normal mental function is maintained in spite of a subnormal cerebral oxygen uptake.

The fact that the brain normally seems to operate with a kind of minimal or basal level of total oxygen uptake requires some further comments. Available evidence supports the idea that under physiological conditions increased function of a local area of the brain may well occur, leading to a local increase in metabolism (103, 266, 293). However, total cerebral metabolism has been found to remain unchanged in most physiological conditions such as sleep (217), the resting waking state, and during intellectual effort (321). This could be an effect of heterogeneity of the brain with respect to function. Conceivably increased function in one cerebral area might cause a depression of function in other areas. It is also possible that the different physiological states of cerebral activity only represent functional and metabolic changes in rather limited cerebral areas, with no measurable effect on total oxygen consumption. Thus, the brain could be compared to an iceberg, most neuronal functions remaining below the surface of consciousness and maintaining a fairly constant rate and oxygen demand. Total cerebral oxygen uptake is increased above the resting level only in a few special conditions, such as during epinephrine infusion (177), during epileptiform seizures (294), and possibly also in some cases of extreme anxiety (161).

A brief outline of the metabolism of the brain will be given in order to explain the fundamental role of oxygen. Oxidative glucose metabolism is the primary and indispensable source of energy for continuously resynthesizing energy-rich phosphate compounds in the brain (142, 319), and the cerebral respiratory quotient remains close to unity in all conditions so far studied (27, 107, 173, 186, 217, 322). The glucose uptake of the brain is about 5.5 mg per 100 gm per minute, or about 80 mg per minute for the total brain (107, 165, 284, 322, 351). This is slightly more than could be accounted for even if the total cerebral oxygen supply were utilized in aerobic glucose metabolism (142). The possibility cannot be excluded that analytical errors of the glucose determinations could be of sufficient magnitude to explain this discrepancy of glucose and oxygen uptake. Another possibility is that the nonoxidized glucose represents a kind of overflow of the initial anaerobic glycolytic process, producing an excess of lactate and pyruvate which escapes via the cerebral venous blood (142).

Although the cerebral capillaries are generally less permeable than other capillaries, this so called blood-brain barrier undoubtedly permits the transmural passage of a great variety of substances, of which many more than oxygen, carbon-dioxide and glucose are of fundamental importance for cerebral metabolic processes (102, 319). It appears reasonably certain, however, that the high and con-

tinuous energy demand of the brain is satisfied predominantly via aerobic glucose metabolism in man in physiological as well as in most pathological conditions.

Normal Values in Young Adults

In normal young adults, examined by means of the inert gas method in the resting recumbent position, the cerebral oxygen uptake per 100 gm of brain (CMRO_2) is, as already mentioned, on the average about 3.5 cc per minute (173, 188). Studies using the modification of Scheinberg and Stead have shown somewhat higher normal values of CMRO_2 , averaging about 3.6 to 3.8 (27, 61, 199, 262, 284). The possible reasons for this discrepancy have been discussed in the section on the inert gas method.

Males and females have the same CMRO_2 values (173, 188, 206, 320), and racial differences apparently do not exist (4, 27, 61, 173, 188, 199, 262, 284). In unilateral inert gas studies a considerable variation of the individual CMRO_2 values have been found. Such studies have in most cases demonstrated a standard deviation of normal CMRO_2 of 0.4 to 0.6 cc per 100 gm per minute. In bilateral studies, using the Kr^{85} modification, the spread of the normal CMRO_2 in a small series of nine cases was less pronounced, the standard deviation of this function being only 0.2 cc per 100 gm per minute (234), a value significantly lower than could be accounted for on the basis of the increased number of analyses alone.

When restudying unilateral CMRO_2 in the same subject under the same external conditions, considerable day-to-day variations often occur (128, 146, 171, 180, 188, 234, 338). A series of such repeated unilateral studies in eight normal subjects, using the Kr^{85} technique, has been reported (188, 234). In these studies the standard deviation of the normal day-to-day variations of CMRO_2 in the individual normal subject can be calculated to be about 0.5 cc per 100 gm per minute. It is of interest that this intra-individual day-to-day variation is of the same magnitude as the above mentioned interindividual variation in a group of normals. Repeated bilateral CMRO_2 studies have so far only been reported in four normal subjects, showing only minor day-to-day variations of CMRO_2 (234).

The results obtained in a great number of clinical studies based on unilateral CMRO_2 determinations using the inert gas method will be discussed in the following sections.

Influence of Age

In a recent study using the original nitrous oxide technique, the cerebral circulation and oxygen uptake of a large group of carefully selected normal aged male subjects, of an average age of 71, was studied (320). The mean value of the CMRO_2 in this group was found to be 3.4 cc per 100 gm per minute, which was not significantly different from the average value of 3.5 cc per 100 gm per minute, obtained in a group of young normal adults studied simultaneously. A moderate decrease of CMRO_2 with age has been found in other studies (279, 289), while an isolated study reports a marked decrease with age (63). It seems most likely that these divergent results were obtained by including among the aged subjects some cases with chronic degenerative brain diseases and subnormal CMRO_2 values

(66, 96, 190). This may also explain the finding of subnormal CMRO₂ in healthy subjects close to 100 years of age (71). Unpublished studies by Lassen, Lane and Feinberg using the bilateral Kr⁸⁵ technique have shown a small (9%), but significant reduction of cerebral oxygen uptake in a group of normal aged subjects of an average age of 72 years.

Considered as a whole, the available data suggest in the opinion of the reviewer a minor reduction of cerebral oxygen uptake per 100 gm brain in normal persons of about 70 years of age. A reduction of brain weight means a correspondingly lower value for total cerebral oxygen uptake. (Obviously this statement is valid in general regarding the results obtained by using the inert gas method; especially when evaluating the results in chronic brain disorders it is well to keep this point in mind.) The slight reduction of oxygen uptake per 100 gm brain in normal old age is presumably due to incipient chronic brain disease. The cause of this cerebral affliction of old age is obscure. Generalized cerebral vascular insufficiency is presumably not operative, since all the above mentioned studies have shown that the values for cerebral perfusion are proportionately no more reduced than those for oxygen uptake.

In childhood and adolescence the normal values for cerebral oxygen uptake are not firmly established. *In vitro* studies of the oxygen uptake of cerebral tissues of lower mammals have repeatedly shown low values at birth, a subsequent phase of high cerebral metabolic activity in young animals, followed by a decrease to the level of the adult animal (cf. 142). In man, two studies under nearly normal physiological conditions have been reported, using modifications of the inert gas method permitting reduction of the volume of blood sampled during the experiment (100, 152). In a study of children 2–3 years of age with various neurological diseases, a CMRO₂ of the same level as in normal young adults were found in those children who had a normal mental development and only minor neurological disorders (100). In a more closely normal group of children about 5–10 years of age, Kennedy and associates have recently reported CMRO₂ values about 5.0 cc per 100 gm per minute, which was considerably above the average value found in a group of normal young adults studied simultaneously (152). In these studies nitrous oxide was administered by means of a plastic dome and, as a result, the arterial curves continued to rise more than usually after 10 minutes of inhalation. It can be calculated that this may have introduced an error tending to give an overestimation of the CBF and CMRO₂ of 5–10 per cent (cf. page 187). This may explain why the young normal adult subjects studied by Kennedy and associates had somewhat high CMRO₂ values. It cannot, however, explain the difference between the young adults and the children. This difference cannot be due to anxiety, since only cooperative and relaxed children were examined. If the data of Kennedy *et al.* are truly representative of the average level of CMRO₂ in children, then the oxygen uptake of the brain in the middle of the first decade of life accounts for about 50 per cent of the total basal oxygen consumption of the body. These same investigators found that the CMRO₂ of adolescents was also somewhat higher than that found in young adults (152).

It may be mentioned that in childhood as well as in senescence the cerebral

blood flow varies in parallel with the cerebral oxygen uptake. Thus, the arterio-venous oxygen difference of the brain remains relatively constant, as do the cerebral venous oxygen and carbon dioxide tensions also. Insofar as these tensions can be taken to represent those of the brain, these observations suggest that the chemical milieu of the cerebral tissues is maintained fairly constant throughout life.

Influence of Physiological Variations of Cerebral Function

The lack of change of cerebral oxygen uptake in physiological conditions characterized by variations of cerebral function has already been discussed. These important findings deserve a more detailed presentation, to be given below.

Intellectual effort. Normal values of cerebral perfusion and oxygen metabolism have been obtained in the resting waking state without regard to the mental activity of the subject. The influence of concentrated intellectual effort has been studied in young normal adults (321). Shortly after a control study, the test subjects were required to solve mentally a series of fairly simple arithmetic problems. No significant change of CMRO_2 or cerebral perfusion and vascular resistance was found.

Physical exercise. Moderate muscular activity has been found to have no influence on the CMRO_2 , whereas the cerebral blood flow was slightly decreased, presumably as a result of mild hypocapnia (182).

Apprehension. Apprehension is in this context taken to mean an acute condition of subjective and objective signs of anxiety, fear and discomfort during the actual test situation of a person of no apparent emotional instability prior to the test. In a series of such observations in normal subjects, no significant effect of apprehension was found (284). An isolated observation by Kety has suggested that severe apprehension may cause a marked rise in cerebral oxygen uptake (161). It was suggested that this rise in oxygen uptake might be due to the stimulating action of *l*-epinephrine on cerebral metabolism (177).

Sleep. In a painstaking study, the influence of normal sleep has been studied (217). Only those normal subjects who managed to fall asleep spontaneously with needles in place and an anesthesia mask on, and who had electroencephalographic evidence of sleep, were accepted in the study. No change in cerebral oxygen uptake was found compared to the presleep control studies in the fatigued waking state on the same subjects. Fatigue alone was shown to be without effect in another series of subjects. The cerebral blood flow increased slightly during sleep, presumably due to a mild hypercapnia. These observations are of interest in relation to various theories of the nature of natural sleep. The possibility that generalized cerebral ischemia was involved can be excluded. These studies also appear to rule out the hypothesis that sleep is a kind of endogenous narcosis with a decreased over-all metabolism permitting the replenishment of certain substrate stores presumably depleted by the active metabolism of the waking state. As will be discussed in the next section, narcosis and other forms of coma are all characterized by a marked reduction of cerebral oxygen uptake. The observation that cerebral metabolism goes on unabated during sleep may be taken to indicate that the difference between sleep and the waking state is not so fundamental as one might believe.

But apart from this, the study does not give any clues to the enigma of why we must sleep.

Other conditions. As mentioned in the section on the regulation of cerebral blood flow, physiological variations of the respiratory gas tensions of the arterial blood and of the perfusion pressure of the brain do not change the oxygen uptake of the brain.

The effect of low body temperatures has been studied mostly in animal experiments. The cerebral oxygen uptake and the cerebral perfusion are reduced roughly in proportion to the reduction in total body oxygen uptake, cardiac output, pulse rate, and myocardial and renal blood flow. These values all decrease to about 50 per cent of the normal levels at a temperature of 28°C (134, 222, 263, 296). At about this temperature the cerebral function is depressed to a level corresponding to that of surgical anesthesia (cold anesthesia). Similar results were obtained in a study of CBF and CMRO₂ in man, using a combination of physical cooling and a variety of pharmacological agents (artificial hibernation) (77).

High body temperatures of about 39°C induced by pyrogen injection have been studied in patients with asymptomatic neurosyphilis and with dementia paralytica (140). An increase of cerebral oxygen uptake of 3–24 per cent was found in the two groups respectively. Only the change of 24 per cent was found to be statistically significant. It may be mentioned, however, that the changes observed in both groups seem to be compatible with the hypothesis that the hyperpyrexia had actually caused a 10–15 per cent increase of CMRO₂ in both groups. A change of this magnitude would be expected to occur, on the basis of the results reported in hypothermia. No studies have been made of cerebral metabolism in fever with mental symptoms. That the cerebral function is severely or even irreversibly affected by extreme hyperpyrexia is well established clinically. The nature of this effect is unknown.

CEREBRAL BLOOD FLOW AND OXYGEN UPTAKE IN DISEASE STATES

The finding of a subnormal cerebral oxygen uptake in a number of disease states may well be considered the most important knowledge gained from the many clinical studies of the circulation and metabolism of the brain. The grey matter of the hemispheres, of which the cerebral cortex forms by far the bulk, has a considerably higher oxygen consumption than the white matter. For this reason, it may be assumed that a subnormal cerebral oxygen uptake signifies a hypometabolism of the cerebral cortex. It is thus not surprising that a subnormal cerebral oxygen uptake is found only in conditions with distinct signs of diffuse hypofunction of the cerebral cortex. Two different types of such a hypofunction may be discerned: 1) acute cerebral depression with a reduction of the level of consciousness, i.e., semicomata and coma; and 2) chronic cerebral degenerative diseases with a reduction of intellectual faculties, i.e., organic dementia. The following section will first review the literature concerning cerebral perfusion and oxygen metabolism in these two types of brain disease. Particular mention will be made of the relation of chronic brain disease to cerebral arteriosclerosis and to psychosis in elderly patients. Finally, various other neuropsychiatric disorders and a variety of systemic diseases will be discussed.

Semicoma and Coma of Varying Etiology

In all conditions of semicomata or coma which have been studied—whether due to anesthetics, acute hypoglycemia, apoplexy, or any other cause—the reduction of consciousness correlates roughly with the decrease of cerebral oxygen uptake, regardless of the cause of the acute cerebral disorder (table 1). This correlation was first noted by Kety, who stated: "In all of our studies we have been impressed with the close correlation between the level of consciousness and the rate of oxygen consumption by the brain. In patients who are comatose for whatever reason, cerebral oxygen consumption falls to a value of less than 2.0 cc per 100 gm per minute, while in those who are semistuporous or confused, the value lies between 2.5 and 3.0" (156).

Apart from this interesting observation, however, the many studies listed in table 1 have not shed any new light on the pathophysiology of coma. Generally the cerebral blood flow seems to be adequate in coma, as the relative reduction in perfusion is no greater than that of oxygen metabolism (in cerebral circulatory failure a disproportionate drop of perfusion is found; refs. 81, 154). In less marked forms of acute cerebral hypofunction than semicomata and coma, the cerebral oxygen uptake is not decreased significantly. The cerebral oxygen uptake is not measurably reduced in subjects with clinical signs of impending cerebral hypoxia caused by arterial hypotension (81), and in subjects with symptoms of cerebral depression due to hyperventilation (174) or the inhalation of 100% O₂ under a

TABLE 1. CEREBRAL OXYGEN UPTAKE IN VARIOUS TYPES OF COMA

TYPE OF COMA	CEREBRAL O ₂ UPTAKE cc/100 gm/min.	REF.
Normal subjects	3.4	65, 173
Intoxication*		
Barbiturate intoxication (coma)	2.3	65
Barbiturate anesthesia	2.1	19, 145, 289, 343
Ethyl alcohol coma	1.6	13
Methyl alcohol coma	2.0	14
Steroid anesthesia	1.7	115
Artificial hibernation	2.2	22, 77, 119, 316
Uremic coma	2.2	139
Hepatic coma	1.7	72, 342
Damage and edema*		
Irreversible post-hypoglycemic coma	1.5	64
Irreversible post-anoxic coma	1.8	65
Post-traumatic coma	1.8	65
Coma after craniotomy	1.9	301
Tumor cerebri with coma	2.5	175
Apoplexy with coma	2.1	65
Lack of nutrients*		
Hypoglycemic coma	1.9	176
Secondary shock with coma	1.9	69

* Presumed pathophysiological mechanism.

pressure of several atmospheres (186). Similarly, barbiturate sedation does not depress cerebral oxygen uptake significantly (176, 210). It is possible, however, that the use of more accurate techniques and appropriate correction for the increased effect of heterogeneous perfusion upon the inert gas method would make it possible to demonstrate a reduction of cerebral oxygen consumption in one or more of these conditions.

As mentioned in the chapter on the inert gas method, the heterogeneity of the cerebral perfusion may be expected to cause a greater error in low values of cerebral perfusion than in normal values. For this reason, the values for cerebral blood flow and oxygen uptake in severe hypotension and hyperventilation are relatively too high. This could be the explanation of the finding of an increase of cerebral oxygen uptake in 9 out of 12 hyperventilating subjects (174), and of the lack of reduction in severe hypotension with quite pronounced symptoms of cerebral hypoxia (81).

Drug-induced forms of coma will be discussed in the following section. In diabetic acidosis and coma a close correlation between reduction of consciousness and of cerebral oxygen uptake was found (169). The finding of increased cerebral blood flow in diabetic coma may be an effect of the severe acidosis (cf. page 204). Severe uremic intoxication with mental symptoms is associated with a reduced cerebral oxygen uptake (139, 276). Uremic anemia is probably the cause of increased cerebral blood flow in some cases (276). In hepatic failure no significant correlation between cerebral depression and oxygen uptake has been found (72, 342). Observations suggesting an increased cerebral ammonia uptake in hepatic coma have been reported (34), but negative or mainly negative studies have since been published (341, 342). It has already been mentioned that in hypoglycemic coma the cerebral perfusion remains normal in spite of a marked reduction of cerebral oxygen uptake (176).

Apoplexy. In acute cerebrovascular accidents a distinct correlation between mental and metabolic depression has been reported (199). As the cerebral blood flow is reduced proportionately to the reduction in oxygen metabolism, there seems to be no sign of general cerebral vascular insufficiency in this condition (65, 138, 199). The lack of effect of stellate ganglion block on total cerebral perfusion in apoplexy has been discussed. The inhalation of 100% O₂ at atmospheric pressure causes moderate cerebral vasoconstriction in apoplectic patients, just as in normal man (138).

Unilateral carotid ligature was found to be without effect on cerebral blood flow and oxygen uptake in three young subjects who tolerated the operation well; but a 53-year-old man who developed hemiplegia and coma showed reduced values of both flow and oxygen uptake of the brain (303). Bilateral studies, using the original nitrous oxide method, were employed in these observations, which provide an example of the advantage of such techniques when attempting to evaluate the results obtained in the individual subject.

Acute hypertensive encephalopathy is associated with a reduction of cerebral oxygen uptake (206, 228). Whether due to essential hypertension or to the hypertensive toxemia of pregnancy, the cerebral perfusion remains normal in these conditions.

This observation is difficult to evaluate, as no values for the arterial carbon dioxide tensions were reported. It is clear, however, that the cerebral symptoms are not caused by a general insufficiency of cerebral perfusion. Animal experiments have suggested that focal arteriospastic ischemia is the cause of acute hypertensive encephalopathy (45). This concept is not incompatible with the finding of normal cerebral perfusion in patients in hypertensive crisis. Presumably the areas of ischemia are quite small, and thus they contribute little to the over-all perfusion rate. Moreover, if the blood flow in the ischemic zones is sufficiently slow, their contribution would be further minimized.

Brain tumor. Kety, Shenkin and Schmidt found a reduced cerebral oxygen uptake and a reduced cerebral perfusion in patients with brain tumor and increased intracranial pressure (175). This observation has been confirmed by several other investigators (25, 30, 118, 120, 121). In the study of Kety and associates, reduced values were found in those patients who had an intracranial pressure higher than about 450 mm H₂O. All but one of these patients were comatose. Pressure reduction by ventricular drainage did not cause a rise of the reduced values for cerebral oxygen uptake and cerebral blood flow in these patients, and did not change their level of consciousness (311). This indicates that the high intracranial pressure cannot be the direct cause of the mental, metabolic, and circulatory disturbances of the brain. The high pressure may indirectly be of importance by causing diffuse cerebral damage of a type not immediately reversible following a normalization of the pressure. This damage, e.g. in the form of a cerebral edema or tissue damage caused by the tumor directly, may then be thought of as constituting the more immediate cause of the coma and the reduced cerebral oxygen metabolism. Homeostatic mechanisms and the increased intracranial pressure may both be of importance for the rise in cerebrovascular resistance causing a reduction in cerebral perfusion roughly proportional to the reduction of cerebral oxygen uptake, despite the rise in driving blood pressure.

The cerebral arteriovenous oxygen difference in patients with increased intracranial pressure is normal or slightly increased (25, 30, 52, 109, 118, 120, 121, 175, 311, 345, 351). In normal man, hyperventilation causing mild cerebral symptoms but no reduction of cerebral oxygen uptake markedly increases the cerebral arteriovenous oxygen difference, and the cerebral venous oxygen saturation reaches as low levels as in hypoxia (171). The above mentioned many studies of patients with increased intracranial pressure showed, relative to the changes induced by hyperventilation, a very moderate and probably quite insignificant reduction of cerebral venous oxygen saturation. Thus there is no convincing evidence of a diffuse cerebral circulatory derangement causing a generalized cerebral hypoxia.

Extraneous influences have been studied to some extent. Pressure reduction by ventricular drainage has, as mentioned above, no effect (311). The intravenous administration of hypertonic glucose was found to reduce the increased pressure in some cases without changing the clinical condition or changing the subnormal value for cerebral oxygen uptake (311). Moderate hypotension induced by a ganglionic blocking agent was found not to change the cerebral perfusion or

oxygen uptake in patients with moderately increased intracranial pressure (24). This observation indicates that the cerebral circulation is not on the verge of collapse, and that induced hypotension may presumably be used safely during operation in such patients. In a small series of cases, tilting 20° head up was found to decrease the cerebral blood flow in patients with brain tumor, whereas tilting 20° head down had no significant effect (310).

Organic Dementia

The cerebral oxygen uptake is subnormal in chronic diffuse organic brain diseases characterized by a reduction of intellectual mental functions. This was first reported by Freyhan, Woodford and Kety in a study of senile brain disorders (96). It has been confirmed since by studies of other chronic brain disorders, such as cerebral syphilis (251), or chronic brain syndrome following acute cerebro-vascular accidents (31, 63, 66, 70, 179, 180, 190, 241, 248, 309).

A definite relation between the degree of reduction of cerebral oxygen uptake and the degree of dementia was found by Garfunkel, Baird and Ziegler (100), who studied mentally retarded children with various severe neurological diseases. The same observation was made in a study of aged patients with degenerative brain diseases of different etiology studied by Lassen, Munck and Tottey (190). The latter results were obtained by employing bilateral studies using the Kr⁸⁵ technique, an approach which was found greatly to facilitate this correlation. The results of these studies may be summarized as follows: In patients whose mental condition is completely dominated by severe loss of intelligence, the cerebral oxygen uptake is reduced to about 2.0 cc per 100 gm per minute, while in those with less apparent dementia the values lie between 2.5 and 3.0.

Severe organic dementia is associated with the same low values of cerebral oxygen uptake per 100 grams of brain per minute as were found in coma.⁵ These two conditions are, however, clinically strikingly different. Subjects with such degrees of organic dementia have no loss of consciousness. Although severely incapacitated socially by loss of intellectual faculties and by some degree of emotional fatuity or instability, such patients are often able to care for personal requirements and, given proper care, to remain in their home environment (190). Possibly the gradual but complete loss of many cortical cells does not affect cortical function as profoundly as the severe hypofunction of all cortical cells supposedly found in coma. It is also possible that in coma the loss of consciousness and reduction of cortical oxygen uptake are both secondary to the depression of subcortical centers, which remain intact in chronic brain disease (see e.g. 215).

Organic dementia of known etiology. It is well established that cerebral oxygen uptake and cerebral blood flow are reduced in patients who develop chronic brain syndrome following an acute cerebrovascular accident (31, 63, 66, 70, 138, 179, 180, 190, 241, 248, 309). Cases with proven thrombosis of the internal carotid artery have the same abnormalities of cerebral circulation and metabolism (245).

⁵ Presumably the oxygen uptake for the total brain is actually lower in such cases of severe chronic brain disease than it is in coma, as only in the former condition is loss of cerebral tissue supposedly quantitatively important.

Cerebral oxygen uptake and cerebral perfusion were also found to be reduced in meningo-vascular lues and in dementia paralytica, whereas normal values were found in asymptomatic neurolues (251). Thus in this condition also a clear correlation between decreased cerebral function and reduced cerebral oxygen uptake could be demonstrated. Clinical improvement in patients with dementia paralytica treated with penicillin or penicillin combined with pyrogen caused an increase of cerebral oxygen uptake towards the normal level (251). In acute experiments, pyrogen therapy (to 39°C) was found to cause only minor changes in asymptomatic cases, but to increase cerebral perfusion and oxygen uptake significantly in patients with dementia paralytica (140). This observation is not easy to interpret. The results reported are not incompatible with the hypothesis that the hyperthermia had in actual fact caused a 10–15 per cent increase in cerebral oxygen uptake in both groups, as was mentioned previously. Children with congenital neurological disorders have been found to have reduced values for cerebral oxygen uptake and cerebral blood flow (100). The reduction of the cerebral metabolic rate of oxygen showed a clear correlation to the degree of retardation of intellectual development. In a study of four patients with microcephalia and a very low level of intelligence, moderately subnormal values for cerebral oxygen metabolism and perfusion were found (78). In such patients, however, where the weight of the brain is so much lower than normal, total cerebral oxygen uptake and perfusion is consequently markedly reduced. A reduction of cerebral oxygen uptake and cerebral perfusion has been reported in advanced cases of chronic encephalitis (314). Bilateral stellatectomy in these patients caused no significant changes.

Cerebral Arteriosclerosis

Chronic brain disease with organic dementia is common in the older age groups. Such patients are clinically characterized by a reduction of intellectual functions which often socially incapacitates the individual. In all the many studies of such patients which will be referred to in this section, the cerebral oxygen uptake is subnormal and seems roughly to correlate with the reduction of mental powers. Chronic organic brain disease in elderly people is in some cases caused by well defined cerebral diseases, such as cerebral syphilis or acute cerebrovascular accidents. These disorders have been discussed in the previous section. In a great many cases, however, the development of chronic brain syndrome is very gradual, and its cause remains obscure. It is common to use the term 'cerebral arteriosclerosis' to describe such cases. This term expresses the opinion that progressive atherosomatous narrowing of the cerebral arteries is the cause of diffuse, slowly progressive cerebral atrophy. If hypertension, retinopathy, stenocardia, or other signs of vascular disease are present, they are taken to constitute supportive evidence for the assumption of a vascular etiology.

The syndrome just described is clinically related to that of various forms of supposedly nonvascular progressive cerebral atrophy affecting the same age groups. Alzheimer's and Pick's diseases are among the more well defined and recognizable of these disorders, which presumably primarily affect the parenchyma of the brain. How can one distinguish clinically between primary atrophy of the cerebral

parenchyma and cellular damage secondary to cerebral vascular disease? With the advent of methods which allow measurement of cerebral blood flow and other important cerebral circulatory parameters in such patients, it was to be hoped that this distinction could be made more clearly. As will become apparent in the following, this has not been the case.

Cerebral circulation in cerebral arteriosclerosis. A high incidence of severe atherosclerosis of the larger cerebral arteries is generally found in elderly patients who die from acute cerebrovascular accidents. This observation has led to the probably correct assumption that elderly patients surviving an apoplectic insult have, as a group, a more pronounced degree of cerebral atherosclerosis than nonapoplectic controls of the same age or normal young adults. On this basis, information regarding the cerebral circulation in 'cerebral arteriosclerosis' has in most cases been deduced from studies of aged post-apoplectic cases and suitable controls.

A normal level of oxygen saturation of the cerebral venous blood is found in postapoplectic patients (63, 66, 138, 289, 309; see also 44 and 315, in which the clinical material was somewhat differently selected). Assuming the gradient of oxygen tension between the brain and the cerebral venous blood is not markedly increased, it must be concluded that the over-all oxygen tension of the brain is maintained at an adequate level in aged patients who have survived a stroke. This important conclusion is supported by the observation that hyperventilation or induced hypotension may reduce the cerebral perfusion and the cerebral venous oxygen tension in such patients below the resting level without causing symptoms of diffuse cerebral hypoxia (31, 66, 179, 180).

Focal cerebral vascular insufficiency is, however, not excluded from these observations. It is clinically well established that marked hypotension in elderly patients may occasionally lead to localized cerebral ischemia or even infarction, presumably because of a local inadequacy of the compensatory vasodilatation (51, 56, 70). Supposedly this syndrome is caused by the preexistence of an occlusion or marked narrowing of a larger cerebral artery. In response to such a pathological obstruction, the collateral vessels to the area are already dilated so much that the further vasodilatation in response to hypotension is inadequate (220).

If focal cerebral hypofunction during induced hypotension were to be taken as the only reliable clinical evidence of significant cerebral vascular disease, then this diagnosis would be a rare one, as it is well recognized that this syndrome is not common (5). In this connection it is relevant to report the results of Fazekas' and co-workers' study of the effect of induced hypotension in 12 elderly hypertensive patients, all with signs of chronic brain disease and presumed cerebral atherosclerosis (70). When the blood pressure was reduced to half the control value, these patients developed signs of diffuse cerebral hypoxia. No signs of focal cerebral hypoxia were found. These results are completely comparable to those obtained in younger hypertensive patients without signs of cerebral disease (168). Undoubtedly many if not all of the elderly patients studied by Fazekas and co-workers had atherosclerosis of their cerebral arteries. Despite this, no focal or general cerebral vascular insufficiency was disclosed by the induced hypotension.

Carbon dioxide inhalation causes cerebral vasodilatation in elderly patients who have survived stroke (63, 66, 241, 248, 289). A detailed evaluation of these studies is difficult, as the values for the arterial pCO₂ have not been reported, but the average percentage increase in cerebral blood flow is the same as found in normal young adults. Fazekas and co-workers found no increase in cerebral perfusion in a few of their old patients (66). This interesting observation remains isolated, however, as no other studies have reported similar cases (63, 190, 241, 248, 289).

It is necessary to discuss two of the above mentioned studies further, as the authors did not draw the same conclusions from their observations as has the present reviewer. Novak and collaborators found that carbon dioxide did not significantly decrease the cerebrovascular resistance in a group of normotensive postapoplectic patients (241). The data reported suggest, however, that this observation was caused by random errors. Let it be assumed that the calculated cerebral oxygen uptake had remained constant in each case of this group (as it is well known that carbon dioxide does not affect the cerebral oxygen uptake (174)). Then it can be calculated that the cerebrovascular resistance actually did decrease significantly in this group just as in the other groups studied.

Schieve and Wilson found that the increase of cerebral perfusion during carbon dioxide inhalation was lower in elderly patients with organic brain syndrome than in normals (289). But these authors failed to take into consideration the fact that the carbon dioxide reactivity depends on the initial value for the cerebral blood flow. This relation was clearly apparent from a study of the carbon dioxide reactivity of anesthetized normal subjects which were studied by the same authors (289). The relative increase in cerebral blood flow during carbon dioxide administration was found to be approximately the same in chronic brain disease and anesthesia as in normal man. This means that the induced changes of the carbon dioxide and the oxygen tensions of the cerebral venous blood is the same in all three groups. Thus it seems permissible to conclude that the results obtained by Schieve and Wilson demonstrated an adequate carbon dioxide reactivity in patients with organic brain disease.

It thus seems that the regulation of the cerebral blood flow is relatively normal in the average old patient who has survived a stroke; the changes of cerebral perfusion induced by hypotension, hyperventilation and carbon dioxide have already been reviewed. Alterations in the inspired oxygen concentration (63, 138) and aminophylline injections (66) also change the cerebral perfusion in elderly postapoplectic patients as in normal man.

The following two statements find support in the many studies reviewed in this section: 1) Atheromatosis of the cerebral arteries usually does not cause progressive narrowing of vessels of functional importance. This has also been demonstrated directly by pathoanatomical observations of the diameter of atherosomatous cerebral arteries (37). 2) The vessels regulating the cerebrovascular resistance are not abnormally rigid in patients who have atherosclerosis of the cerebral arteries. This statement is likewise supported by independent evidence, as atherosclerosis of the cerebral arteries is confined to arteries of a diameter of more than 0.2 mm

(3), whereas the cerebrovascular resistance is presumably mainly regulated by even smaller arteries (82).

Chronic brain disease and cerebral arteriosclerosis; conclusion. The measurement of total cerebral perfusion or the cerebral venous oxygen tension cannot, in the average case, disclose the presence of atheromatosis of the cerebral arteries, not even when studies are made during induced hypotension or carbon dioxide inhalation. Thus it is not possible by using such techniques to divide the many presenile and senile patients into two groups, one of vascular etiology and one of nonvascular etiology. This negative conclusion is, however, not the only one which can be derived from the many studies reviewed above. The adequacy of the oxygen delivery of the brain and of the regulation of cerebral blood flow in patients with atheromatosis of the cerebral arteries deserves some further comments. On this basis one may question whether a gradual atheromatous narrowing of the larger cerebral arteries is actually a common cause of progressive presenile and senile chronic brain disease. The studies of the cerebral circulation in elderly patients thus deemphasize the pathogenetic importance of cerebral atheromatosis in chronic progressive brain disease in the higher age groups. The possibility of primary parenchymatous processes must be considered in all such patients regardless of circumstantial evidence of atheromatosis of the cerebral vessels.

Chronic Brain Disease and Psychoses in Aged Patients

Freyhan and collaborators (96) studied a group of ten aged patients (average age 72 years) who were institutionalized because of gross mental defects of psychotic proportion (confusion, pronounced loss of recent memory, severe emotional lability etc.). These patients had moderately lower values for the cerebral perfusion and oxygen uptake than normal young adults studied by the same group of investigators. The subnormal cerebral oxygen consumption may be taken to indicate diffuse chronic organic brain disease in the group of aged psychotic patients as a whole.

Nonpsychotic aged subjects with no obvious signs of disease have been found to have a similar reduction of the cerebral metabolic rate of oxygen (63, 279, 289), while very highly selected, optimally normal old subjects showed no demonstrable reduction (320). These observations, which have already been discussed in the section on the influence of age, may be interpreted to indicate that many elderly nonpsychotic subjects have a reduced cerebral oxygen uptake on the basis of chronic brain disease. Thus it seems that with regard to diffuse organic brain disease as evidenced by a decreased cerebral oxygen uptake, psychotic old patients are not more severely affected than many alert, sane persons of the same age. In the latter cases the clinical signs of cerebral hypofunction are restricted to an inconspicuous reduction of intellectual abilities. The study of Fazekas and associates on the cerebral circulation and oxygen uptake in elderly patients seems to support this hypothesis (63, 68). The authors failed to find any significant difference of cerebral oxygen metabolism between 'alert' and 'confused' aged patients. The cerebral oxygen uptake was reduced to the same extent in both groups.

Thus, in psychosis developing in aged patients, just as in schizophrenic psychosis, the derangement of cerebral function does not correlate with the cerebral

oxygen uptake. The clinical syndrome of psychotic behavior in old patients is usually described by the terms 'senile psychosis' or 'organic psychosis.' Both terms imply an intimate connection between organic (and presumably irreversible) brain lesions and the abnormal behavior. The studies mentioned above suggest that these concepts may be too simple. They do suggest that psychotic behavior in old people more frequently develops in the presence of chronic organic cerebral disease, but they do not indicate a close relation between the severity of diffuse organic brain disease and the degree of psychiatric disturbance.

Miscellaneous Neuropsychiatric Disorders

Grant and co-workers found in patients with idiopathic epilepsy that when no seizure occurs during the actual study, the cerebral oxygen uptake and blood flow are normal (116). This has also been reported by Gibbs and associates, employing the indicator injection method (104). (This is the only study, so far, in which the indicator injection method was used to study a distinct disease entity.) No change of cerebral blood flow occurs immediately preceding a seizure (109). Studies in monkeys during induced epileptiform attacks have demonstrated that cerebral oxygen uptake and perfusion increase to about twice the control value (294). Direct observations in man by Penfield have suggested a local increase of perfusion through that portion of the cortex which is involved in the convulsive discharge (254). As mentioned previously, it is possible that during spontaneous seizures in man, arterial hypoxia may interfere seriously with the cerebral oxygen delivery. Patients who are semicomatose immediately following induced seizures have been found to have subnormal values for cerebral oxygen uptake and cerebral perfusion (116, 176). The effects of repeated electric shock therapy have been studied on a group of 21 psychotic patients without evidence of organic brain disease (347). Following a series of, in average, 10 electroshock treatments, no significant change in cerebral oxygen uptake or cerebral blood flow could be demonstrated.

Disseminated sclerosis. Reduced values for cerebral oxygen uptake and cerebral blood flow have also been reported in this disease (114, 277, 338). Due to the large scatter of values obtained in the pathological groups and in the control groups, these reductions were not statistically significant. The fact that in all three clinical studies distinctly subnormal average values were reported does, however, suggest that the cerebral oxygen uptake and perfusion actually are reduced in severe cases of this disease.

Lobotomy. Following lobotomy cerebral oxygen uptake and cerebral blood flow have been found to be reduced (313). The authors suggest as one possible explanation, that the disruption of association neurones decreases the total number of stimuli and thus the total number of discharges from the brain—thereby reducing the cerebral oxygen uptake and accordingly the cerebral blood flow also.

Intracranial arteriovenous aneurisms. Cerebral blood flow is markedly increased in this condition, while the cerebral oxygen uptake is maintained at the normal level. In spite of unilateral localization of the shunt, some patients have high values for the calculated cerebral blood flow per 100 gm of tissue in both internal jugular veins, whereas others have high values predominantly on the affected side (26, 28,

33, 189, 286, 312). It has been estimated that the smallest shunt which can be demonstrated using the Kr⁸⁵ modification is about 200 cc per minute (189).

Schizophrenia. A large series of chronic schizophrenic patients studied by Kety and co-workers (176) showed completely normal values for cerebral oxygen uptake and cerebral perfusion. Wilson and his collaborators (347) and Sokoloff *et al.* (322) have reported similar findings. Moderately subnormal values were reported by Gordan and co-workers (114). It is difficult to explain these divergent results, as the case materials studied and the experimental techniques used seem to have been quite similar in all studies. On the basis of the four studies mentioned, however, it is unlikely that chronic schizophrenic patients have a significant impairment of total cerebral perfusion and oxygen metabolism.

The finding of a fairly normal cerebral oxygen uptake in schizophrenia is interesting. A marked reduction of intellectual performance is not rare in such patients. This dementia, however, is apparently quite different from the dementia found in degenerative brain diseases, where the mental and metabolic functions of the brain are both reduced. These observations support the widely accepted view that when dementia occurs in schizophrenics, it is secondary to the more fundamental derangement of affective cerebral functions. The lack of obvious changes in gross energy requirement of the brain in schizophrenia may be commented on by using Kety's words regarding the lack of correlation between cerebral oxygen uptake and cerebral dysfunction in hypoxia and hyperventilation (174): "The higher psychic functions are associated with biochemical changes so subtle and complex as to render any attempt to describe them in terms of mere oxygen utilization no more adequate than to predict the fidelity of a radio by its power requirements."

Various Systemic Disorders

Hypotension. Patients with spontaneous orthostatic hypotension were studied by Finnerty and co-workers (81). A reduction of the mean arterial blood pressure at head level induced by tilting was found to cause clinical symptoms of inadequate cerebral perfusion when the pressure was reduced to about 40–50 per cent of the control level. Concomitantly the cerebral blood flow was reduced to a critical level of about 60 per cent of the control value, while the cerebral oxygen uptake was not significantly reduced. This response is typical for all forms of severe hypotension, whether induced by changes of posture in susceptible patients (81), by spinal anesthesia (159, 184, 185), or by various drugs (81, 229, 230). In moderate hypotension, adequate dilatation of the cerebral vessels occurs, maintaining cerebral blood flow at the normal level (1, 23, 49, 58, 124, 125, 130, 179, 278).

Studies in acute hemorrhagic shock have demonstrated a pronounced reduction of arterial pCO₂ due to hyperventilation (331). This was presumably the cause of the reduction of cerebral blood flow to levels lower than could be explained by the hypotension per se. A small dose of morphine sulphate caused a rise in arterial pCO₂ towards normal values and a normalization of the cerebral blood flow without any change in blood pressure. The subjective state of the patients was also considerably improved by the drug. Subnormal values for cerebral blood

flow and oxygen uptake have been reported in secondary shock of varying etiology (69). Owing to the heterogeneity of the material and the paucity of the clinical information it is difficult to interpret these results.

Essential hypertension. Cerebral blood flow and oxygen uptake are normal in patients with essential hypertension without cerebral complications (122, 166, 172). This means that cerebrovascular resistance is increased in proportion to the increase in mean arterial blood pressure, as is the vascular resistance of the organism as a whole (257). A correlation between the increased values for cerebrovascular resistance and the degree of retinal vascular changes has been reported (195). This correlation suggests, just as does general clinical experience, that inspection of the retinal vessels may give some idea of the state of the cerebral vascular bed. A positive correlation between cerebral blood flow and cerebral oxygen consumption has been reported in a series of unilateral studies of patients with essential hypertension (122). Excluding the influence of random technical errors in the nitrous oxide method (which alone might explain the phenomenon) this correlation signifies that the cerebral arteriovenous oxygen difference is not inversely proportional to the cerebral blood flow. The results obtained in a series of bilateral studies are of some help in evaluating the significance of this finding (234). Analyzing the 34 bilateral studies in a heterogeneous group of subjects without evidence of intracranial vascular shunts, it was found that the jugular vein with the highest cerebral blood flow tended also to have the largest arteriovenous oxygen difference ($r = 0.36; 0.05 > P > 0.02$); Thus the side with the highest cerebral blood flow value usually also had the highest value for cerebral oxygen uptake ($r = 0.82; P < 0.001$). Hence it follows that true side-to-side differences may explain the above mentioned findings in patients with essential hypertension (122). It may well be, however, that some degree of real variation in cerebral oxygen uptake was present independent of side-to-side variations. If so, cerebral perfusion would presumably vary in parallel with the variations of the metabolic demand. But, owing to the above mentioned relationships, such a correlation cannot readily be disclosed.

Essential hypertension complicated by severe headache is apparently not associated with abnormal values for cerebral perfusion and oxygen uptake (233). Acute hypertensive encephalopathy has already been discussed, and it was mentioned that the cerebral oxygen uptake was reduced in this condition (206, 228). Patients with chronic brain syndrome and arterial hypertension have reduced values for cerebral oxygen uptake and cerebral blood flow and very high values for the cerebral vascular resistance (309).

The regulation of the cerebral blood flow in essential hypertension has been studied intensively. Moderate tilting head-up has been found to cause a mild reduction in cerebral perfusion both before and after sympathectomy (126). Carbon dioxide inhalation has been found to increase cerebral blood flow as much as in normotensive subjects (241). Other investigators have reported a decreased carbon dioxide reactivity (66, 127, 131), but available data on the induced changes of the arterial pCO_2 (127, 131) suggest that the cerebral circulation did actually react normally. The vasodilating effect of acutely induced hypotension has been estab-

lished in numerous studies, demonstrating that this effect is independent of the agent used in producing the hypotension (23, 24, 29, 31, 49, 54, 55, 57, 80, 81, 125, 128, 130, 168, 179, 213, 223, 224, 228, 232, 332). Thus in hypertensive patients, just as in normotensive subjects, the fall in blood pressure induced by spinal anesthesia (168) was found to cause a similar reduction of cerebrovascular resistance, as, e.g., hexamethonium bromide (55, 57, 80, 213, 223, 224, 332). The effects of sympathectomy and/or subtotal adrenalectomy have also been studied. Both forms of treatment are followed by a significant reduction of the cerebrovascular resistance, so that cerebral perfusion is maintained at the normal level in spite of a moderate drop in mean arterial blood pressure (129, 305).

It has been clearly shown that patients with essential hypertension are abnormal insofar as they cannot tolerate a blood pressure reduction to as low pressure levels as can normotensive subjects (cf. 81). This indicates that the cerebral blood vessels are unable to relax normally, presumably because of increased rigidity (81). When seen in relation to their habitual blood pressure, however, the tolerance of the hypertensive subjects was the same as in the normotensive group. In both groups a reduction of about 50 per cent in the initial blood pressure was required in order for clinical symptoms of cerebral circulatory failure to develop. Concomitantly, a critical reduction of the cerebral blood flow to about 60 per cent of the initial value was also found in both groups.

The effect of more prolonged hypotensive therapy has also been studied. After several weeks of intensive treatment of elderly hypertensive patients, hypoxic cerebral symptoms developed at the same level of blood pressure reduction as before the treatment (180).

The cerebral circulation in essential hypertension seems to be adapted so that the perfusion is regulated in a normal fashion at the increased level of pressure. The abnormal cerebrovascular rigidity demonstrated by acutely induced hypotension is intriguing. It would be of considerable interest to know whether a very prolonged efficient antihypertensive treatment would normalize the tolerance to hypotension.

The above mentioned studies of the cerebral circulation in essential hypertension have not shed any light on the etiology of this disorder. The fact that cerebral circulation is regulated normally at the increased level of pressure does not necessarily indicate the action of a general humoral vasoconstrictor on the cerebral vessels. For, as indicated in the section on the regulation of the cerebral blood flow, this kind of adaptation would presumably be found in hypertension irrespective of the etiology.

Hypertensive toxemia of pregnancy. In normal pregnancy and in hypertensive toxemia without eclampsia, the cerebral blood flow and oxygen uptake are normal (203-212, 337). In patients with eclampsia, the cerebral oxygen uptake is reduced, while the cerebral blood flow remains normal (46, 206; see also the discussion of acute hypertensive encephalopathy). The effect of morphine, barbiturates, dihydrogenated ergot alkaloids and papaverine on the cerebral circulation and metabolism seems to be the same in patients with toxemia as in normal man (205, 207-212, 337; cf. the section on the action of drugs).

Intense relative hypotension—an approximately 50 per cent reduction of the mean arterial blood pressure—induced by veratrum alkaloids or Apresoline (*l*-hydrazinoptalazine) was found to cause no decrease of cerebral blood flow, and no hypoxic cerebral symptoms developed (206). This observation is of interest in relation to the above discussion of the tone of the cerebral vessels in essential hypertension. It seems to indicate that the ability of the cerebral vessels to relax normally is maintained in the relatively short-lived hypertensive state of hypertensive toxemia of pregnancy.

Thyroid diseases. Several clinical studies of the cerebral circulation and oxygen metabolism have been reported (274, 285, 297, 324). Scheinberg and his co-workers reported normal values of cerebral oxygen uptake and cerebral blood flow in hyperthyroidism, and decreased values in hypothyroidism (274, 285). Sokoloff and associates found an increase in cerebral perfusion, but no increase in cerebral oxygen uptake in hyperthyroidism (324). In the most extensive study so far reported, Sensenbach *et al.* found that the cerebral oxygen uptake was not measurably changed in thyroid diseases, whereas the cerebral perfusion was increased in hyperthyroidism and decreased in hypothyroidism (297).

The apparent lack of influence of the thyroid hormone on cerebral oxygen uptake in adults is of considerable theoretical interest. Mental symptoms may be prominent in thyroid diseases, but seemingly these mental symptoms are not associated with changes of the total cerebral energy requirements as measured by the cerebral oxygen uptake. Animal studies have demonstrated that the thyroid hormone causes the cerebral oxygen uptake to rise more rapidly from the postnatal level to the adult level, whereas, in the mature animal, hyperthyroidism did not influence the cerebral oxygen uptake (67). That also the immature human brain is quite sensitive to lack of thyroid hormone is borne out by the marked mental retardation of cretins. So far no quantitative studies of the cerebral circulation and metabolism in this disorder have been published, but judging from the semiquantitative studies of Himwich and co-workers, the cerebral oxygen uptake is subnormal in cretinism (143).

The observed changes of cerebral perfusion in thyroid disease in adults is puzzling. No adequate explanation for these changes have been demonstrated, as the chemical composition of the arterial blood and the arterial blood pressure was found to remain normal in the above mentioned studies (274, 285, 297, 324).

Cardiac and pulmonary diseases. In compensated heart disease normal values for cerebral perfusion and oxygen uptake have been reported (39, 40, 226, 273). The reduced values found in patients with compensated aortic stenosis are presumably due to concomitant cerebral disease (40, 183). Severe cardiac decompensation without mental symptoms does not cause significant change of cerebral blood flow and oxygen uptake relative to the values obtained in comparable control groups (39, 40, 226, 227, 240, 273).

In cardiac failure causing marked mental symptoms, such as confusion, a decrease of cerebral blood flow has been found, whereas the cerebral oxygen uptake was not significantly decreased (60). In these patients the cerebral blood flow returned to the normal level following adequate therapy, relieving the

cardiac failure and restoring normal mental function. Patients with cardiac failure and Cheyne-Stokes respiration have been found to have values for cerebral perfusion and oxygen uptake similar to those of cardiac patients with normal respiratory rhythm (227). Theophylline was found temporarily to abolish the Cheyne-Stokes respiration in these patients and to cause a reduction of cerebral blood flow, just as in normal man (227).

Only few studies have been reported on congenital heart disease demonstrating adequate cerebral perfusion (39, 40, 123). High values for cerebral oxygen uptake and cerebral blood flow have been found in coarctation of the aorta (123). As only two cases were reported, it is not easy to evaluate the significance of these findings.

Pulmonary insufficiency of a moderate degree does not affect the cerebral blood flow or oxygen uptake (280). In severe pulmonary failure with marked cor pulmonale and pronounced arterial hypercapnia and hypoxia an increase of cerebral blood flow was found, whereas the cerebral oxygen uptake remained normal (250). If normal subjects were acutely exposed to such changes of the blood gases as found in these two studies of chronic pulmonary diseases, then the cerebral blood flow would be expected to increase much more. This means that the cerebral circulation in patients with chronic arterial hypercapnia and hypoxia is in part adapted to the abnormal chemical milieu. The cerebral vessels of such patients are, however, still reactive to hypercapnia. Oxygen inhalation administered to the group of patients with the severest degree of pulmonary insufficiency resulted in normalization of the arterial oxygen saturation, a decrease in ventilation and a further increase in arterial pCO_2 and in cerebral blood flow (250). The cerebral depression which may be seen when giving oxygen to such patients is caused by the extreme hypercapnia due to a critical reduction of pulmonary ventilation.

Anemia and polycythemia. In anemia and polycythemia the cerebral blood flow is increased and decreased respectively. The mechanism of these changes of perfusion have been discussed in the section on the regulation of the cerebral blood flow. The cerebral oxygen uptake has been found to be reduced in anemia, but normal in polycythemia (137, 238, 261, 275, 292). The low value for cerebral oxygen uptake in anemia deserves further comment. It has been reported both in pernicious anemia (275) and in sickle cell anemia (137), as well as in other types of anemia. Of special interest is the finding of subnormal values for the cerebral oxygen uptake in a group of 18 young anemic patients, the majority of whom had simple iron deficiency anemia (137). No mental symptoms were reported, nor were they likely to have been present, as the degree of anemia was not extreme.

Probably the low values for cerebral oxygen uptake found in uncomplicated anemia are due to technical errors. The nitrous oxide method was used in all these studies without correction for the lower solubility of nitrous oxide in anemic blood or for the fact that high perfusion values would cause the heterogeneity of the cerebral blood flow to influence the perfusion values less than in normal man. These two factors have both been discussed in the section on the inert gas method. It can be estimated that an underestimation of cerebral perfusion and oxygen uptake of about 10–20 per cent will result, if no correction for the influence of these

two factors are employed in patients with marked anemia. This explains why the observed value of cerebral oxygen uptake increases when the anemia is corrected (275), and also why oxygen inhalation in anemia, which reduces the cerebral perfusion, causes a slight increase in cerebral oxygen uptake (137).

Presumably some of the aged patients with pernicious anemia studied had some degree of chronic cerebral disease, as the values remained moderately subnormal even after correction of the anemia (275). It is not possible to come to any conclusion regarding the cause of the chronic brain disease in these patients.

ACTION OF DRUGS ON CEREBRAL BLOOD FLOW AND OXYGEN UPTAKE

General Anesthetics and Other Cerebral Depressants

The effect of the various drugs which can cause a depression of the level of consciousness to the extent of semicomia or coma is well exemplified by the effect of barbiturates. Regardless of the specific drug used—amytal, phenobarbital, thiopental, etc.,—and regardless of the doses used, the barbiturates all cause a reduction of the cerebral oxygen uptake which correlates with the degree of cerebral depression. Light sedation reduces the cerebral oxygen uptake only a few percentages, a reduction which was not found to be statistically significant (176, 210); marked sedation, causing loss of consciousness when the subject is not exposed to painful stimuli, results in a significant (about 25 %) reduction of cerebral oxygen uptake (210). Surgical anesthesia reduces the cerebral oxygen uptake by about 40–50 per cent (19, 145, 289, 343).

In all these studies, cerebral blood flow was found to be relatively less reduced than the cerebral oxygen uptake. This lack of proportionate reduction in perfusion is probably due to a barbiturate-induced hypoventilation. This is evidenced by a rise in the arterial pCO_2 found in all the studies where this value was reported. This hypoventilation was especially pronounced in the study by Wechsler and collaborators, in which the cerebral blood flow values actually rose slightly above the control values. In animal experiments where artificial ventilation was maintained, pentothal anesthesia was found to cause a relatively more pronounced reduction of cerebral blood flow than of cerebral oxygen uptake (294).

Severe acute barbiturate poisoning is rarely followed by permanent brain damage. An increased cerebral blood flow due to arterial hypercapnia and hypoxia and a low cerebral oxygen demand presumably protect the brain against noxious influences of the severe hypotension and hypoxia found in such patients.

No reports have been published concerning the influence of volatile anesthetics on the perfusion and oxygen uptake in the human brain. Animal studies reviewed by Sokoloff strongly suggest that the drugs have the same effect on the cerebral oxygen uptake as the barbiturates. Changes of cerebral perfusion, however, depend also upon the influence on the pulmonary gas exchange of the particular drug (318). General anesthesia induced by the steroid 21-hydroxypregnane-3,20-dione sodium succinate has been found to cause about a 50 per cent reduction of the cerebral blood flow and oxygen uptake in man (111, 115).

The cerebral oxygen uptake is reduced in severe methyl or ethyl alcohol

intoxication (13, 14, 15) and also in the Antabuse⁶ ethyl alcohol reaction (146). A moderate dose of ethyl alcohol producing a blood concentration of 0.1 per cent has no significant effect on cerebral perfusion or oxygen uptake (13, 14, 62), even when given in combination with 100 mg chlorpromazine (62).

Small analgesic doses of Methadon and morphine do not change the cerebral blood flow or oxygen uptake under normal conditions (1, 209). The effect of such doses of morphine in hemorrhagic shock (331) has already been mentioned. Heavy doses of Demerol (pethidine) have been used in combination with chlorpromazine, phenergan and cooling in the so called artificial hibernation. In these conditions the cerebral oxygen uptake and blood flow are reduced (22, 77, 119, 316). Morphine in doses (60 mg) causing distinct depression of mental function and of respiration also decreases the CMRO₂, while the CBF. is unaffected (229b). The hypoventilation caused an average rise in arterial carbon dioxide tension from 43 to 52 mm Hg. This hypercapnia may well be of importance for maintaining the cerebral blood flow at a high level. The effect of 25 mg *n*-allylmorphine on morphine intoxication was studied in the same subjects, and a rapid but only partial reversal of the metabolic and mental depression was observed.

A hypothesis of the action of anesthetic drugs has been formulated on the basis of the above mentioned *in vivo* experiments and certain *in vitro* observations. Barbiturate-induced depression of oxygen uptake of isolated nervous tissues *in vitro* (258) requires much higher substrate concentrations than the blood concentrations causing a proportionate reduction of cerebral oxygen uptake *in vivo* (19, 145, 210, 289, 343; see also 187). Also, a substrate concentration of 6.0% ethyl alcohol is required in order to reduce the oxygen uptake of isolated cerebral tissues to about two-thirds of the control value (144), while a similar reduction *in vivo* results when the blood alcohol level is only 0.3% (13). These observations support the hypothesis that *in vivo* the anesthetic drugs in low concentrations depress the function of the synapses, thus reducing the number of nervous impulses and hence the cerebral oxygen demand. In the *in vitro* state, where spontaneous neuronal impulses and synaptic transmissions are absent, much higher concentrations are required to reduce the low level of resting oxygen uptake.

Other Drugs Acting Directly on the Brain

The effect of convulsant drugs (e.g. strychnine, picrotoxin, Metrazol, Nikethamide) on the cerebral blood flow and oxygen uptake has not been studied in man (see 318). Probably the most accurate animal studies were made by Schmidt and his co-workers, using the bubble flow-meter technique, in lightly anesthetized monkeys (59, 294). Cerebral oxygen uptake and blood flow were invariably increased during the actual convulsions, while low values were found in the post-convulsive semicomatose state. In the absence of convulsions, even using large doses of convulsant drugs, no change of cerebral oxygen uptake or blood flow was observed. This indicates that it is the seizure, and not the drugs as such, which causes the observed cerebral metabolic and circulatory effects.

The various psychotropic drugs studied seem to have no effect on the cerebral

⁶ Tetraethylthiuram disulfide.

oxygen uptake or the cerebral blood flow in man. The lack of effect of sedative doses of the *Rauwolfia* alkaloid reserpine (130, 179) and the phenothiazine derivative chlorpromazine (62, 229a) is perhaps not surprising in view of the similar lack of influence of sedative doses of barbiturates (176, 210). Of more interest is the lack of effect of 100–120 micrograms of *d*-lysergic acid diethylamide (LSD-25) (322). In these studies of normal as well as schizophrenic subjects, characteristic mental disturbances were produced as well as a slight pressor effect. The absence of a measurable change in cerebral oxygen uptake in this form of toxic psychosis is noteworthy, as it corroborates the previously mentioned findings of a lack of correlation between psychotic behavior and cerebral oxygen uptake in schizophrenia and in psychoses in elderly patients.

Xanthine Compounds

The xanthine compounds have a well recognized stimulatory effect on the mental functions of the brain, and have also a stimulatory effect on the respiratory center (344). Theophylline (with ethylenediamine) and caffeine cause a distinct reduction of the cerebral blood flow in man without changing cerebral oxygen uptake (66, 227, 233, 300, 344).⁷ It is possible that the xanthine compounds per se cause the cerebral vasoconstriction, as the hyperventilation observed was seemingly inadequate to produce the observed reduction of cerebral blood flow to about 75 per cent of the control values. Theophylline also decreases cerebral blood flow in cardiac patients with Cheyne-Stokes respiration (227, 231) and in patients with hypertensive headaches (233). The therapeutic effect on the Cheyne-Stokes respiration is presumably due to a direct stimulation of the respiratory center, whereas in the case of patients with hypertensive headache the therapeutic effect of theophylline may be due to the decreased distention of the pain receptors adjoining the cerebral arteries.

Anti-Hypertensive Drugs and Other Vasodilator Drugs

The various vasodilator drugs have no direct influence on the cerebral oxygen uptake. The influence on the cerebral circulation is in most cases nonspecific, i.e., the response depends only on the degree of hypotension achieved and not on the drug or dose employed (see e.g. 230). This suggests that most vasodilator drugs have no significant direct effect on the cerebral vessels, and that the cerebrovascular relaxation observed is due to the effect of the hypotension. This conclusion is supported by observations demonstrating a similar cerebrovascular relaxation during acute hypotension induced by spinal anesthesia (168, 184, 185), a procedure which can hardly be expected to have any direct influence on the cerebrovascular tone.

The regulation of cerebral circulation in moderate and severe hypotension induced by drugs or by other means has been discussed previously. The observa-

⁷ Parephylline (diethyl-aminoethyl-theophylline-HCl) has been studied in a small series of cases, and was found to cause no change of cerebral perfusion, but to increase the cerebral oxygen uptake 25% (231). These divergent observations are surprising, as the drug presumably has the same effect as theophylline. Additional observations on parephylline seem to be indicated.

tion that patients with essential hypertension have a reduced tolerance to an acute reduction of the blood pressure has also been mentioned. This section gives only the references to the many quantitative studies of the circulation of the human brain during hypotension induced by the various antihypertensive drugs of seemingly unspecific action. Other vasodilator drugs, a few of which appear to exert an independent and direct dilative action on the cerebral vessels, will be discussed subsequently.

Some ganglionic blocking agents have been studied in normotensive as well as in hypertensive subjects: Tetraethyl ammonium (31), hexamethonium (55, 57, 80, 81, 148, 213, 223, 224, 229, 230, 332), Pendiomide (24, 29, 229, 230), and trimethaphan (Arfonad) (213, 229, 230). Of the various adrenergic blocking agents, only Dibenzyline (phenoxybenzamine) (232) and dihydrogenated ergot alkaloids (1, 124, 125) have been studied. Miscellaneous other antihypertensive drugs studied include 1-hydralazine (Apresoline) (128, 206), veratrum alkaloids (54, 206, 228) and rauwolfia alkaloids (130, 179).

The imidazoline compounds phentolamine (Regitine) and tolazoline (Priscoline) cause only a slight reduction of the blood pressure and have no decisive effect on the cerebral circulation (23, 49, 58, 278). Histamine, also an imidazoline compound, was found to cause distinct hypotension without significantly affecting cerebral blood flow in two groups of patients studied (8, 300). In one of these studies (300), however, moderate doses of histamine causing only a small decrease in blood pressure actually increased cerebral blood flow, possibly by direct vaso-dilatation.

The effect of nitrites has not been studied in man, but observations in experimental animals suggest a direct cerebral vasodilatory action in addition to the systemic effect (see 318). While nicotinic acid (270, 338) and procaine (282, 283) seem to have no effect on the cerebral circulation, the opium alkaloid papaverine has a distinct vasodilatory effect on the cerebral vessels, increasing the cerebral blood flow above the control level (149, 205, 207, 283, 300). Papaverine presumably acts directly on the cerebral vessels. This is not definitely proved, however, as in none of the studies referred to above has the possible influence of hypercapnia been excluded.

Hormones and Related Drugs

l-Nor-epinephrine in pressor doses does not change the cerebral oxygen uptake, but causes a moderate reduction of cerebral blood flow by reason of a slight drop in the arterial pCO₂ (177, 230, 298) or by reason of an effect via the pressoreceptor reflexes affecting the resistance at the periphery and the cardiac output, exempting the cerebral vascular resistance. *l*-Epinephrine administered intravenously in pressor doses has been found to cause a significant increase in cerebral perfusion and oxygen uptake (177). Other investigators found no effect when administering *l*-epinephrine and USP epinephrine intramuscularly in oil, in doses causing a slight drop in mean arterial blood pressure (298). It is noteworthy that in both studies *l*-epinephrine produced distinct symptoms of anxiety (177, 298).

Some other sympathicomimetic amines have been studied. Amphetamine and

Aramine (1-1-(*m*-hydroxyphenyl)-2-amino-1-propanol) were found to cause a rise in blood pressure without changing cerebral blood flow or oxygen uptake (1, 2, 230, 300). Mephentermine (*N*,*a*,*a*-trimethylphenethylamine sulphate), however, was found to increase the cerebral oxygen uptake significantly without changing cerebral blood flow (73). Sympathicomimetic amines were able to normalize the blood pressure and the cerebral perfusion in patients in whom both values had been reduced by ganglionic blocking agents (230).

Adrenocorticotropic Hormone (ACTH) and cortisone were found to increase the arterial blood pressure moderately, while the cerebral blood flow either remained unchanged or decreased slightly (7, 287, 299). The cerebral oxygen uptake remained unchanged in these studies. Vasopressin has been studied in only a few cases (323), showing no effect on cerebral blood flow despite a sustained pressor response.

The injection of desoxycorticosterone does not affect the cerebral circulation or oxygen uptake (20). Gordan and associates reported preliminary studies of the effect of androgenic hormones (111, 112, 113). The results are far from clear, and their interpretation must await further investigation permitting a statistical evaluation of the data. The effect of thyroxine has already been discussed in the section on thyroid diseases.

Miscellaneous Drugs

Heparin (336) does not affect cerebral circulation or oxygen uptake. Hypertonic solutions of sodium chloride (288) or glucose (311) cause an acute reduction in the hemoglobin concentration and a corresponding increase in cerebral perfusion.

General Pharmacological Considerations

In the preceding sections the action of drugs on cerebral blood flow and oxygen uptake in man has been briefly presented. The most important findings may be summarized:

The cerebral oxygen uptake is relatively little influenced by drugs. Reduced values are found only in drug-induced semicomia and coma, while increased values only occur in drug-induced convulsions and during the intravenous infusion of large doses of *l*-epinephrine. Drug-induced changes in the cerebral oxygen uptake, the arterial blood pressure, the arterial pCO_2 , and the blood hemoglobin concentration cause the same changes of cerebral blood flow as discussed in the section on the regulation of the cerebral blood flow. An independent, direct effect of drugs on the cerebral circulation is rare, and in no case is marked. The direct vasodilator effect of the alkaloid papaverine is best established. Possibly histamine, nitrites and thyroxine have the same effect. Only the various xanthine compounds seem to cause a direct constriction of the cerebral vessels.

CONCLUDING REMARKS

Until about 1930 the cerebral circulation was generally believed to vary passively with changes in the perfusion pressure (18, 141). This concept was based

mainly on the Monro-Kellie doctrine of a constant volume of the intracranial contents (151, 235), from which it was deduced that no significant changes in intracranial blood volume or vascular diameter were likely to occur. The possibility of redistribution of blood within the cerebral vascular bed or of an increase of blood volume at the expense of the transference of cerebrospinal fluid into the spinal channel was considered. No experimental data, however, were available to support such a contention.

Unequivocal evidence of active changes of vascular diameter of the cerebral vessels was first obtained by direct observation of the pial vessels through a cranial window, a technique developed by Forbes (89). As a result of these and other animal studies, a theory of a highly developed intrinsic control of cerebral circulation was developed. Two types of stimuli were found to be of importance for the physiological regulation of the myogenic tone of the vascular walls, namely, certain chemical agents, primarily carbon dioxide and oxygen (292), and the distending pressure (82). Neurogenic control of cerebrovascular resistance was studied extensively without it being possible to assign any definite physiological role to the cerebral perivascular nerves.

During the last decade quantitative studies in man have confirmed these results on all essential points. The cerebral perfusion in normal man varies only moderately, the most important regulating factor probably being the tissue carbon dioxide tensions and the direct reaction of the muscular cells of the cerebral arteries in response to variations of the distending blood pressure. The cerebral circulation has also been studied in many disease entities, and it appears in general that the cerebral perfusion is ample relative to the cerebral metabolism. Of particular interest is the finding of adequate over-all cerebral perfusion in so called cerebral arteriosclerosis. Only in severe hypotension and during marked hyperventilation has total cerebral perfusion been found to be critically lowered.

These clinical studies have also given a wealth of information concerning the oxygen consumption of the human brain. This is of considerable interest, as studies in experimental animals had previously only permitted a rough estimate of this value under relatively abnormal experimental conditions. In normal man, not given pharmacological agents, the cerebral oxygen uptake is remarkably constant. With the possible exception of severe anxiety states, no significant changes of cerebral oxygen uptake have been reported in a variety of conditions studied. Thus, cerebral oxygen consumption is unchanged during sleep and during physical or intellectual effort, and also unaffected by relatively marked changes of the arterial blood pressure and gas tensions of the arterial blood. In all these conditions changes of cerebral blood flow are accompanied by inversely proportionate changes of the cerebral arteriovenous oxygen difference. This means that in such conditions it is possible to calculate changes in the cerebral perfusion from observations of variations of the cerebral arteriovenous oxygen difference. This method for evaluating changes of cerebral blood flow was proposed on a theoretical basis by Lennox and Gibbs as far back as 1932 (192). It may be useful, as it enables one to follow fairly rapid changes in cerebral blood flow (136, 247).

It has also been established that the cerebral oxygen uptake is subnormal only

in acute and chronic cerebral disorders characterized by distinct signs of mental hypofunction, depression of consciousness in acute disorders, and loss of intellectual faculties in chronic disorders. Thus, correlation between mental function and the over-all energy expenditure of the brain in certain conditions has been established.

These major findings and the wealth of additional observations have very substantially increased our understanding of this important area of human physiology. Undoubtedly our knowledge is still incomplete at various points. However, a solid foundation for relevant physiological thinking and for future studies has been established.

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