THE ACTION OF DRUGS ON THE CEREBRAL CIRCULATION

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I. INTRODUCTION

The tissues of the central nervous system are acutely sensitive to the effects of circulatory insufficiency. Interruption of the cerebral circulation is followed within seconds by a loss of consciousness and within minutes by irreversible changes in the brain (308). Lesser degrees of cerebral ischemia also lead relatively rapidly to permanent tissue damage, as is seen, for example, in irreversible shock. It is because the maintenance of the normal functions of the brain is so vitally essential to the organism as a whole and so completely dependent on a continuously adequate blood supply that the action of drugs on its circulation assumes a special significance. Furthermore, the physiological and pharmacological behavior of the cerebral circulation is sufficiently unique that drug actions exerted on most other vascular beds can only rarely be assumed to be operating similarly in the brain.

The pharmacology of the cerebral circulation has been intensively investigated, and the literature in this field is voluminous. There have been several reviews of the general subject of cerebral circulation and metabolism, and recently two annotated bibliographies (186, 276) limited to the period between 1936 and 1952 have appeared. The literature prior to 1936 has been excellently reviewed by Wolff (399). Bouckaert and Jourdan (34) and Schmidt (337) have extended the coverage to the beginning of this last decade. The development of the nitrous oxide technique (200, 202) approximately ten years ago, which made possible the quantitative estimation of cerebral blood flow and metabolic rate in man, has been followed by numerous studies in this field including many on the effects of drugs only recently available. The reviews of Kety (191), Scheinberg and Jayne (322), and Mangold (245) cover the earlier results obtained with this method.

Although included in these general reviews of the cerebral circulation and metabolism, the action of drugs was of necessity relatively briefly discussed. The author is aware of no previous comprehensive treatment of the subject. An attempt has, therefore, been made in the present review to do so. Although the most reliable and almost all of our quantitative data have been acquired recently in man by means of the nitrous oxide method, the results of earlier studies in animals have also been included. This was done not so much for historical reasons as because the early methods employed in animals often permitted observations of a type and under conditions not possible in man.

II. METHODS OF STUDY

A. Anatomical Problems and Their Implications

The great complexity of the anatomy of the cerebral circulation has imposed a major hindrance to the development of methods for studying its blood flow.

The nature of the anatomical problems has been reviewed in detail by Batson (15) and Schmidt (337). In contrast to organs which possess a pedicle or hilum through which the major blood vessels pass, the arterial and venous channels of the brain are extensively divided and dispersed. Each of the major vascular trunks, therefore, carries only a fraction of the total cerebral blood flow and usually of a fairly well delineated portion of the brain. The anastomoses at the circle of Willis do not normally cause a mixing of the streams so that the blood in each of its tributaries is ultimately rather discretely distributed within the brain (214, 235, 337). Furthermore, there are extensive communications between the cerebral and the extracranial circulations, particularly in the common laboratory animals such as the cat and dog (15). The larger accessible cerebral vessels, both arteries and veins, therefore, carry blood, not only of the brain, but also to some extent of the extracerebral tissues as well.

There are serious implications in these anatomical relationships to the measurement of cerebral blood flow. Measurement of flow in any one of the major cerebral vessels by one of the numerous flow meters available is subject to the following limitations: 1) the blood flow is representative of only an indeterminate portion of the brain; 2) it generally includes to a greater or lesser degree some extracerebral blood flow. In addition, errors arise from the inherent inaccuracies of many of the flow meter devices (145). It is, perhaps, possible by radical surgical intervention to isolate the cerebral from the extracerebral circulation and to restrict the entire cerebral arterial supply to common channels to which perfusion (95, 118) and/or flow meter (73, 339) techniques can be applied. This has apparently been satisfactorily accomplished in the monkey (73, 339). In the cat and dog the anastomoses between the intracranial and extracranial circulations are so extensive and inaccessible that such procedures must always be regarded with suspicion (15, 337, 338). In all animals the existence of anastomoses with the vertebral plexus of veins as well as other pathways almost precludes the possibility of measuring cerebral blood flow on the venous side, except in the isolated head (15). In man the availability of representative, relatively uncontaminated cerebral venous blood from the superior bulb of the internal jugular vein (275, 354) has permitted the development of quantitative methods for measuring cerebral blood flow (130, 190, 202) which minimize these anatomical problems.

Of specific relevance to the action of drugs is the discrete distribution of the arterial tributaries of the cerebral circulation. Following intravenous administration this presents no problem, for the concentration of the drug is uniform in all arterial blood. However, when administered intra-arterially, the distribution of the drug follows that of the injected artery. Variable results may be obtained depending upon the artery used and the cerebral circulatory area observed.

B. Techniques

Despite the difficulties presented by the anatomy, a number of methods have been fruitfully employed in studies of the actions of drugs on the cerebral circulation. They do not all yield information on the same phenomena. Some describe the behavior of the cerebral vessels in response to drugs and others the changes in blood flow; these are not necessarily equivalent. Also they are not equally

reliable in the information they provide. An attempt has, therefore, been made throughout the discussion on the action of drugs to indicate the methods employed in the studies, particularly where conflicting results have been obtained. It is not our purpose to review thoroughly the methods employed in studies of the cerebral circulation. These have been adequately described and critically evaluated elsewhere (145, 190, 337). However, to facilitate the evaluation and interpretation of the results obtained with drugs, a brief description of the salient features of the more important techniques is presented.

1. Direct observations of intracranial or related blood vessels. These include the gross, microscopic, or photographic examination of changes in the diameters of the pial or superficial cerebral vessels (98, 101, 402). By inserting a cranial window (101, 402), observations can be made under more physiological conditions including the unanesthetized state. A similar technique more readily applicable to man is the simple ophthalmoscopic examination of the retinal vessels which are anatomical extensions of the cerebral vessels and react similarly to them in many instances (49, 61, 164). These techniques provide qualitative information only on the behavior of the cerebral vessels and not on cerebral blood flow which is dependent on other factors as well. Furthermore, observation of the superficial vessels of the brain is limited to relatively large vessels whose responses may differ in direction or degree from those of the small intracerebral arterioles which are most important in influencing the cerebral blood flow.

2. Thermoelectric techniques. Thermoelectric devices have been frequently employed to detect changes in cerebral blood flow (145, 337, 338). These include various types of thermostromuhrs (145, 338) which permit measurements in intact cerebral vessels but generally have low degrees of reliability even for qualitative observations (145, 338). Thermocouples inserted into the blood stream of the otherwise intact vessel have proved to be more convenient and satisfactory (145, 337, 338). Both heated and cooled types have been used (122, 340). In the former the thermocouple is cooled and in the latter warmed by the flow of blood, the change in temperature resulting in a change in electrical current varying with the rate of blood flow. The Gibbs thermoelectric flow recorder (122), a thermocouple made in the form of a hypodermic needle, has been employed in studies in the internal jugular vein of man (121, 124, 125). Both the Gibbs needle and its Schmidt and Pierson modification (340) have also been inserted directly into localized areas of brain tissue and found capable of indicating directional changes in blood flow. The advantages of the thermocouple techniques are their simplicity, convenience, and ability to follow continuously the pattern of change in blood flow. They do not, however, provide reliable quantitative data. When employed within blood vessels, they are subject to the previously described limitations imposed by the anatomy of the cerebral circulation. Moreover, there are numerous technical difficulties associated with their use (145, 338). Temperature changes in the blood or immediate environment, clot formation around the needle, changes in vessel diameter or in the relation of the stream of blood to the position of the needle, and alterations in direction of flow are some of the variables which can lead to erroneous results. When employed

directly in the tissue, there are further complications arising from local tissue damage and/or local changes in metabolic rate and heat production. Despite these limitations, reliable qualitative information on the behavior of the cerebral circulation can and has been obtained with them.

3. Miscellaneous flow meter techniques. A number of instruments, when inserted in series with a vascular channel, can measure with reasonable accuracy the rate of blood flow through that vessel (145). One of these, the bubble-flow meter, was used by Dumke and Schmidt (73) in probably the first reliable quantitative measurements of cerebral blood flow. Essentially it is a glass tube of known cross-sectional area which, when inserted between the cut ends of a severed blood vessel, permits the measurement of the velocity of blood flow by means of a trapped air bubble within it. From these data volume of blood flow is calculated. Anatomical problems were overcome by the intercalation of the instrument into a single, isolated, common arterial pathway to the brain and the surgical occlusion of all other possible arterial channels and anastomoses with the extracerebral circulation. The experiments were performed in monkeys in whom there are fewer and more accessible anastomoses than in the more usual laboratory animals. The values for resting cerebral blood flow obtained in these studies appear to be reliable; however, it is not unlikely that the major surgery and anesthesia required in such procedures may alter the normal cerebral circulatory responses to drugs.

4. Perfusion techniques. Artificial perfusion of the brain has been occasionally employed in studies of drug actions on the cerebral circulation (95, 118, 330). The advantage of such techniques lies in their ability to control the various factors involved in blood flow so that the effects on one individual variable may be examined. For example, complicating effects of changes in blood pressure can be avoided by perfusion at constant arterial blood pressure (95). On the other hand, they require the formidable surgical procedures necessary to isolate the cerebral circulation.

5. Arteriovenous oxygen differences. The difference in oxygen contents or saturations between arterial and cerebral venous blood is directly proportional to the oxygen consumption and inversely proportional to the blood flow of the brain. When cerebral metabolic rate remains constant, a change in the arteriovenous oxygen difference reliably indicates the direction and degree of change in cerebral blood flow. A further requirement is that the venous blood be representative of the brain as a whole and uncontaminated by blood from extracerebral sources. Such blood is easily sampled in man from the superior bulb of the internal jugular vein (128, 275, 354) but is difficult to obtain in most laboratory animals except the monkey because of the extensive communications between the two venous systems. However, uncontaminated blood representative of indeterminate portions of the brain can be obtained from the sagittal sinus, confluence of the sinuses, and other intracranial venous channels. When cerebral metabolic rate is unaffected, this method, because of its simplicity, is of considerable usefulness in determining the direction and degree of change in cerebral blood flow, particularly in man.

6. Plethysmographic method. Since the normal, adult craniovertebral cavity is essentially a rigid, indistensible container completely filled with incompressible material, any increase in volume of one of its contents must be at the expense of another. On this basis, Ferris (88) has applied the principles of venous occlusion plethysmography to the measurement of intracranial blood flow in man. It was assumed that inflation of a cuff around the neck to a pressure of 60 to 80 mm Hg would occlude the venous outflow from the cranium and that the rate of displacement of spinal fluid through a needle in the lumbar subarachnoid space would then equal the rate of the continued arterial blood flow into the cranium. The method, however, neglects the numerous pathways other than the internal jugular veins through which venous blood may leave the cranial cavity. These include the extensive communications between the cerebral venous system and the spinal venous plexus, anastomoses between the cerebral and extracerebral veins via the emissary veins penetrating the skull, and the communications between the internal jugular and the facial veins. Blockage of both the internal jugular and extracranial venous drainage without interrupting arterial inflow may result in a flow of blood from the rigid cranial cavity into the more readily distensible extracranial tissues. Furthermore, procedures or drugs which raise extracranial but not intracranial blood flow may result in a reverse flow from the extracranial tissues back into the cranial cavity causing a more rapid displacement of cerebrospinal fluid and leading to the erroneous conclusion that cerebral blood flow was accelerated. The cerebrospinal fluid outflow cannot, therefore, bear a constant relationship to the rate of intracranial arterial blood flow. The values for cerebral blood flow thus obtained have been quantitatively too low (88), and the method cannot be expected to provide reliable data on the effects of drugs on the cerebral circulation.

7. Quantitative methods in man. Nitrous oxide method: Since its introduction by Kety and Schmidt (200, 202) approximately ten years ago, the nitrous oxide technique has become the standard method for studying the cerebral circulation. The details of its theory and procedure have been presented elsewhere (190). Based upon the Fick Principle, it utilizes nitrous oxide as a freely diffusible, inert tracer substance which is administered in the inspired air in low concentrations. During a minimum 10 minute period of inhalation of the gas, multiple timed samples of arterial and cerebral venous blood are drawn. The former is obtained from the femoral or brachial artery; the latter is obtained in man from the superior bulb of the internal jugular vein by the method of Myerson *et al.* (275) as modified by Gibbs *et al.* (128). From these samples the integrated arteriovenous N_2O concentration difference over the 10 minute period is determined. Division of this quantity into the amount of N_2O taken up by the brain during the same time interval yields the rate of cerebral blood flow. Since the N_2O content of the brain cannot be determined directly, the brain N_2O concentration at 10 minutes is estimated from the tenth minute value of the cerebral venous N_2O concentration to which it is assumed to be equal. This assumption is based on evidence that by the tenth minute brain and mixed cerebral venous blood have achieved approximate equilibrium and the brain:blood partition

coefficient is normally 1.0 (196). Since concentration rather than total content of N_2O in the brain is employed in the calculation, the derived values of blood flow represent the average blood flow rate per unit mass of brain taken as a whole and not that of the total brain.

Because its basic assumptions are rarely completely satisfied, several types of errors are associated with the method. Some question has arisen whether unilateral internal jugular venous blood is representative of the brain as a whole and uncontaminated by extracerebral venous blood (89, 170, 273). Simultaneous bilateral measurements of cerebral blood flow indicate that in most cases such blood is approximately representative although comparative values with other cerebral venous outflow channels, for example, the spinal venous plexus, are not available. The average extracerebral contamination of internal jugular venous blood has been estimated on the basis of dye injection studies to be about 3% (354). Usually the errors derived from these sources are minor, but occasionally unilateral internal jugular venous blood is sufficiently deviant from being truly representative (273) or is so severely contaminated by extracerebral blood (194, 316) that markedly erroneous results are obtained. In all cases the loss of N_2O into the cerebrospinal fluid has an effect like that of extracerebral contamination and has been found to lead normally to an approximately 4 to 6% underestimation of cerebral blood flow (6). Recently the assumption that N_2O concentration equilibrium between the brain and its mixed venous blood is reached after 10 minutes of inhalation has been critically examined (314). Failure to achieve such equilibrium leads to erroneously high values for cerebral blood flow, and complete equilibrium is never actually reached within 10 minutes. Proximity to complete equilibrium is a function chiefly of the rate of blood flow within the tissues of the brain, and the blood flow even in the most slowly perfused portions of the brain is normally sufficiently rapid (220, 363) for reasonably close approximation to equilibrium to be achieved. The error is usually probably less than 10%. Occasionally, however, particularly when cerebral blood flow is slow, errors of considerable magnitude may be encountered because of the invalidity of this assumption. The problem is to some extent alleviated by extending the period of measurement beyond 10 minutes.

Despite these limitations, the N_2O method usually provides reasonably reliable quantitative values for cerebral blood flow in a representative fraction of the brain taken as a whole, and it can be employed in unanesthetized man. Typical normal values obtained with it are evident in the control periods of the studies included in Table 1. The method is incapable, however, of measuring total blood flow of the entire brain or the flow in specific areas of the brain. It also requires at least 10 minutes for a single determination so that rapid changes in blood flow cannot be detected. Several modifications of the original method have appeared. Scheinberg and Stead (324) have simplified it and reduced the amount of blood sampling required but probably at the expense of accuracy. Kennedy and his coworkers (188) have adapted it to children; others have modified it for use in animals (211, 292). Radioactive krypton-85 has been substituted for nitrous oxide, and bilateral measurements have been added with some gain in precision (224,

TABLE 1

Effects of alterations in arterial blood tensions of respiratory gases on cerebral circulation and related functions in man

Experimental Condition	Inspired Air	Clinical State	Cerebral Blood Flow, ml/100 g min		Cerebral Vascular Resistance, mm Hg/ml 100 g min		Mean Art. Blood Press., mm Hg		Art. Blood CO_2 Tension, mm Hg		Art. Blood pH		References
			C	E	C	E	C	E	C	E	C	E	
High CO_2 Normal O_2	2.5% CO_2 in room air	Normals and convalescent patients	51	52	1.7	1.8	87	90	38	43	7.41	7.36	294
	3.5% CO_2 in room air	Normals and convalescent patients	52	57*	2.0	1.8*	98	95	39	45*	7.40	7.35*	294
	5–7% CO_2 in room air	Young normals	53	93*	1.6	1.1*	82	93*	43	52*	7.38	7.33*	203
	5% CO_2 in room air	Young normals	53	74*	1.8	1.2*	91	95*	43	50*	7.36	7.30*	290
	5% CO_2 in room air	Normotensive elderly	35	56*	2.9	2.2*	95	115					86
	5% CO_2 in room air	Essential hypertension	52	86*	2.6	1.7*	136	150*	40	48*	7.41	7.35*	290
	5% CO_2 in room air	Hypertensive elderly	39	47*	3.6	3.2	132	143					86
	5% CO_2 in room air	Arteriosclerosis	47	55*	2.1	1.9	94	98	46	53*	7.34	7.30*	290
	5% CO_2 in room air	Hypertensive arteriosclerosis	36	49*	3.7	3.0*	132	139*	38	48*	7.41	7.33*	290
	5% CO_2 in room air	Cerebral vascular disease	35	51*	3.5	2.8*	112	130*					83
High CO_2 High O_2	5% CO_2 in 85–90% O_2	Essential hypertension	57	66	3.0	2.7	160	164	40	45*			151
Hyperventilation (low CO_2)	Room air	Young normals	52	34*	1.7	2.9*	90	98*	45	26*	7.38	7.54*	203
		Normotensive elderly	54	39*	1.9	2.6*	90	90					86
		Hypertensive elderly	45	32*	3.1	3.8*	128	116					86
High O_2	95–100% O_2 at 3.5 at.	Young normals	57	43*	1.1	1.7*	79	84*	39	34*	7.40	7.43*	219
	85–100% O_2	Young normals	52	45*	1.7	2.2*	87	98*	42	41	7.40	7.41	203
	85–100% O_2	Young normals	55	47*	1.2	1.5	78	79*	40	38	7.40	7.41	219
	85–100% O_2	Convalescent patients	49	43*	1.9	2.1†	93	91					162
	85–100% O_2	Acute and chronic cerebral vascular disease	36	33†	2.8	3.2†	105	105					163
	85–100% O_2	Chronic pulmonary emphysema	68	79*	1.5	1.5	91	89	58	70*	7.36	7.24*	295
	85–100% O_2	Sickle cell anemia	72	65	1.3	1.5	92	90	37	36	7.39	7.40	162
	85–100% O_2	Miscellaneous chronic anemias	64	54*	1.5	1.7*	87	85	41	40	7.35	7.38	162
	50% O_2	Convalescent patients	47	43†	1.9	2.1†	86	89†					163
	50% O_2	Acute and chronic cerebral vascular disease	37	35†	3.4	3.5†	115	116†					163
Low O_2	10% O_2	Young normals	54	73*	1.7	1.1*	86	78*	40	36*	7.41	7.46*	203
	10% O_2	Elderly with cerebral vascular disease	30	39*	4.1	3.3*	113	116					83

* $p < 0.05$. † No statistical data available. C = Control; E = Experimental.

273). By employing the γ-emitting radioactive gas, krypton-79, Lewis and his associates (233, 234) have been able to determine directly and continuously the quantity of tracer present in the brain; this permits the rapid, continuous measurement of total cerebral blood flow in man.

Tracer dilution methods: A non-diffusible tracer substance which remains in the circulation when injected into a cerebral artery, is diluted by the cerebral blood flow in passing through the cerebral vascular bed. The degree of dilution, as determined from the quantity or rate of injection of the tracer material and the difference between its concentrations in arterial and representative cerebral venous blood, is a measure of that cerebral blood flow. Gibbs *et al.* (130) have attempted to measure human cerebral blood flow on the basis of this principle by injecting Evans blue dye (T-1824) into an internal carotid artery and sampling cerebral venous blood from the superior bulb of the internal jugular vein. However, as demonstrated by Shenkin *et al.* (354), dye injected into a single cerebral artery is not uniformly mixed, and the blood drained in one internal jugular vein is then not representative of that of the brain as a whole. This difficulty can, perhaps, be overcome by bilateral intracarotid injection or bilateral internal jugular venous sampling; possibly both are required. Nylin and his associates (291) have apparently done so successfully in a similar method employing thorium-B labeled red cells. Although tracer dilution techniques permit more rapid determinations of cerebral blood flow than the nitrous oxide method, they have been infrequently employed probably because internal carotid arterial injections and bilateral internal jugular venous sampling are required.

8. Radioactive inert gas technique for the quantitative determination of regional cerebral blood flow. Blood flow within the brain is far from uniform and varies quite independently in its component structures (220, 362, 363). None of the methods previously described provides quantitative data on the blood flow of individual regions of the brain. Thermocouples inserted in the brain indicate local changes in blood flow, but they are subject to numerous limitations and yield only qualitative information about a few areas at one time. Recently Kety and his associates (198, 220, 362) have described a method which measures simultaneously and quantitatively the blood flow in as many as 28 structures of the brain. The method is based on the principle that the uptake of an inert radioactive gas, in this case I^{131}-tagged trifluoroiodomethane, by a tissue is a function of the preceding history of the arterial concentration of the gas, the partition coefficient of the gas between the tissue and blood, the time, and the blood flow to that tissue. During an intravenous infusion of a solution of the radioactive gas, arterial concentration is continuously monitored by means of a scintillation counter; at a specific time the head is removed and frozen, and the concentrations of the gas in the various cerebral structures are determined by a unique radioautographic technique. From these data, as well as from the measured solubilities of the gas in blood and brain tissues, blood flow in the various structures is calculated. The method appears to yield reliable quantitative results (220, 362, 363) but is obviously limited to applications in laboratory animals.

III. NORMAL REGULATION OF THE CEREBRAL CIRCULATION

Drugs influence the cerebral circulation by altering the physiological mechanisms which normally regulate it. The physiology of the cerebral circulation has been previously reviewed (34, 191, 245, 322, 336, 337, 399), and it is not our purpose to repeat this function. However, in view of recent rapid developments in this field, particularly as regards man, and because of the uniqueness of the mechanisms normally regulating the cerebral circulation, a brief discussion of them has been included to facilitate the understanding of the subsequent discussion on the action of drugs.

As in all vascular beds, the cerebral blood flow is ultimately determined by two hemodynamic factors: 1) the net pressure gradient across the cerebral vascular bed; 2) the total resistance to blood flow in the cerebral vascular channels. Both are in turn subject to the influences of numerous factors which alter, regulate, or contribute to them. It is by action on one or more of these various factors that physiological or pharmacological changes in cerebral blood flow are achieved.

A. Cerebral Blood Pressure Gradient

The driving force for the cerebral circulation is the pressure gradient between the cerebral arteries and veins. Because cerebral venous pressure, normally approximately 5 mm Hg in the recumbent position, is low compared to that of the arteries, it is usually of negligible importance in the regulation of blood flow. In some situations in which it may be altered greatly, it may, however, assume a significant role. Thus, a marked fall in cerebral venous pressure may be an important mechanism in the maintenance of cerebral blood flow under the gravitational stress of positive g (161). Similarly, elevation of cerebral venous pressure might be expected to have a deleterious effect on cerebral blood flow, but none has yet been demonstrated. Moyer *et al.* (264) have raised internal jugular venous pressure from 67 mm H_2O to 235 mm H_2O by means of a neck tourniquet without altering cerebral blood flow. There are, however, adequate alternative pathways for cerebral venous drainage, for example, the anastomoses with the spinal venous plexus, whose pressures are not altered by this technique. These results do not, therefore, disprove the influence of cerebral venous pressure changes of this magnitude on cerebral blood flow.

Of far greater importance is the mean arterial blood pressure. It was previously believed that cerebral blood flow followed more or less passively the mean arterial blood pressure (165, 337, 399), and the stability of the cerebral circulation under physiological conditions reflected only the relative constancy of the arterial pressure maintained by the homeostatic pressor reflex mechanisms. Recent studies in man, however, have demonstrated that intrinsic regulation of the cerebral vascular resistance also occurs and tends to maintain the cerebral blood flow within normal levels despite changes in blood pressure or even to alter it independently. They have tended to confirm the direct observations of Fog (99) on the pial vessels of animals, which were found to constrict in response to a rise and to dilate in response to a fall in arterial blood pressure. Thus, cerebral blood flow in man does not increase in essential or drug-induced arterial hypertension

(195, 206, 345, 366) because of a concomitant increase in cerebral vascular resistance, but the effects of hypertension clearly unassociated with circulating vasoconstrictor substances remain to be studied. Similarly, an accompanying decrease in cerebral vascular resistance has been found to buffer the effects of arterial hypotension (197, 212, 353) although Finnerty *et al.* (97) have found in normotensive subjects that reductions of mean arterial blood pressure to approximately 30 mm Hg, or one-third the normal level, by means of hexamethonium and/or tilting result in clinical signs and symptoms of cerebral ischemia. Patients with malignant hypertension or postural hypotension do not reduce their cerebral vascular resistance as effectively, and clinical symptoms appear with lesser decreases in arterial blood pressure. In all cases signs and symptoms of cerebral ischemia occurred when the cerebral blood flow fell to a mean of 31.5 ml/100 g min, approximately 60% of the control level. It is likely that in secondary shock (87) and other hypotensive states resulting in unconsciousness, arterial blood pressure similarly falls below the limits of compensation by changes in cerebral vascular resistance.

B. Cerebral Vascular Resistance

Regulation of the cerebral circulation is accomplished, at least under physiological conditions, chiefly by adjustment of the cerebrovascular resistance. This function, defined for quantitative purposes as the ratio of cerebral blood pressure gradient to blood flow (202), is actually the net effect of a number of factors which tend to impede the flow of blood through the cerebral vessels. These factors will be considered individually.

1. Blood viscosity. The viscosity of whole blood, varying mainly with red cell concentration and almost negligibly with other corpuscular and plasma protein concentrations, rises markedly with increasing hematocrit particularly from normal levels and above (394). It is in all likelihood the basis for the extremely low cerebral blood flow and high cerebrovascular resistance which have been observed in polycythemia vera (191). Increased cerebral blood flow resulting from a decreased cerebrovascular resistance attributable to a reduced red cell concentration has been observed in several types of anemia (162, 318). These observations may in fact have under-estimated the magnitude of the changes because of a failure to correct for the altered solubility of nitrous oxide in the blood, an important factor in the nitrous oxide method which was employed (190, 196, 202). Although changes in cerebrovascular tone secondary to the alterations in cerebral venous oxygen tension in these conditions may have been contributory factors (203, 219, 381), they cannot explain fully the degree of the change observed in polycythemia (191) or in the anemias in which oxygen inhalation failed to eliminate the effects (162).

2. Intracranial pressure. The thin-walled cerebral vessels within the cranial cavity have imposed upon them the pressure of the cerebrospinal fluid, and this pressure might be expected, as in the Starling resistance valve, to contribute to the vascular resistance by its effect on the size of the blood vessels. Earlier conflicting observations on the effects of increased intracranial pressure on cerebral

blood flow (54, 88, 396) have to a great extent been clarified by Kety *et al.* (204), who applied the nitrous oxide method to patients with mass intracranial lesions. Their results indicate that cerebrovascular resistance progressively increases with rising cerebrospinal fluid pressure, but below a critical level of approximately 450 mm H_2O cerebral blood flow is maintained by a concomitant increase in mean arterial blood pressure. Above the critical level cerebral blood flow decreases markedly, and cerebral anoxia and impairment of consciousness occur. On the other hand, Shenkin and coworkers (355) found that acute reduction of high intracranial pressure by means of ventricular drainage or infusion of 50% glucose solution does not restore the cerebral blood flow or vascular resistance toward normal. A moderate decrease in the vascular resistance and increase in the blood flow in the brain did follow the 50% glucose administration, but these changes were probably the result of the associated hemodilution and consequent reduction in blood viscosity. Shenkin (351) has also observed a high cerebrovascular resistance and low cerebral blood flow in postoperative intracranial hypotension, but in these cases the low cerebrospinal fluid pressure may result from a primary reduction in cerebral blood flow. These observations on the effects of reduced intracranial pressure cannot be explained on the basis of the known mechanical and physiological principles which must apply, and additional mechanisms peculiar to the pathological states of the experimental material may have been operative. More pertinent observations made in normal subjects indicate that reduction in intracranial pressure, as occurs, for example, on assumption of the erect position (324) or under the influence of positive radial acceleration (310), tends to support the cerebral circulation by a lowering effect on cerebrovascular resistance.

3. Size and tone of cerebral vessels. The major portion of the cerebrovascular resistance lies in the frictional resistance encountered by the blood as it traverses the long, narrow blood vessels, particularly the arterioles, and this resistance can be markedly altered by changes in the diameters of the vessels. Within the limitations imposed by their anatomy and by any intrinsic pathological changes which permanently narrow the cerebral vessels and raise the cerebrovascular resistance, as, for example, ir arteriosclerosis (83, 164, 290, 320, 328), the diameters of the vessels are subject to a considerable degree of variation. It is chiefly by adjustment of the diameters or tone of the cerebral vessels and the consequent effect on cerebrovascular resistance that the normal regulation and remarkable homeostasis of the cerebral circulation is accomplished. Similarly, it is through their effects on cerebrovascular tone that most drugs or diseases influence the cerebral circulation. These effects may be produced either by direct action on the cerebral vessels or by alterations in the following normal regulatory control mechanisms of the cerebrovascular tone.

Neurogenic control: Abundant anatomical evidence has confirmed the existence of a nerve supply to the dural, pial, and intracerebral vessels of man and other animals (256). Included in the supply are myelinated fibers, suspected to be sensory afferents, and unmyelinated fibers, believed to mediate the neural vasomotor regulation of the cerebral circulation. Perivascular nerves have been demonstrated on intracerebral arterioles as small as 25 to 30 μ in diameter (44),

and nerves of sympathetic and parasympathetic origins have been identified (256). Sympathetic postganglionic fibers from synapses in the stellate and superior cervical ganglia (256) and probably also in small, intermediate ganglia in the internal carotid nerve (44) form the sympathetic nerve plexuses on the vertebral and internal carotid arteries and on the circle of Willis. From these plexuses nerve fibers may follow the pial vessels into the cerebral substance (256). Forbes and Wolff (109) have described a sympathetic vasoconstrictor pathway which, when activated by stimulation of the cervical sympathetic nerve, constricts the pial arteries overlying the parietal cortex. A parasympathetic cerebral vasodilator pathway has been traced by Chorobski and Penfield (44); its fibers pass from the facial nerve through the geniculate ganglion, the greater superficial petrosal nerve, and then by a distinct branch of the latter to the internal carotid plexus. Stimulation of the facial nerve near the medulla oblongata (44, 48) or at the geniculate ganglion (103) causes an ipsilateral dilatation of the pial arteries in the parietal region mediated over this pathway. Fibers associated with other cranial nerves have been observed but these may have sensory functions (256).

Considerably less definitive is the evidence concerning the functional significance of the neural vasomotor pathways. Artificially stimulated neural vasomotor effects have been repeatedly demonstrated in laboratory animals. Constriction of the pial arteries in the ipsilateral parietal area has been visualized directly by Forbes and his coworkers (103, 109) during stimulation of the cervical sympathetic nerve in cats, dogs, and monkeys. The sympathetic fibers mediating the effect were found to pass through the middle ear in close association with the caroticotympanic nerves; sympathetic fibers passing via the stellate ganglion or vertebral plexus were without influence. On the other hand, section of the cervical sympathetic trunk and extirpation of the superior cervical ganglion caused neither dilatation of the vessels nor, after a suitable delay to permit nerve ending degeneration, any increased sensitivity of the arteries to adrenalin (103). Neural vasodilator effects in the parietal area of the monkey and cat have been observed through a pial window during stimulation of the facial nerve near the medulla oblongata (44, 48) or at the geniculate ganglion (103). By means of a thermocouple inserted in the brain substance, Schmidt and his coworkers obtained direct evidence during cervical sympathetic stimulation of a reduction in blood flow in the parietal cortex (333) and hypothalamus (332) of the cat and the parietal cortex of the rabbit (338), but no such effects were observed in the medulla (340), pons (332), and occipital cortex (338) of the cat. Others have obtained similar results with thermoelectric devices (103, 399), and Ludwigs and Schneider (243) observed during cervical sympathetic stimulation a reduction in blood flow in the cerebral white matter of the dog which could be lessened or prevented by sympathetic blocking agents. Thermocouple techniques have demonstrated an increased blood flow in the parietal cortex of the cat produced by stimulation of the facial nerve (108) but have failed to demonstrate a vasodilator effect of vagodepressor or carotid sinus nerve stimulation in the medulla (340), hypothalamus (332), and parietal cortex (333) of the cat.

Some of the negative results may conceivably be attributable to a lack of

anatomical neural pathways between the site of stimulation and the areas observed. If so, measurement of total cerebral blood flow might be a more sensitive indicator. Several such studies involving measurement of blood flow in the internal carotid artery may be discounted because of the unreliability of the blood flow measuring device, the difficulty in excluding extracerebral components of the blood flow, and the contaminating effect of associated changes in arterial blood pressure (337, 399). When successfully accomplished in the monkey by Dumke and Schmidt (73) by means of the bubble-flow meter, no effects on the cerebral circulation were observed during cervical sympathetic stimulation. Studies in man by means of the nitrous oxide method have also failed to detect any direct sympathetic vasomotor influences on cerebral blood flow. Procaine block of the stellate ganglion performed bilaterally in normotensive and hypertensive patients (160) and unilaterally in patients with chronic cerebral vascular disease or acute cerebral vascular accidents (315) does not alter cerebral blood flow or vascular resistance. Shenkin and his coworkers (352) observed a reduction in cerebral vascular resistance and an increased blood flow following bilateral stellate ganglionectomy in patients with Parkinsonism, but these effects were probably secondary to an anemia which developed in the interval between the control and postoperative measurements as indicated by the significantly lower arterial oxygen contents in the second studies.

It is clear from the foregoing discussion that neural vasomotor mechanisms in the cerebral vasculature exist, at least under laboratory conditions, but their role in the regulation of cerebrovascular tone is obscure. The evidence is against any resting neurogenic vasoconstrictor tone mediated through the cervical sympathetics; neither is there convincing evidence of a resting neural vasodilator tone. Furthermore, there is little likelihood that the cerebral vasomotor mechanisms are integrated into the general circulatory reflexes, as, for example, those initiated by the carotid and aortic pressoreceptors. When neurogenic vasomotor effects have been demonstrated, they have been minimal. For example, faradic stimulation of the cervical sympathetics results in an average decrease in the diameters of the pial arteries of approximately 8% or about one-tenth the degree of constriction observed simultaneously in the arteries of the skin (103, 109). The average increase in pial artery diameter during geniculate ganglion stimulation is only 16% (103). There still remains the possibility that the neural vasomotor mechanisms play some role in local readjustments or intrinsic reflexes within the cerebral circulatory system, but this matter is still an open question.

Chemical control: The only major experimentally induced alterations in cerebrovascular tone thus far observed have been achieved by means of chemical substances. These include not only pharmacological agents but also substances of physiological significance. Since the actions of these various chemical agents are discussed in detail in subsequent sections, it is necessary for present purposes to summarize only briefly the effects of those endogenous chemical substances believed to be most prominently involved in the normal regulation of the cerebrovascular tone.

It has been repeatedly demonstrated by a variety of techniques in a variety

of animals including man that the respiratory gases profoundly influence the tone of the cerebral vessels. The effects of alterations in their blood tensions on human cerebral blood flow and vascular resistance are illustrated in Table 1. It is clear that increased blood carbon dioxide tension markedly dilates cerebral vessels and increases cerebral blood flow; changes in the opposite direction attend a reduction in blood pCO_2, as, for example, during hyperventilation. These effects exceed any yet demonstrated by any other means of physiological significance. Also potent are the effects of altered blood oxygen tension. The hypoxemia associated with the breathing of inspired air mixtures containing only 10% oxygen causes substantial reductions in cerebral vascular resistance and increases in cerebral blood flow. There has been some conflict concerning the relative effectiveness of low oxygen and high carbon dioxide tensions as cerebral vasodilators (73, 337), but except for the studies by Schmidt and his coworkers (73, 339) in the monkey, most results in other laboratory animals and in man attest to the greater potency of carbon dioxide (191, 337, 399). If the hypoxemia is great enough, however, it can overcome the vasoconstrictor effect of low carbon dioxide tension (126, 203, 288). Increased blood pO_2 produced by the breathing of high oxygen concentrations at normal or elevated atmospheric pressures (Table 1) also constrict cerebral vessels and reduce cerebral blood flow, but these effects are only moderate compared to those of low pCO_2 and may in fact be secondary to the usually associated hypocapnia (203, 219, 381).

Acids and bases have been reported to cause cerebral vasodilatation and vasoconstriction, respectively (118, 337, 399, 402), but these effects have been neither profound nor consistent. In fact, opposite effects have also been observed (39, 329) although it is likely that in these cases other factors such as secondary changes in blood pCO_2 obscured any direct effects of pH on the cerebral circulation. The reduced cerebrovascular resistance and increased cerebral blood flow which occur in diabetic coma in man despite a markedly lowered blood pCO_2 have been tentatively attributed to the severe acidosis existing in that state (199). If so, then it would appear that the cerebral vasodilator action of reduced blood pH is not secondary to its effect on blood CO_2 tension and can be sufficiently great in some circumstances to overcome the vasoconstrictor effect of a low blood pCO_2. Such conclusions must, however, remain only tentative in view of the presence in diabetic coma of numerous other unevaluated chemical abnormalities, such as high levels of circulating ketones and keto acids and disturbances in water and electrolyte balance.

The fact that the cerebrovascular tone is far more sensitive to changes in the amounts of normally circulating chemical constituents of blood than to any other factors yet described has led to the widely accepted hypothesis that the regulation of cerebrovascular tone is almost entirely accomplished by the interplay of these chemical actions and a normally present vasoconstrictor tendency within the cerebral vessels (334, 337, 338). The chief determinants of the vascular tone are believed to be the inherent tendency of the vessels to contract and the antagonistic vasodilator effects of carbon dioxide. Other chemical factors such as oxygen tension and pH are undoubtedly also involved, but to a lesser degree,

except perhaps when they are altered beyond their normal physiological range. In such circumstances they may exert a greater influence on cerebrovascular tone than does the carbon dioxide tension.

Furthermore, since the normal chemical products or consequences of increased tissue metabolism, for example, increased pCO_2, reduced pO_2, and also, perhaps, lowered pH, tend to produce cerebral vasodilatation, and since changes in the opposite direction which would accompany decreased cerebral metabolic activity cause vasoconstriction, it has been suggested that cerebral blood flow may be adjusted via such chemical means to local metabolic activity, thus providing a mechanism for the maintenance of chemical homeostasis in the tissues of the brain (102, 126, 334, 337, 338). Chemical vasomotor effects have been most clearly demonstrated by altering the chemical composition of the circulating blood, and this hypothesis presupposes that similar alterations in the surrounding tissues or external milieu of the cerebral vessels are also effective. That such a mechanism for chemical homeostasis within the brain exists is suggested by the generally good correlations observed between the levels of cerebral blood flow and oxygen consumption in man (191) and in the monkey (339) and by the parallel increases in both during Metrazol convulsions in the monkey (339).

An obvious consequence of such a mechanism would be a close relationship between cerebral functional activity and blood flow, provided, of course, that neuronal activity like that of most cells is associated with an increased metabolic rate. The latter association has been observed in electrically stimulated sympathetic ganglia of the rabbit (223) and cerebral cortex of the cat (64). Similar findings have been obtained in the cerebral cortex of the cat (65, 66) and the whole brain of the monkey (339) during Metrazol convulsions. The increased neuronal functional and electrical activity has been held by Davies and Rémond (65) to be the direct cause of the accelerated metabolic rate because the fall in cerebral tissue oxygen tension always occurred together with or following the onset of the convulsion and never prior to it or in its absence. Others, however, have reported the opposite sequence (66). In man low cerebral metabolic rates have been observed in various pathological states of depressed mental function (191), but during normal variations of mental activity, for example, natural sleep (246) and the performance of mental arithmetic (364), no changes in cerebral oxygen consumption occur. The latter findings do not necessarily refute a relationship between neuronal function and metabolic rate but may rather indicate changes during normal mental processes too subtle to be observed in gross studies of the brain as a whole. On the basis of present evidence, scanty though it may be, it is difficult to avoid the conclusion that increased functional activity of the neurons of the brain is accompanied by an accelerated oxidative metabolism.

There is, therefore, available a mechanism for the adjustment of the local cerebral blood flow to local functional activity, and indeed experimental evidence suggests that such regulation occurs. In animals thermoelectric techniques have indicated changes consistent with increased blood flow in the olfactory areas of the brain during olfactory stimulation with strong odors (119, 347), in

the thalamus and sensory cortex during tactile stimulation of the paw (119, 347), and in the lateral geniculate ganglia and visual cortex during illumination of the retina (119, 338, 347). The bubble-flow meter technique (339) has demonstrated an increased total cerebral blood flow in the monkey during drug induced convulsions and a decreased blood flow during the postconvulsive depression. Similar postconvulsive depressions of cerebral blood flow and oxygen consumption have been observed in man by means of the nitrous oxide method following spontaneous epileptic convulsions (143) or those induced by electroshock (205). On the other hand, the performance of mental arithmetic is unassociated with any change in cerebral blood flow (364), and despite the presumably reduced functional activity of the brain during natural sleep (246), insulin coma (205), diabetic coma (199), and thiopental anesthesia (387), cerebral blood flow may be increased. In these conditions, however, alterations in the pH or pCO_2 of the circulating blood may occur to obscure the effects of reduced functional activity. In fact, there is little reason to expect that measurement of total cerebral blood flow should demonstrate a correlation between functional activity and circulation in view of the functionally reciprocal relationships between many portions of the brain which may tend to keep the net total cerebral blood flow and metabolic rate constant. To avoid this difficulty, Landau *et al.* (220) have quantitatively measured the blood flow in 28 structures of the cat brain by means of the radioactive inert gas technique (198, 362). During light thiopental anesthesia marked reductions in blood flow were observed in the primary sensory areas of the cortex; blood flow in other areas was either unchanged or only slightly reduced. In view of the extreme unlikelihood of a specific effect of thiopental on only these local vascular beds, the most likely explanation for the observed decreases in flow is the reduction in functional activity of the sensory cortex during anesthesia. The same technique has been employed to demonstrate increases in blood flow in the visual cortex, lateral geniculate ganglia, and superior colliculi during retinal illumination (362).

On the basis of present knowledge, it appears then that the normal regulation of the cerebral circulation is chiefly dependent on two factors, both zealously adjusted to maintain a constancy of the cerebral blood flow or chemical homeostasis within the brain. First, the mean arterial blood pressure tends to be maintained constant at the head level as a result of nervous vasomotor reflexes of the baroreceptor type. The cerebral vessels, apparently independent of such neural vasomotor mechanisms, are singularly unaffected by the vascular readjustments attending these reflexes. As a result, blood flow to the brain may be maintained in some circumstances at the expense of other tissues. Secondly, the tone of the cerebral vessels is regulated by chemical substances involved in metabolism in such a way that chemical homeostasis in regard to these agents is maintained within the brain. As a result of this homeostatic mechanism, cerebral blood flow is adjusted to local metabolic demand and to functional activity as well. Furthermore, chemical regulation of cerebrovascular tone provides a reasonably effective buffer against, at least, moderate changes in arterial blood pressure. The cerebral circulation is, therefore, amply supplied with mechanisms to maintain

its constancy, but it can be influenced by agents such as drugs which exert an effect upon these mechanisms.

IV. THE EFFECTS OF DRUGS ON THE CEREBRAL CIRCULATION

The previous discussion has emphasized the remarkable stability of the cerebral circulation and the mechanisms which normally maintain it within relatively narrow limits. The capacity of the homeostatic mechanisms responsible for this constancy can, however, be exceeded, and there are circumstances during which the aid of exogenous influences, as, for example, drug therapy, is desirable to restore the cerebral circulation to normal. Conversely, drugs employed for completely independent purposes in both therapeutics and research are commonly associated with side effects, often undesirable, on the cerebral circulation. The subject of drug action on so vital a circulatory bed is, therefore, not without considerable importance and interest. These actions are often unique compared to those on other vascular beds. Therefore, in order to facilitate reference to them, drugs are grouped in the following discussion not on the basis of their effects on the cerebral circulation but rather according to their chemical class or most familiar pharmacological actions.

A. The Respiratory Gases

The respiratory gases, oxygen and carbon dioxide, have been implicated as key agents in the normal regulation of the cerebral circulation. By virtue of their powerful influence on the cerebral circulation and their role in its regulation, these gases provide an avenue or mechanism by which other drugs may exert their effects. It is in consideration of their fundamental role as well as the known importance of oxygen and carbon dioxide as pharmacological or therapeutic agents that we introduce the discussion of drug effects on the cerebral circulation with a detailed examination of the actions of the respiratory gases.

1. Carbon dioxide. It is at present almost generally agreed that the chemical agent with the most potent action on the cerebral circulation is carbon dioxide (50, 102, 191, 334, 337, 399). Elevation of arterial blood carbon dioxide tension has been observed by direct visualization to result in marked dilatation of the pial vessels (360, 402) in animals and the retinal vessels in man (49). Qualitative evidence that increased blood pCO_2 is associated with increased cerebral blood flow has been repeatedly obtained by thermoelectric techniques in localized areas of the brain (178, 289, 332, 333, 338, 340, 399), in the carotid arteries of animals (39, 338), and in the internal jugular vein of man (125). In the spinal cord of the rabbit only variable responses have been observed (91). Perfusion techniques in animals (118, 330) and changes in arterial cerebral venous oxygen differences in both animals (179, 288) and in man (126, 229, 280) have also suggested an augmentation of cerebral blood flow by excess carbon dioxide. Quantitative studies in the monkey (73, 339) and in the perfused cat brain (118) have indicated definite but less profound effects of carbon dioxide on cerebral blood flow than suggested by earlier qualitative studies or observed in subsequent quantitative studies in the cat (158) and in man (83, 86, 151, 203, 290, 294). It is likely

that the major surgical interference with the cerebral vasculature required by the techniques employed in these studies grossly altered the physiological responsiveness of the preparation. This is particularly to be suspected in the studies in the monkey (73, 339) by means of the bubble-flow meter in which the reflex hyperpnea usually produced by anoxemia at the beginning of the experiment was almost entirely eliminated by the surgical procedure, evidence that the normal carotid innervation was damaged by the operation. Also, mechanical manipulation of the cerebral vessels during the surgical procedure could lead to their artificial constriction (74), and pial vessels in such spasm have been reported to be unaffected by carbon dioxide (74). Indeed, in recent quantitative studies of local blood flow in the component structures of the cat brain by means of the radioactive inert gas technique, which requires no surgical interference with the cerebral vasculature, relatively enormous increases in cerebral blood flow were elicited by the inhalation of 5 and 10% carbon dioxide (158). The plethysmographic method of Ferris (88) and the dye dilution method of Gibbs and coworkers (123, 130) have both demonstrated marked increases in human cerebral blood flow during the inhalation of elevated concentrations of carbon dioxide, but the most reliable quantitative data on the effects of CO_2 on cerebral circulation have been obtained in man by the nitrous oxide technique. Numerous studies employing this method and its modifications have clearly demonstrated that CO_2 is a more powerful cerebral vasodilator and can produce greater increases in cerebral blood flow than any other chemical agent yet studied (83, 86, 151, 203, 233, 234, 290, 294). The results obtained in many of these studies are summarized in Table 1 and are discussed in detail below.

That the carbon dioxide normally present in blood exerts a continuous tonic vasodilator action on cerebral blood vessels is indicated by the effects of hyperventilation. Reduction of blood pCO_2 by either passive or voluntary over-ventilation of the lungs results in constriction of the pial vessels in animals (402), in reduced blood flow in the carotid artery (39) and brain tissue (332) of animals and in the internal jugular vein (125) of man, in increased arterial-cerebral venous oxygen differences, a change to be expected from a reduced cerebral blood flow, in both animals (179, 288) and in man (126, 229, 232, 280), and reductions in quantitatively determined cerebral blood flow in man (86, 123, 130, 143, 201, 203, 234).

Apparently then changes in arterial blood carbon dioxide tension from the normal level alter cerebral blood flow in the direction of the pCO_2 change. Since carbon dioxide is continuously being produced by the brain and removed by its circulation, such changes in cerebral blood flow are in a direction tending to maintain a constancy of the tissue pCO_2. Thus, increased arterial pCO_2 results in an increased blood flow which tends to remove more rapidly from the tissues the carbon dioxide produced by the metabolism; reduction in arterial pCO_2 does the reverse. The effectiveness of this homeostatic mechanism is evident in the changes observed in pCO_2 in the cerebral venous blood which reflects much more closely than arterial blood the conditions in the cerebral tissues (55, 126, 203, 232). Alterations in arterial pCO_2 produced by the inhalation of carbon

dioxide or hyperventilation are greatly damped and only partially reflected in the pCO_2 changes in the cerebral venous blood (126, 203, 232) because of the compensatory effect of the concomitant changes in cerebral blood flow.

A homeostatic mechanism of this type, which tends to regulate blood flow so as to maintain a constancy of the tissue pCO_2, would by virtue of the relationship between carbon dioxide production and metabolic rate serve also to adjust the blood flow to the local tissue metabolic demands. Increased carbon dioxide production resulting from an increased metabolic rate tends to raise the pCO_2 of the tissues; this in turn causes vasodilatation and elevated tissue blood flow. The mechanism by which tissue carbon dioxide alters the tone of the cerebral vessels is uncertain, but it conceivably can be a local axon reflex yet to be demonstrated or, as is more likely, the direct action of CO_2 upon vascular smooth muscle following its diffusion from the surrounding tissues through the vessel walls. Evidence for the diffusion of the other respiratory gas, oxygen, through the walls of a relatively large pial vein has been obtained by means of the oxygen electrode (65). Reduction in metabolic rate leads to opposite effects so that the blood flow is always altered in the direction of the change in metabolic rate. Although the mechanism operates to maintain homeostasis as regards local tissue pCO_2, its net effect is the adjustment of the cerebral blood flow to local metabolic needs. Indeed, it is this chemical mechanism, the modulation of the continuous action of carbon dioxide, and also, perhaps, to a lesser extent the effects of other vasodilator products of metabolism, on the tone of the cerebral vessels that is currently believed to be the chief means of regulation of the cerebral circulation (102, 126, 191, 337, 338, 399).

Quantitative studies in man: The quantitative effects of carbon dioxide on the cerebral circulation are probably best described by the studies in man by means of the nitrous oxide method and its modifications. In Table 1 are summarized the results of some of these studies. It is seen from these data that the original observation by Kety and Schmidt (203) of an approximately 75% rise in cerebral blood flow during the inhalation of 5 to 7% CO_2 in room air has been repeatedly confirmed in normal human subjects, both young (290) and elderly (86). Since cerebral oxygen consumption is unaffected by these concentrations of carbon dioxide (83, 86, 151, 203, 290, 294), cerebral blood flow during carbon dioxide inhalation has been validly calculated in a number of studies (294, 320, 328, 397) from the arterial-cerebral venous oxygen difference determined during the period of carbon dioxide breathing and the cerebral oxygen consumption determined quantitatively along with blood flow during a preceding control period. These studies have yielded similar results. In normal subjects an inspired air concentration of 5% CO_2 raises cerebral blood flow approximately 50% (203, 294, 328); 7% CO_2, the concentration with approximately the maximal effects on pulmonary ventilation and blood pressure (72), more than doubles the blood flow (203, 233, 234, 294, 328). Whether 7% CO_2 also produces a maximal cerebral circulatory change is uncertain, for there are no reliable comparative quantitative data in man obtained with greater inspired air concentrations. Gibbs *et al.* (123, 130) found 10% CO_2 also to double the cerebral blood flow in man, but they

employed the dye dilution method with unilateral internal jugular venous sampling only, a technique subject to serious error (190). Their results also appeared to support the observation previously made in some very questionable animal perfusion experiments (331) that 10% CO_2 may reduce cerebral oxygen consumption. If true, this finding invalidates the use of alterations in arterial-cerebral venous oxygen difference for the estimation of the degree of change in cerebral blood flow produced by this concentration of the gas (229, 320).

Recent studies by Patterson *et al.* (294) indicate that the response of human cerebral vessels to increased carbon dioxide is a threshold phenomenon, as has also been suggested for the respiratory response (155, 279). The inhalation of 2.5% CO_2 in room air fails to alter cerebral blood flow, but 3.5% CO_2 produces a slight but significant increase of about 10% (294). At these concentrations pressor effects of carbon dioxide are absent; the increased blood flow results only from a dilatation of the cerebral vessels. The threshold for cerebral vascular dilatation lies, therefore, between these two inspired air concentrations and has been estimated by Patterson and his coworkers (294) to correspond to approximately a 4.5 mm Hg change in arterial pCO_2. This value exceeds somewhat the one observed in anesthetized dogs by Noell and Schneider (288), who found a 2 mm Hg change in arterial pCO_2 sufficient to alter the arteriovenous oxygen difference by an amount indicative of an 8 to 10% change in cerebral blood flow.

The effects of hypocapnia have also been studied quantitatively in man (86, 123, 130, 201, 203, 233, 234), and the results suggest marked tonic cerebral vasodilator activity by the normally circulating carbon dioxide. A greater degree of cerebral vasoconstriction has been achieved by hyperventilation than by any other means. For example, Kety and Schmidt (201, 203) observed reductions in cerebral blood flow to 60% of the control value when arterial pCO_2 was lowered from 45 to 26 mm Hg by active or passive hyperventilation on room air. The cerebral blood flow at this low level of arterial pCO_2 was close to the critical level below which syncope occurs (97), and indeed mental signs and symptoms of cerebral ischemia were present. Cerebral metabolic rate was moderately but significantly increased during the active but not the passive hyperventilation. The reasons for the discrepancy in the effects of the two types of hyperventilation are obscure and may represent simply a chance phenomenon. In other studies in man by means of the nitrous oxide method (86) or the dye dilution method (130), no consistent changes in cerebral metabolic rate were observed during voluntary hyperventilation although the changes in cerebral blood flow were comparable to those reported by Kety and Schmidt (201, 203).

The quantitative studies in man previously cited were all performed after several minutes of equilibration with the altered respiratory state, whether it was a change in the CO_2 concentration of inspired air or hyperventilation. By this time a more or less steady state has ensued. The time course of the changes during the equilibration period following the onset of either inhalation of 7% CO_2 or active hyperventilation on room air has been studied in man by Lewis *et al.* (233, 234). The method employed was the radioactive krypton-79 method (233, 234) which permits continuous minute-by-minute quantitative measure-

ments of human cerebral blood flow. The effects of 7% CO_2 on cerebral blood flow were slight but detectable within the first minute following the onset of its inhalation; cerebral blood flow then rose rapidly until, after approximately 4 min, it had increased an average of 86% and was still rising when the measurements were terminated. Moderate hyperventilation at a rate of 30 l/min, approximately three times the control level, was followed within 1½ min by detectable changes in cerebral blood flow which then continued to fall almost linearly with time; after 6½ min, when the arterial pCO_2 and pH had changed from 44 and 7.4 to 25 mm Hg and 7.6, respectively, it was at a level approximately 70% of the resting value. The response of the cerebral blood flow to alterations in arterial carbon dioxide tension is, therefore, prompt, almost immediate, and it follows them closely; most of the latency noted in the above responses is attributable to the resolution time of the method.

Effects of carbon dioxide on cerebral circulation in altered physiological and pathological states: The effects of carbon dioxide have also been studied in a wide variety of abnormal states which might be expected to alter the responsiveness of the cerebral circulation to the gas. Numerous studies have been performed in man (126, 127, 151, 169, 229) and animals (169, 178, 284, 285, 288) during concomitant alterations in blood tensions of both carbon dioxide and oxygen. The published data on their combined effects on the cerebral blood flow in man have recently been integrated in the form of a nomogram (42). Although the threshold of the cerebral circulatory response to increased carbon dioxide concentrations in the inspired air may be reduced when they are also combined with low oxygen contents (42, 294), it appears, despite some contrary evidence in anesthetized dogs (284), that in conscious man, at least, a cerebral blood flow already increased by hypoxemia is percentagewise altered less by changes in arterial pCO_2 than normally. For example, Lennox and Gibbs (229) have found that the combined effects of high carbon dioxide and low oxygen contents in inspired air on the arteriovenous oxygen difference were not entirely additive; they were less than the sum of their individual actions and, in fact, were no greater than that of increased carbon dioxide alone. Similarly, a given reduction in arterial pCO_2 by means of hyperventilation produces a lesser reduction in cerebral blood flow during hypoxemia than under normal conditions (126, 229). Apparently the cerebral vasodilatation already produced by hypoxemia (73, 83, 127, 203, 229, 337, 399, 402) represents a contributory part of that which would result from a raised carbon dioxide tension alone and tends to combat the vasoconstrictor effect of a reduced carbon dioxide tension. Whatever the mechanism, the net effect is that at lowered blood oxygen tensions the cerebral circulation is not so greatly altered by changes in carbon dioxide tension as normally. One might expect a point of lowered oxygen tension at which the effects of carbon dioxide are negligible. Indeed, Noell and Schneider (288) have found in dogs that the lower limit of cerebral blood flow resulting from hypocapnia occurs when the cerebral venous oxygen tension falls to about 19 mm Hg; at this point cerebral blood flow cannot be further reduced by additional lowering of arterial pCO_2 because of the vasodilator effects of the low tissue oxygen tension. Evidence for

a similar phenomenon has been obtained in man (126). It would be of interest to know whether the same degree of cerebral venous oxygen unsaturation achieved in the presence of a high cerebral blood flow by arterial hypoxemia would similarly eliminate cerebral vascular responses not only to reduced but also to raised carbon dioxide tensions as well. Nevertheless, except, perhaps, at the most extreme levels of hypoxemia, carbon dioxide does strongly influence the cerebral circulation in the presence of reduced blood oxygen tensions. In conditions of combined hypoxemia and carbon dioxide retention, such as respiratory arrest (178) or rebreathing (127), this action provides at least temporarily an important protective mechanism for the central nervous system. The administration of additional carbon dioxide to improve cerebral oxygenation would then probably add little of value and might, in fact, be contraindicated because of the danger of raising cerebral tissue pCO_2 to excessively high and depressant levels. Furthermore, carbon dioxide tends to become less effective as its blood tension deviates from the normal physiological range (288). On the other hand, in conditions of hypoxemia not complicated by carbon dioxide retention but rather by hypocapnia resulting from the reflex respiratory response to low blood pO_2, carbon dioxide provides effective aid against the cerebral effects of oxygen lack (127).

The action of carbon dioxide on the cerebral circulation is altered very little, if at all, by elevated blood oxygen tensions (229). This is probably because of the relatively weak cerebral vasoconstrictor effect of increased oxygen (162, 163, 203, 219, 229, 295, 381, 402). The combination of high oxygen and high carbon dioxide concentrations in inspired air so frequently employed clinically is, therefore, associated with almost the same degree of augmentation of the cerebral blood flow as obtained by increased carbon dioxide alone.

Acidosis, which also dilates cerebral vessels (118, 241, 337, 399, 402), may reduce the responsiveness to carbon dioxide in much the same manner as low blood oxygen tension. In fact, it may override the effect of a reduced blood pCO_2 as, for example, it appears to do in diabetic coma (199). Five % CO_2 has been found to be as effective as normally in raising cerebral blood flow in the presence of a reduced arterial pH caused by the infusion of ammonium chloride (329); the degree of acidosis, however, was negligible compared to that of the diabetic coma patients previously cited (199). In metabolic alkalosis (329) produced by bicarbonate infusions, cerebral circulatory responses to carbon dioxide appear to be unaltered.

In *thiopental anesthesia* (328, 397) there appears to be a slight but significant decrease in the responsiveness of the cerebral circulation to increased carbon dioxide in the inspired air. During deep thiopental anesthesia arterial pCO_2 is already elevated (387, 397), and the reduced reactivity to additional carbon dioxide may reflect only the decreasing effectiveness of the gas as its blood tension deviates further from the normal physiological range (288).

There has been considerable comment concerning a possible reduction in the reactivity of the cerebral circulation to increased carbon dioxide with *advancing age* (83, 86, 225, 320, 328) and/or *cerebral vascular disease* (83, 86. 225, 290, 328).

In Table I are included the results of studies made in such patients by means of the nitrous oxide method (83, 86, 290). The data indicate that the inhalation of 5% CO_2 in room air is usually capable of dilating the cerebral vessels and/or increasing the blood flow to the brain, even when the latter is initially reduced presumably by cerebral vascular disease. In one study of *essential hypertension* (151) in which 5% CO_2 failed to do either, it was administered together with high concentrations of oxygen and was also not accompanied by as great an elevation of arterial pCO_2 as usual. Others have found the same cerebrovascular responses to CO_2 in uncomplicated essential hypertension (290) and normal old age (86) as in normal young subjects. On the other hand, the cerebrovascular response to 5% CO_2 appears to be somewhat diminished in elderly patients with hypertension (86) and/or arteriosclerosis (86, 290) or with obvious cerebral vascular disease (83). Novack *et al.* (290) found it unable to alter cerebrovascular resistance in normotensive arteriosclerotic patients; others (86), however, have observed in similar patients appreciable reductions in this function during CO_2 inhalation. Cerebrovascular resistance is elevated in both uncomplicated hypertension (195, 290) and in organic vascular disease (83, 86, 290). Although in the former it can be reduced to normal levels by carbon dioxide (290), in the latter conditions it remains above normal even after cerebral vasodilation by carbon dioxide inhalation (83, 86, 290). Novack and his associates (290) have suggested, therefore, that the response to carbon dioxide may provide a convenient means for determining in such patients the relative contributions of overlying functional vasoconstriction and fixed organic narrowing of the lumina of the cerebral vessels to the high cerebrovascular resistance. On the basis of the changes produced in the arteriovenous oxygen differences, Schieve and Wilson (328) have also concluded that cerebral vascular reactivity to the inhalation of 5 and 7% CO_2 decreases gradually with age, falls markedly with cerebral vascular disease, and can be employed clinically to distinguish between senile dementia arising from primary brain degeneration and that secondary to cerebral vascular disease. However, Lassen and his coworkers (225), employing the same technique, found the responses to 7% CO_2 to be the same in demented patients of both types as in normals, and Scheinberg and his associates (320) also failed to observe any noteworthy change in cerebrovascular reactivity to 10% CO_2 with age. The effects of a reduction of arterial pCO_2 by means of hyperventilation have been studied by Fazekas and coworkers (86) in both normotensive and hypertensive elderly patients with cerebral arteriosclerosis. The cerebrovascular responses in the two groups were not only similar to each other but also to those in normal young subjects (203). The results of all these studies indicate that even though there may be sufficient disease in the cerebral vessels to raise cerebrovascular resistance and reduce blood flow markedly, there still remains a considerable degree of labile tone which can be reduced by carbon dioxide. There is evidence that the degree of reactivity is somewhat reduced, particularly when the disease is organic and associated with old age, but the change in reactivity does not appear to be sufficiently pronounced or uniform to form the basis of a reliable test for organic cerebrovascular disease.

Effects of carbon dioxide on local cerebral circulation: Thermocouple techniques have demonstrated the ability of carbon dioxide to increase blood flow in a number of component structures of the brain, for example, the medulla (340), hypothalamus (332), and parietal (289, 333, 338) and occipital cortex (338). They have not, however, provided information on the relative effectiveness of CO_2 in the various areas. Recently the radioactive inert gas technique of Kety and associates (198, 220, 362) has been employed for the quantitative determination of the effects of carbon dioxide on the local cerebral blood flow in unanesthetized cats (158). The results indicate that blood flow is raised by carbon dioxide in all parts of the brain, but the increases are not entirely uniform. The changes are both absolutely and percentagewise considerably greater in gray matter than in white.

Mechanisms of action: As can be seen in Table 1, the increased cerebral blood flow caused by carbon dioxide is frequently associated with significant elevations in mean arterial blood pressure (83, 203, 290). A pressor effect of CO_2 has often been observed in man (72, 125) and animals (73, 289) and undoubtedly contributes to the increased cerebral blood flow; it does not, however, occur regularly enough and is never of sufficient magnitude to explain the effect. Furthermore, reduction in blood pCO_2 by hyperventilation lowers cerebral blood flow despite, if anything, a rise in arterial blood pressure (86, 203). It is almost entirely by its pronounced effect on cerebrovascular resistance (Table 1) (83, 86, 203, 290, 294) that carbon dioxide alters cerebral blood flow. Of the various factors which contribute to this function only two are appreciably influenced by carbon dioxide. One, the intracranial pressure, is raised by carbon dioxide (49, 397), a change which would increase rather than lower cerebrovascular resistance. The other, cerebrovascular tone, must, therefore, be decreased, and indeed active dilatation of pial vessels by carbon dioxide has been directly visualized (360, 402). The rise in intracranial pressure is secondary to the effects of vasodilatation, namely, increases in blood content (393), volume (393, 397), and blood flow (312, 313) of the brain.

Since CO_2 raises arterial blood pressure and cerebral blood flow without increasing cardiac output (203), vasoconstriction must occur in other vascular beds. Indeed, numerous investigations have demonstrated that rebreathing (301) and respiratory arrest (178) reduce muscle blood flow, and CO_2 administration causes simultaneously with the increase in cerebral blood flow a depression of the circulation in the extracranial (338) and peripheral tissues (39, 178, 179, 229, 232). A reduction in blood pCO_2 by hyperventilation does the opposite (39, 179, 229, 232). The coronary circulation appears to be unaffected by carbon dioxide (76). Following interruption of their vasomotor innervation, however, these other vascular beds respond to CO_2 like the cerebral vessels with vasodilatation (296, 301, 338, 369). The vasoconstriction in the extracerebral and peripheral vascular beds is, therefore, mediated by neurogenic mechanisms and is probably secondary to a stimulation of the vasomotor center by increased carbon dioxide (338, 399). The fact that the cerebral vessels normally respond to CO_2 like other vascular beds do only after denervation is further evidence of a lack of neurogenic

control of the cerebral circulation mediated via the vasomotor center and its usual efferent pathways. Furthermore, spinal transection, decerebration, section of the sixth, seventh, and eighth cranial nerves, and cervical sympathectomy, operations which would interrupt all known vasomotor pathways to the cerebral vessels, do not prevent the rise in cerebral blood flow, as determined by a thermocouple in the parietal cortex, in response to CO_2 administration (399). Local vasodilator reflexes of the axon type are not interrupted by these procedures, but there is no evidence that carbon dioxide is capable of activating such reflexes in any vascular bed. No such mechanism may be needed in view of the observation that carbon dioxide dissolved in Ringer solution dilates isolated strips of carotid artery (57). It is difficult to escape the conclusion that carbon dioxide dilates cerebral vessels and denervated peripheral vessels by direct action on the smooth muscle of the vessel walls.

Changes in blood pCO_2 are generally associated with inverse changes in blood pH (Table 1). Since acids (118, 241, 337, 402) and alkalis (118, 241, 337, 402) may alter the cerebral circulation in the same directions as increases and decreases in pCO_2, respectively, there may be some question whether the action of carbon dioxide might not be mediated through its effect on pH. This is not likely, for the administration of acids or alkalis does not alter the cerebral circulation as consistently or to the same degree as do changes in pCO_2. Furthermore, there have been observations of decreases in cerebral blood flow caused by acids (329) and increases caused by alkalis (39, 329). Such contrary effects might be expected in partially compensated metabolic acidosis or alkalosis in which, if the actions of carbon dioxide and pH are truly independent, their effects on the cerebral circulation conflict. There is then acidosis with decreased blood pCO_2 and alkalosis with increased pCO_2, and depending on the degree of acidosis or alkalosis and the extent of compensation, either pH or pCO_2 may dominate. It is only in respiratory acidosis and alkalosis that their effects on the cerebral circulation augment each other.

Useful applications of the cerebral circulatory effects of carbon dioxide: Carbon dioxide has been extensively used postoperatively to hasten *recovery from general anesthesia*. It does so effectively not only by stimulation of pulmonary ventilation and, hence, respiratory elimination of the volatile anesthetics but also by a more rapid clearance of the anesthetic agent from the tissues of the central nervous system as a result of the accelerated blood flow through them. Carbon dioxide has been reported to inhibit *petit mal seizures* (227), but since the cerebral circulation does not seem to be involved in the etiology or pathogenesis of epileptic convulsions (47, 143), this action is probably more related to the effects of carbon dioxide on the electrical activity of the brain (126, 232). Its therapeutic use in *chronic cerebral vascular insufficiency* is probably not practicable nor useful, and its value in testing for the degree of organic cerebral vascular disease (290, 328), is questionable. Gibbs and his associates (127) found the addition of 5% CO_2 to the inspired air to be effective in *counteracting the deleterious effects of low oxygen* on intellectual functions, electroencephalographic tracings, and cerebral oxygen tension. In all cases studied by them the breathing of 6% O_2 in nitrogen was

accompanied within a few minutes by mental confusion or unconsciousness, a shift to slow, high voltage waves in the electroencephalogram, and a marked drop in the oxygen saturation of cerebral venous blood. The addition of 5% CO_2 to the inspired air restored the mental functions and the electroencephalographic activity to normal and improved the cerebral venous oxygen saturation by an amount equivalent to that achieved by raising the oxygen concentration in the inspired air 2 volumes %. Three per cent CO_2 may also be helpful in counteracting the mental effects of anoxemia (120). The rise in cerebral venous oxygen saturation and, therefore, the brain tissue pO_2 also, is unquestionably the result of the augmentation of cerebral blood flow by carbon dioxide. The improvement in mental and electrical activities, however, is not entirely attributable to the improved oxygenation of the brain. In some of their subjects, Gibbs and his coworkers (127) observed mental and electroencephalographic abnormalities during the breathing of the CO_2-free low oxygen mixtures even though cerebral venous oxygen saturation had fallen no lower than the level existing during the breathing of CO_2-enriched low oxygen mixtures when these functions were normal. It is likely that the hyperventilation associated with the anoxemia lowered the pCO_2 of the blood and brain tissues, and brain tissue pCO_2 plays an important role in the maintenance of normal cortical electrical activity and mental functions (126, 232). Gibbs and his coworkers (127) suggest that carbon dioxide is beneficial when the inspired air is low in oxygen because of two major effects: 1) improvement in the oxygenation of the brain resulting from stimulation of pulmonary ventilation, redistribution of the cardiac output in favor of the brain because of cerebral vasodilatation and peripheral vasoconstriction, and a shift in the hemoglobin dissociation curve in the direction favoring unloading of oxygen in the tissues; 2) the maintenance of a near optimal brain tissue pCO_2, so essential to normal cerebral functions, despite the hyperventilation associated with the anoxemia. Himwich *et al.* (169) have reported that the addition of 10% CO_2 to pure oxygen respired at low barometric pressures equivalent to those existing between 35,000 and 38,000 feet does not raise cerebral venous pO_2 above that obtained with 100% oxygen alone. This finding does not refute the beneficial effect of carbon dioxide under such conditions. It indicates only that the cerebral circulation was not sufficiently accelerated to do more than just compensate for the replacement of 10% of the oxygen in the inspired air by carbon dioxide. Furthermore, since at such low barometric pressures 10% CO_2 is equivalent in tension to only 2% CO_2 at sea level, it is below the threshold level reported for its effects on the cerebral circulation in man (294).

When anoxemia is complicated by carbon dioxide retention, as, for example, during asphyxia or enforced rebreathing, the use of CO_2 is probably contraindicated. In such circumstances, the cerebral vessels are already dilated by the combination of the altered gas tensions, and the brain pCO_2 is elevated. The addition of CO_2 to the inspired air would then have relatively little beneficial effect on cerebral blood flow but might further raise the brain tissue pCO_2 to dangerously high and depressant levels. On the other hand, when cerebral anoxia is caused by ischemia of the brain as, for example, during circulatory collapse or secondary

shock, carbon dioxide may be beneficial. In these conditions also, brain tissue pCO_2 is elevated but only because cerebral blood flow is inadequate. By dilating cerebral vessels, constricting peripheral vessels (39, 178, 179, 229, 232, 301, 338, 369), and leaving the coronary vessels unchanged (76), CO_2 redistributes the cardiac output to favor the brain at the expense of less vital tissues. It may also combat the hypocapnia resulting from the hyperventilation not infrequently seen in secondary shock, and which, when it occurs, further jeopardizes the circulation to the brain. For example, in experimental hemorrhagic shock in man Stone *et al.* (373) found a low cerebral blood flow attributable not only to the hypotension but also to a moderate hypocapnia secondary to a hyperventilation of undetermined origin. Mental functions were also impaired. The administration of morphine depressed the respiration, restored the arterial pCO_2 and also the cerebral blood flow toward normal, and caused dramatic improvement in the mental state. The beneficial effect of morphine was attributed chiefly to its action in raising the arterial pCO_2. It would be of interest to know if the administration of carbon dioxide alone might have had a similar effect.

Carbon dioxide has been reported to increase the tolerance to positive radial acceleration (positive g) (35, 36, 384) and delay "blackout". Its beneficial effect is probably related to its peripheral vasoconstrictor and cerebral vasodilator actions, thus reducing peripheral pooling and distribution of blood and aiding in the maintenance of the cerebral circulation under that stress.

2. Oxygen. General effects: Oxygen also has potent effects on the cerebral circulation, but they are opposite in direction to those of carbon dioxide. As indicated by direct observations of the pial (30, 402) and retinal (61, 164, 356) vessels, increased blood pO_2 constricts and reduced blood pO_2 dilates cerebral vessels. Evidence of corresponding changes in blood flow has been obtained repeatedly in animals from measurements of affluent or effluent cerebral blood flow during natural (286, 330) or artificial (118, 330) perfusion of the brain, from thermocouples inserted in brain tissue (289, 332, 340) or cerebral vessels (283), and from changes in arterial-cerebral venous oxygen differences (56, 179, 282, 287). Similar evidence has been obtained in man by means of the Gibbs thermoelectric flow recorder inserted in the internal jugular vein (125) and by measurements of the changes induced in cerebral arteriovenous oxygen difference (126, 127, 229, 232). Quantitative methods have confirmed in the monkey (73, 339), cat (157, 158, 159), and man (83, 162, 163, 203, 219, 295, 381) that elevated blood pO_2 reduces and hypoxemia accelerates cerebral blood flow.

Quantitative studies in man: In Table 1 are included the results of quantitative studies by means of the nitrous oxide method on the effects of altered blood oxygen tensions on the cerebral circulation of man and on some physiological variables which influence it. It is seen that the breathing of 85 to 100% oxygen at one atmosphere by normal subjects or miscellaneous convalescent patients causes only a mild reduction in cerebral blood flow of approximately 12 to 15% (162, 203, 219). Even when arterial pO_2 is raised to approximately 2100 mm Hg, by the breathing of 95 to 100% oxygen at an ambient pressure of 3.5 atmospheres (219), the reduction in cerebral blood flow and increase in cerebrovascular resistance

are, although percentagewise twice as great as at one atmosphere, still relatively small. Furthermore, part of these effects can be attributed to an associated hyperventilation and hypocapnia. At one atmosphere 80% (381) and 50% (163) oxygen in the inspired air have negligible effects on the cerebral circulation. On the other hand, reduction in arterial pO_2 to the degree attending the inhalation of 10% O_2 has been found by Kety and Schmidt (203) to cause a marked rise in cerebral blood flow of almost 50% and a considerable drop in cerebrovascular resistance. These changes occurred despite a significant fall in mean arterial blood pressure and the development of a mild hypocapnia and alkalosis resulting from the associated anoxic hyperpnea. Since these concomitant changes would tend to constrict cerebral vessels and lower blood flow, it is likely that they reduced somewhat the effectiveness of the hypoxemia in altering the cerebral circulation. Turner *et al.* (381) have studied the effects of 8% O_2 under conditions which maintained the alveolar pCO_2 "constant" at 43 mm Hg. Although the cerebral circulatory changes then reflect only the actions of low blood pO_2 unmodified by the antagonistic effects of the hypocapnia which normally accompanies this degree of hypoxia, their results were similar to those of Kety and Schmidt (203). It is apparent from both studies that hypoxemia markedly increases cerebral blood flow by reducing cerebrovascular resistance. Its effects on the cerebral circulation are, therefore, not only opposite in direction to that of increased blood pO_2 but are also more pronounced.

Cerebral homeostasis and mental symptoms during hypoxemia: The changes induced in the cerebral circulation by altered arterial oxygen tensions tend to maintain some degree of constancy of the brain tissue pO_2, particularly in response to hypoxemia. Indeed, internal jugular venous pO_2, which probably reflects that of the cerebral tissues, falls more slowly than arterial pO_2 on inhalation of low oxygen mixtures (232). The fact that it falls at all indicates, of course, that the circulatory compensation is not complete, but it undoubtedly permits the brain to withstand a greater degree of hypoxemia than would otherwise be true. The critical level of cerebral venous oxygen saturation below which consciousness is invariably lost has been found by Lennox *et al.* (231) to lie between 24 and 30%, corresponding to an oxygen tension of approximately 15 to 20 mm Hg in the usual cerebral venous blood. It is also at this level that the effects of oxygen lack on the cortical electrical activity are first manifest as an abrupt fall in the average frequency of the cortical potentials (232). The homeostatic nature of the cerebral circulatory response to hypoxemia permits a greater degree of arterial oxygen unsaturation before the critical level in the cerebral venous blood and tissues is reached.

Mental symptoms of cerebral anoxia do appear before the level of unconsciousness is reached and before there is any evidence of a restriction of cerebral oxygen utilization by an inadequate oxygen delivery to the brain. Thus, Kety and Schmidt (203) have observed distinct mental disturbances during the inhalation of 10% O_2 without any concomitant change in cerebral oxygen consumption. Eight per cent O_2 also fails to alter the cerebral metabolic rate (381). It is possible that the mental symptoms are associated with changes in processes more subtle

than those reflected in gross oxygen consumption of the brain or that they arise from changes in pO_2 and oxygen consumption in portions of the brain too small and discrete to be detected by measurements in the brain as a whole. Hansen and his coworkers (158, 159) have found the effects of 10% O_2 inhalation to be non-uniform in the various component tissues of the cat brain. In general, the circulation in gray matter, whose blood flow and metabolic rate are normally higher, is absolutely and percentagewise more greatly increased than in white matter. The effects, however, are not uniform within the various gray areas; it is, therefore, possible that some gray structures with normally higher metabolic rates but with lesser circulatory responses to hypoxemia may suffer a greater degree of anoxia and a restriction of oxygen utilization. There remains the possibility that early mental symptoms of hypoxemia which precede detectable changes in cerebral oxygen consumption reflect not so much the effects of oxygen deficiency as those of pCO_2 reduction in the tissues of the brain (127). In favor of this explanation is the fact that cortical electrical activity is far more sensitive to reduction in cerebral venous pCO_2 than of pO_2 (232), and both arterial and cerebral venous hypocapnia result from the reflex hyperpnea of hypoxemia (203). Indeed, the same mechanism, rather than cerebral ischemia, may explain the mental symptoms without lowered cerebral oxygen utilization during hypocapnia produced by hyperventilation (203). Of particular relevance to this question is the study by Turner *et al.* (381) who experimentally maintained a "constant" and normal alveolar pCO_2 during the inhalation of 8% O_2; their preliminary report points out the lack of change in cerebral oxygen consumption but makes no mention of the occurrence of mental symptoms.

Role of oxygen in the physiological regulation of the cerebral circulation: Because oxygen like carbon dioxide is intimately related to metabolism and acts on the cerebral circulation in a manner tending to maintain a constancy of pO_2 in the cerebral tissues, it has also been implicated in the possible chemical mechanisms for the adjustment of blood flow to the metabolic demands of the brain (126, 334, 337, 338, 339). An increased cerebral metabolic rate tends to lower oxygen and raise carbon dioxide tensions in the brain (65, 66). Both effects dilate cerebral vessels and increase cerebral blood flow, thus delivering oxygen and removing carbon dioxide more rapidly to and from the tissues, respectively. A reduction in metabolic rate results in opposite changes. The net effect is the maintenance of homeostasis as regards both carbon dioxide and oxygen by adjustment of the cerebral circulation to changes in cerebral metabolic rate. The actions of carbon dioxide and oxygen on the cerebral vessels have been determined chiefly during induced changes in their tensions in the circulating blood, but it is likely that the thin-walled cerebral vessels are similarly affected by altered gas tensions in the tissue medium surrounding them. Evidence that oxygen can readily diffuse though the walls of cerebral vessels has been obtained by Davies and Rémond (65), who observed by means of the oxygen electrode that the pO_2 on the outer surface of a pial vein varied with that of the blood within it.

The relative importance of oxygen and carbon dioxide to the normal regulation of the cerebral circulation has been a matter of considerable interest (73, 334,

337, 339). Since the respiratory quotient of brain is approximately unity (129, 202, 228), oxygen is consumed and carbon dioxide produced at equal rates. Because of differences in their dissociation curves (300) pO_2 and pCO_2 in brain and blood might be expected to change differently for equal changes in molecular concentration. Actually, however, at the usual gas tensions and pH (202, 219) existing in cerebral venous blood with which the tissues are, at least, close to equilibrium (55), the dissociation curves are such that the rates of change of tension with respect to concentration are fairly similar for both gases. The relative contributions of the two gases to the normal chemical regulation of the cerebral circulation are, therefore, dependent mainly on the relative sensitivities of the cerebral vessels to equivalent changes in their tensions.

Present evidence indicates a greater sensitivity of the cerebral vessels to carbon dioxide than to oxygen at normal or elevated oxygen tensions. The cerebral vasoconstriction caused by increased blood pO_2 is only moderate (125, 157, 162, 163, 203, 219, 229, 381, 402) and may be predominantly secondary to an associated hypocapnia (381); it does not approach the degree of vasoconstriction caused by the hypocapnia of hyperventilation and never overrides but is readily overcome by the vasodilator effect of increased carbon dioxide (125, 229). On the other hand, hypoxemia markedly increases cerebral blood flow (125, 127, 203, 229, 282, 381) despite the antagonism of a usually occurring secondary hypocapnia (126, 127, 203, 282). Low pO_2 can, therefore, overcome the cerebral vasoconstriction of hypocapnia, and Noell and Schneider (288) have reported that it is the low pO_2 developing in the brain and cerebral venous blood which limits the degree of blood flow reduction obtainable by hypocapnia. When cerebral venous pO_2 falls to 19 mm Hg, cerebral vessels begin to dilate despite further reduction in arterial pCO_2 by continued passive hyperventilation. Apparently at this critically low level of cerebral venous pO_2, whether achieved by reduction in blood flow, as in the studies of Noell and Schneider (288) or, perhaps, also by arterial hypoxemia, oxygen becomes the almost exclusive regulator of the cerebral circulation. It is interesting that at approximately the same critically low level of cerebral venous pO_2 both consciousness (231) and the normal electroencephalographic pattern (232) are lost. The relative sensitivities of the cerebral vessels to oxygen and carbon dioxide are, therefore, variable and depend on the existing state of blood gas tensions. At normal or elevated blood oxygen tensions, the effectiveness of oxygen in altering cerebral blood flow is negligible compared to that of carbon dioxide. In mild arterial hypoxemia, oxygen still remains relatively ineffective, perhaps, because of the buffering effects of the shape of the oxyhemoglobin dissociation curve on cerebral venous pO_2. Courtice (56) has found in chloralosed cats that the cerebral blood flow, as indicated by arteriovenous oxygen differences, does not increase until the oxygen concentration in the inspired air is reduced below 15%. With increasing hypoxemia, the effectiveness of reduced oxygen tension increases progressively (56), and the relative importance of oxygen and carbon dioxide undergoes a gradual reversal so that ultimately at a critical level of anoxemia, close to the level of unconsciousness, the influence of oxygen is paramount and that of carbon dioxide negligible. The observation by Schmidt

and his coworkers (73, 339) of a relative insensitivity of the monkey's cerebral circulation to carbon dioxide as compared to oxygen may well have been a reflection of such an anoxemic state as indicated by their data on arterial oxygen contents (339). In the transitional zone between mild and extreme hypoxemia, cerebral blood flow is adjusted to the blood and brain tensions of both respiratory gases, and its level is determined more or less by their net effect. The actions of altered oxygen and carbon dioxide tensions, either alone or in combination, on the cerebral blood flow have recently been summarized graphically by Cannon (42). In general, the available evidence supports the view expressed by Gibbs and his coworkers (126, 130) that cerebral blood flow is normally regulated chiefly by carbon dioxide to maintain homeostasis as regards brain tissue CO_2; a similar homeostatic mechanism for oxygen exists, but it is primarily an emergency one that becomes important only when adequate oxygenation of the brain is threatened.

Mechanism of action: The mechanisms of the oxygen effects on the cerebral circulation are not entirely understood. Changes in arterial blood pressure are too slight or in an opposite direction to explain the changes in cerebral blood flow or vascular resistance observed with either high or low oxygen tensions (83, 162, 163, 203, 219). Of the various factors which might contribute to the alterations in cerebrovascular resistance, it is unlikely that blood viscosity is changed, and intracranial pressure is normally altered in the opposite direction (247, 258, 295). It appears then that the changes in cerebrovascular resistance are, as indicated by direct observations of the retinal (61, 164, 356) and pial (30, 402) vessels, the results of active vasodilatation by low and definite though slight vasoconstriction by high oxygen tensions. The slight increase in cerebrovascular resistance associated with higher than normal oxygen tensions may reflect chiefly the vasoconstrictor effect of a secondary hypocapnia (219, 381) although it has been observed in the absence of any significant change in arterial pCO_2 (162, 203).

Although the current bias is that oxygen, like carbon dioxide, alters the tone of the cerebral vessels by direct action on their smooth muscle (337, 338), nervous mechanisms have not been conclusively excluded. Unlike the cerebral vascular responses to carbon dioxide, which resemble those of other vascular beds only after their denervation (296, 301, 338, 369), the effects of oxygen on the cerebral vasculature are similar to those on normally innervated peripheral vessels. For example, in the dog coronary blood flow is also decreased by O_2 administration and increased by anoxemia (76). In man Lennox and coworkers (229, 232) found by means of simultaneously determined arteriovenous oxygen differences in brain and leg that blood flow in both areas are increased in hypoxemia; high oxygen tensions, however, also increased leg blood flow while decreasing that of the brain. The significance of these observations is uncertain because of the strong possibility that extraneous influences, such as secondary changes in blood pCO_2, may have obscured the effects of oxygen on both vascular beds. Furthermore, even if cerebrovascular and peripheral vascular responses to altered oxygen tensions were identical, it would not necessarily prove that the mechanisms of action were the same in both areas. More striking is the fact that the cerebral circulatory

responses to both carbon dioxide and oxygen are remarkably like those of the respiration. Carbon dioxide over a wide range of tensions exerts a continuous and direct effect on both the respiratory center and the cerebral vessels. At normal and high tensions, oxygen plays a negligible role in regulating both ventilation and cerebral circulation. At approximately the same degree of hypoxemia, however, both cerebral circulation and ventilation are accelerated, and with increasing hypoxemia oxygen tension takes over from carbon dioxide the regulation of both functions. It would indeed be coincidental if such similar response patterns by two such diverse functions involving dissimilar tissues were to be achieved through different mechanisms. Since the mechanism of the low oxygen effect on respiration is a reflex one via the chemoreceptors, one might wonder if the parallel cerebrovascular dilatation is not similarly mediated. This possibility has by no means been eliminated. There is some evidence obtained by means of the cranial window technique in dogs under chloralose anesthesia that severance of the vagus and carotid sinus nerves, which interrupts the afferent pathways from the aortic and carotid bodies, reduces or eliminates the dilatation of the pial vessels in response to anoxia (30). The failure to duplicate the effects of hypoxemia on the cerebral circulation by electrical stimulation of the vagodepressor or carotid sinus nerves, which carry the afferent fibers from these chemoreceptors, does constitute some negative evidence against this possibility (332, 338, 340), but it is less direct and is subject to extraneous technical and physiological complications. Furthermore, there is also the possibility that other chemoreceptors, similar in structure and function to the carotid and aortic bodies but located intracranially close to the cerebral vessels, are involved in the cerebrovascular response to hypoxemia. The mechanism of the action of oxygen on the cerebral vessels remains, therefore, an open question.

Altered and pathological responses of the cerebral circulation to oxygen: The reactivity of the cerebral circulation to changes in blood pO_2 has been reported in some cases to be quantitatively and even qualitatively different from normal and in other cases to lead to pathological results. In elderly subjects with acute or chronic cerebral vascular disease, Heyman *et al.* (163) found 85 to 100% O_2 to cause reductions in cerebral blood flow and increases in cerebrovascular resistance which were somewhat less than those reported by others in subjects free of such disease (161, 203, 219) (see Table 1). Hickam and his associates (164) have reported that the retinal vessels are less constricted in arteriosclerotic patients than in normal subjects during the inhalation of 100% O_2 and that this reduced reactivity is well correlated with a reduction in cerebrovascular responsivity to inspired air concentrations of 5 to 7% CO_2. Although diminished, the ability of 85 to 100% O_2 to constrict cerebral vessels is considered by Heyman and his associates (163) to be sufficiently great to constitute a hazard in acute cerebrovascular accidents; they suggest instead the use of lesser concentrations, for example, 50%, which have negligible effects on cerebral blood flow. The response of the cerebral circulation to hypoxemia induced by the inhalation of 10% O_2 is also significantly reduced in elderly subjects with cerebrovascular diseases (83).

Changes in the cerebral circulation have frequently been suggested as possible

etiological factors behind the generalized convulsions which occur during the prolonged inhalation of oxygen at pressures greater than one atmosphere (20, 368). Carbon dioxide retention in the brain tissues has also been considered since at high oxygen tensions the raised oxygen saturation of hemoglobin in cerebral venous blood might be expected to interfere with CO_2 transport from the tissues (20, 219, 368). Lambertsen and his associates (219), however, have clearly shown that the cerebral vasoconstriction produced by oxygen inhalation at pressures up to 3.5 atmospheres is inadequate to explain its toxic effects on the central nervous system, and no appreciable accumulation of carbon dioxide occurs in the brain. By elimination of these major hypotheses their work tends to implicate a direct toxic effect of high oxygen tensions on central nervous system enzymes as the etiological basis of oxygen toxicity.

In premature infants, the prolonged inhalation of high concentrations of oxygen, even at one atmosphere, is associated with the severe and irreversible retinal changes characterizing *retrolental fibroplasia* (10, 297). The pathological changes appear to be the consequences of a vaso-obliterative effect of elevated oxygen tensions on the retinal vessels and suggest that when immature, these vessels and, perhaps, the cerebral vessels to which they are similar are peculiarly sensitive to oxygen.

The use of high concentrations of oxygen may be associated with paradoxical effects on the cerebral circulation (295) as well as on mental and nervous functions (19, 51, 63, 258) in *chronic pulmonary disease*. Neurological changes, confusion, delirium, somnolence, coma, and even death have been observed to occur occasionally when 50 to 100% O_2 is administered to patients with chronic anoxemia secondary to pulmonary disease (19, 51, 63, 258). In patients with only moderately severe pulmonary disease, cerebral circulatory functions have been found to be normal (321), but in severe pulmonary emphysema accompanied by a high pCO_2 and a low pO_2 in the arterial blood, cerebrovascular resistance is low and cerebral blood flow high, the expected effects of the altered gas tensions (295). The administration of oxygen to the latter patients is, in contrast with the effects in normal subjects, associated with a further elevation of cerebral blood flow (295) and an increase in cerebrospinal fluid pressure (63, 258, 295). These apparently paradoxical effects of oxygen on the cerebral circulatory hemodynamics are secondary to the depression of respiration and the increased respiratory acidosis, for example, a further fall in blood pH and a rise in pCO_2, which oxygen administration causes in these patients (51, 295) in contrast to its effects in normals (162, 163, 203, 219, 295). The paradox is, therefore, not in the reaction of the cerebral vessels but in the abnormal response of the respiratory functions which may, perhaps, be the result of a removal of anoxic stimulation of the respiration. The pathological effects on nervous and mental functions cannot on the basis of present evidence be attributed to the changes observed in the cerebral circulation. A primary increase in intracranial pressure can reduce cerebral blood flow to the point of coma (204), but the rise in cerebrospinal fluid pressure attending the administration of oxygen in severe pulmonary disease is a secondary effect of a cerebral vasodilatation and increased blood flow (312, 313) and cannot, therefore,

be the cause of a cerebral anemia. It is more likely that the mental disturbances are the results of a rise in the tissue pCO_2 to depressant levels or of the acidosis which is also suspected as a cause of coma in other conditions such as diabetes (199).

3. Miscellaneous agents which alter respiratory gas transport or function. Chemical agents which interfere with normal respiratory gas functions also influence the cerebral circulation. *Acetazoleamide* (*Diamox®*) in single intravenous doses of 10–50 mg/kg, sufficient to inhibit practically all carbonic anhydrase activity, produces in anesthetized dogs an increase in cerebral blood flow which is sustained for more than 80 min after injection (259). This rise in blood flow occurs despite an increased pulmonary ventilation and reduction in alveolar and, therefore, also arterial pCO_2. Cerebral venous pCO_2, however, is elevated secondarily to the effects of carbonic anhydrase inhibition in the tissues, and it is this rise in pCO_2 in brain tissue and venous blood which is probably responsible for the cerebral vasodilatation. A concomitant rise in cerebrospinal fluid pressure occurs which is undoubtedly a consequence of the cerebral vasodilatation and increased blood flow.

Interference with blood oxygen transport by *carbon monoxide* causes cerebrovascular responses typical of hypoxemia. Inspired air concentrations of carbon monoxide as low as 0.2 to 0.3% dilate pial arteries in cats 40 to 80% (358), and 0.5% CO increases cerebrospinal fluid pressure approximately 75% (247), an indication of substantial cerebral vasodilatation and blood flow acceleration. Since carbon monoxide lowers only the oxygen content and not the pO_2 of arterial blood, the cerebral vasodilatation is probably the result of lowered cerebral tissue and venous oxygen tensions. *Cyanide* also appears to produce cerebral vasodilatation as suggested by an increased volume of the brain subsequent to its administration (392) although the degree of swelling is too great to be attributable to the vasodilatation alone. Since cyanide does not interfere with blood oxygen transport, the mechanism of its action is not through a reduction in blood pO_2. Its cytotoxic anoxic effect, however, causes tissue changes like those of hypoxemic anoxia. Whether its cerebrovascular effect is the result of such direct changes in the vessel walls or secondary to the activation of chemoreceptor reflexes by cyanide is still undetermined, as, indeed, is also true of the effects of low blood oxygen tensions.

B. Acids, Alkalis, Electrolytes, Inorganic Ions, and Fluids

Acids and alkalis: The influence exerted by acids and bases on the cerebral circulation has not yet been conclusively determined. Cerebral vasodilatation by acids and vasoconstriction by alkalis have been reported in animals (118, 241, 330, 331, 337, 340, 399, 402), but these effects have been neither impressive nor consistent. For example, transient dilatations of the pial arteries of cats have been observed following intravenous injections of lactic acid; bicarbonate caused marked vasoconstriction (402). Comparable though less consistent changes have been observed with hydrochloric acid and sodium carbonate when given in sufficient amounts to raise or lower the respiratory rate, respectively (241). In large

amounts hydrogen sulfide, like other acids, has been reported to dilate pial arteries; in small amounts it may constrict (105). Similar actions of acids and alkalis have been observed on the circulation of the perfused dog (330, 331) and cat (118) brain. In the latter the effects were elicited only by extreme changes in pH (118). On the other hand, the effects of pH changes on medullary blood flow, as indicated by thermocouple techniques, have been variable and uncertain (340), and opposite effects of alkalis were observed by Bronk and Gesell (39), who found the intravenous administration of carbonate or bicarbonate to increase the blood flow in both the carotid and femoral arteries of dogs. Since carotid blood is distributed to extracerebral tissues also, changes in its flow are not necessarily representative of the cerebral circulation.

The results of studies in man have been no more decisive. In the severe metabolic acidosis of diabetic coma, Kety and his coworkers (199) found an approximately 20% elevation in flow and a 30% reduction in cerebrovascular resistance despite a markedly lowered pCO_2 in both arterial and cerebral venous blood. In the absence of any other obvious cause of cerebral vasodilatation sufficiently powerful to overcome the antagonistic effects of the hypocapnia, it was suggested that the remarkably low arterial pH, for example, 6.98, might be responsible. Furthermore, the cerebral blood flow was found to correlate rather well with the arterial hydrogen ion concentration. On the other hand, in similar patients who were not quite in coma, arterial pH was only slightly higher, for example, 7.13, and blood pCO_2 was reduced to the same degree, but cerebral blood flow was decreased and cerebrovascular resistance increased by a proportionate amount. The fact, however, that the degree of cerebrovascular constriction in the latter group was still markedly less than occurs in normal subjects with even lesser degrees of hypocapnia achieved by hyperventilation (203) is evidence that in these patients too cerebral vasodilator influences were operating in opposition to the vasoconstrictor effects of the low pCO_2. If these vasodilator influences could truly be attributed to the acidosis, then one might conclude from a comparison of the results obtained in the comatose and non-comatose diabetic acidotic patients that within the arterial pH range of 6.98 to 7.13, the cerebral vasodilator effect of acidosis becomes so great as to match and overcome the vasoconstrictor effect of an almost 50% reduction in arterial pCO_2. With less severe hypocapnia, milder degrees of acidosis would presumably achieve the same. However, in view of the extensive chemical disorders present in diabetic acidosis, other vasodilator influences cannot be excluded with certainty. For example, blood ketones are elevated in diabetes, and at least one of them, acetone (402), has been suspected of having some cerebral vasodilator effect.

Schieve and Wilson (329) have questioned the role of pH in the cerebral circulatory changes in diabetic coma. In experimentally induced metabolic acidosis and alkalosis in man, they found conditions in which acidosis is associated with cerebral vasoconstriction and decreased blood flow and alkalosis with vasodilatation and increased blood flow. Acidosis was produced by the intravenous infusion of 350 ml of 0.8% ammonium chloride solution over a period of 60 to 90 minutes. Alkalosis was produced by the infusion of a liter of isotonic (1.2%) or hypertonic

(3%) sodium bicarbonate solutions over a one-hour period. In control studies comparable infusions of isotonic and hypertonic (2.0%) sodium chloride solutions were without significant effects. In the ammonium chloride studies the decrease in arterial pH, although statistically significant, was so minimal, for example, 0.04 pH units, and changes in blood gas levels including pCO_2 were so negligible that it is difficult to attribute to any of them the cause of the appreciable increase in cerebrovascular resistance and decrease in cerebral blood flow which were observed. One must, therefore, suspect the existence of other extraneous influences as, perhaps, a possible direct cerebral vasoconstrictor action of the ammonium ion or a rise in intracranial pressure secondary to the ammonium chloride administration. In the bicarbonate studies moderate degrees of metabolic alkalosis were achieved, and the cerebral vasodilatation and increase in cerebral blood flow were greater than any thus far observed in man except during the inhalation of carbon dioxide. Indeed, it is probable that the cerebral circulatory changes were caused not by the increase in pH but by an associated rise in blood pCO_2. Unfortunately, Schieve and Wilson (329) doubted that blood pCO_2 might be significantly altered because of a lack of visible changes in respiratory depth and rate and failed to determine blood pCO_2 in their bicarbonate studies. The question of respiratory compensation in metabolic alkalosis is presently controversial (304, 357), but Singer *et al.* (357) have found significant increases in arterial pCO_2 to accompany intravenous infusions of hypertonic sodium bicarbonate solutions in man. Such changes could account for the cerebral vasodilatation produced by bicarbonate.

A final evaluation of the direct action of acids and alkalis on the cerebral circulation is difficult because of the usual association of secondary extraneous influences, particularly changes in blood pCO_2. However, some tentative conclusions seem justified. Early studies in animals suggest a mild cerebral vasodilator action by acids and a weak vasoconstrictor effect of alkalis (118, 241, 330, 331, 337, 340, 399, 402). Reverse results (39, 329), the most noteworthy of which are those of Schieve and Wilson (329), do not disprove these early findings but do indicate that other factors often associated with acidosis and alkalosis, for example, changes in blood pCO_2, may overcome the effects of pH, if any, on the cerebral circulation. The studies of Schieve and Wilson (329) dissociate the actions of carbon dioxide from those of pH, more or less prove that CO_2 effects are not indirectly mediated through changes in pH, and demonstrate that within blood pH ranges not too distant from normal, pCO_2 is a more potent regulator of cerebrovascular tone than pH. The findings of Kety and coworkers (199) in diabetic acidosis and coma suggest that in extreme acidosis, far beyond the range studied by Schieve and Wilson, the effects of pH may overcome those of carbon dioxide and become the chief determinants of cerebral vascular tone and blood flow.

Electrolytes, inorganic ions, and fluids: Substances in these groups which promote alkalosis or acidosis, such as carbonate, bicarbonate, lactic acid, hydrochloric acid, and ammonium chloride, have already been discussed in relation to their effects as acids or alkalis. There is little evidence of any remarkable effects

on the cerebral circulation on the part of other agents in these groups although actual experimental data are meager. The potassium ion has been suspected of being a cerebral vasodilator (337, 339). Calcium ion is without apparent effect (232). Barium ion, as 5% barium chloride solution, is a powerful constrictor of the cortical and medullary vessels (98) as it is in other vascular beds; lower concentrations of barium chloride have no effect (98). Bromine ion does not seem to affect the pial vessels (361), and although water-soluble organic iodized preparations of the diodrast group (38) constrict cerebral vessels, there is no evidence that iodine ion or chlorine ion have any specific effects.

Isotonic (0.9%) and mildly hypertonic (2%)sodium chloride solutions, even after a liter has been infused over an hour period, have no effects on human cerebral circulation (329). Neither do isotonic glucose solutions (232), and Locke solution (402) does not affect the pial vessels of cats. Markedly hypertonic solutions, however, do appear to influence the cerebral circulation in a rather complex manner. Intravenous or intraperitoneal injections of highly hypertonic glucose, urea, or sodium chloride solutions cause considerable reductions in cerebrospinal fluid pressure (106, 116, 216, 355, 389, 401). Howe and McKinley (175) found no associated changes in the diameters of the pial vessels following the injection of 10 ml of 25 g% sodium chloride or 100 g% dextrose solutions; most investigators (216, 399, 401), however, have reported that intravenous or intraperitoneal injections of comparable volumes and concentrations of urea, glucose, or saline solutions cause an immediate transient dilatation followed by a delayed but prolonged constriction of the pial arteries and arterioles coinciding with a momentary rise and then prolonged fall in cerebrospinal fluid pressure. In subsequent studies with an improved cranial window technique, Forbes and Nason (106) found evidence of some inaccuracies in the previous observations. They too observed the initial transient dilatation of the pial arteries, but during the period of reduced intracranial pressure these returned to normal or only a mildly constricted state. The most prominent changes in the pial vessels during the delayed period were dilatation and cyanosis of the veins and venules; these changes were no different from those produced by a primary reduction in intracranial pressure by a withdrawal of cerebrospinal fluid (106). They concluded, therefore, that the initial pial arterial dilatation was the result of a direct action of hypertonic solutions on the vessel walls, but the delayed reaction, the dilatation of veins and venules, was secondary to the reduction in cerebrospinal fluid pressure by the hypertonic solutions. During these pial vascular changes the intracerebral or cortical vessels are apparently dilated too, as indicated by flushing of the cortex (216) and by thermoelectric evidence of an increased blood flow (289); presumably these changes are also secondary to the reduced intracranial pressure as well as to a raised systemic blood pressure. Hypotonic solutions, for example, distilled water, have been reported to produce pial and cortical vascular changes in the opposite direction (216). In patients with brain tumors whose increased intracranial pressure was reduced to approximately normal by the intravenous injection of 150 ml of 50% glucose solution, Shenkin and his coworkers (355) measured by means of the nitrous oxide method a significant rise

in cerebral blood flow and reduction in cerebrovascular resistance. However, in view of a considerable fall in arterial oxygen content which indicated significant hemodilution, they attributed the cerebral hemodynamic changes to a reduction in blood viscosity rather than to the decrease in intracranial pressure produced by the hypertonic solution.

C. Drugs Acting on the Central Nervous System

1. *Central nervous system depressants. General anesthetics.* Data on the effects of general anesthetics on the cerebral circulation are sparse. Animal experiments are generally performed under anesthesia so that comparison with the unanesthetized state is difficult, or one anesthetic is tested in the presence of another. The nitrous oxide method cannot readily be applied in the presence of volatile anesthetic agents because they interfere with the determinations of blood nitrous oxide concentration. The recently developed modifications which employ radioactive krypton (224, 233, 234, 273) instead of nitrous oxide avoid this difficulty, but they have not yet been exploited in studies of anesthesia.

The available experimental evidence suggests that most volatile general anesthetics dilate cerebral vessels (337, 338, 399). These results must be viewed with caution, for in most studies there was little attempt to control or to determine the effects of the secondary respiratory depression which occurs so readily in general anesthesia and can itself cause dilatation of the cerebral vessels. The cerebral vasodilator properties of diethyl ether (ether) have been repeatedly demonstrated by a variety of techniques. It has been observed by direct visualization to increase pial arterial diameters (92, 94, 335, 399), and small increases in brain volume (213) and brain blood content (393) attend its administration. Evidence that it actually increases brain tissue blood flow has been obtained in the parietal cortex (338), hypothalamus (332), and medulla (340) of cats by means of thermoelectric techniques. Such increases have been observed in the absence of changes in blood pressure (340) or prior to respiratory depression and carbon dioxide accumulation (338), indicating a specific cerebral vasodilator effect of ether. Simultaneously, extracerebral muscle blood flow decreases until evidence of depression of the medullary centers appears; it then rises while intracranial blood flow increases even further (338). The fall in extracranial blood flow is eliminated by section of the cervical sympathetics (338) indicating that ether, like carbon dioxide, causes reflex extracerebral vasoconstriction while simultaneously dilating the cerebral vessels, probably by direct action. Kety (194), employing special analytical techniques, has applied the nitrous oxide method in several human subjects under ether anesthesia and found the cerebral blood flow to be approximately 20% higher than the mean value in normal unanesthetized man despite a depression in cerebral metabolic rate. This observation lends credence to the earlier qualitative findings concerning the cerebral vasodilator action of ether.

When administered to the point of respiratory depression, all anesthetics undoubtedly cause cerebral vasodilatation and increased blood flow because of the resultant carbon dioxide retention and oxygen lack. Nitrous oxide in anoxic concentrations probably regularly increases cerebral blood flow secondarily to the

anoxemia. As for their primary effects on the cerebral circulation, there are few experimental data concerning most other general anesthetics. The action of cyclopropane (Cyclopropane, U.S.P.; trimethylene) is uncertain (335); it has been found to increase carotid arterial blood flow in the dog (22), but the same artery carries blood to the extracranial tissues as well. For example, in the same experimental preparation ether decreased carotid blood flow, indicating that changes in extracranial rather than cerebral circulation were being detected; sodium hexobarbital [Hexobarbital Sodium, N.F.; Hexobarbitone Sodium; Evipal Sodium®; sodium 5-(1-cyclohexenyl)-1,5-dimethylbarbiturate] caused the same changes as ether (22). Chloroform has been observed to dilate pial vessels (94), and both chloroform and chloralose (chloralosane; anhydroglucochloral) increase brain volume (213) presumably because of cerebral vasodilatation and increased brain blood content. Allobarbital (allobarbitone; Dial®; 5,5-diallylbarbituric acid) has been reported to cause slight or negligible dilatation of the pial vessels (360, 361) in the intact cat and slight cerebral vasoconstriction in the perfused cat brain (118). Among the *basal anesthetics*, amylene hydrate (Amylene Hydrate, U.S.P.; tertiary amyl alcohol) causes pial vascular dilatation (361), but this effect may be secondary to a fall in blood pressure (99). Tribromoethanol (Tribromoethanol Solution, U.S.P.; Avertin®), which is dissolved in amylene hydrate, has been reported by one group to cause marked and prolonged pial vasodilatation (360, 361) and by another a distinct vasoconstriction (94) despite a fall in blood pressure.

Barbiturate anesthesia is the one type in which the cerebral circulation has been thoroughly studied in both animals and man. In the animal experiments, correlations among administered dose, effects on cerebral functional activity, and actions on the cerebral circulation are usually obscured by the depressant effects of the previously employed anesthetic agents and/or the surgical procedure. It is, perhaps, for such reasons that all possible cerebrovascular actions, no effect, vasoconstriction, or vasodilatation, have been attributed to the barbiturates. Sodium amobarbital (Amobarbital Sodium, U.S.P.; Amytal Sodium®; isoamylethylbarbiturate sodium) and sodium phenobarbital (Phenobarbital Sodium, U.S.P.; Phenobarbitone Sodium, B.P.; Luminal Sodium®; phenylethylbarbiturate sodium) have been observed to dilate pial arteries (94, 399) while sodium pentobarbital [Pentobarbital Sodium, U.S.P.; Nembutal Sodium®; sodium 5-ethyl-5(1-methylbutyl)barbiturate] has been reported to have little effect (360). Thermocouple techniques have given evidence of a vasoconstrictor effect of pentobarbital in the spinal cord (91). In the perfused cat brain (118), the sodium salts of amytal and phenobarbital were without effect, and sodium thiopental [Thiopental Sodium, U.S.P.; Thiopentone Sodium, B.P.; Pentothal Sodium®; sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate] constricted cerebral vessels although all reduced the cerebral metabolic rate. Thiopental anesthesia is often associated with an increased brain volume (393, 397) which is very rapidly reversed by increased respiratory exchange (397) and, therefore, probably arises from dilatation and congestion of the cerebral vessels rather than from cerebral edema. According to White and his associates (393), cerebral swelling and vascu-

lar congestion are observed during barbiturate anesthesia only when anoxia and hypercapnia are present, and the work of Wilson *et al.* (397) indicates that they are the effects chiefly of carbon dioxide retention. Arterial-cerebral venous oxygen differences are low in barbiturate anesthesia (62, 81), but since cerebral oxygen consumption is also reduced in the anesthetized state (170, 174, 339, 387, 397), they are more a reflection of the lowered metabolic rate than an increased blood flow in the brain.

Recent quantitative studies have clarified the action of the barbiturates on the cerebral circulation. Experiments in the monkey by means of the bubble-flow meter (339) and in the dog by means of the nitrous oxide method (174) have demonstrated that in deep thiopental anesthesia both cerebral blood flow and cerebral metabolic rate are lower than in the lightly anesthetized state. Nitrous oxide studies in relatively normal man (205) and in women with toxemia of pregnancy (253) have shown that the barbiturates, phenobarbital, thiopental, and amytal, in doses sufficient to cause sedation but not loss of consciousness, are without significant effects on cerebral circulation and metabolic rate. With anesthetizing or narcotic doses, however, cerebral oxygen consumption is always reduced, and cerebral blood flow may be unchanged (85, 397), decreased (170, 253, 254, 328, 378), or increased (387). Cerebrovascular resistance is either unchanged or altered in a direction opposite to that of the change in cerebral blood flow. In one study in which cerebral blood flow was not significantly affected (397), cerebrospinal fluid pressure remained relatively constant, but it is likely that when cerebral blood flow is altered, it deviates in the same direction. There is no evidence from human quantitative studies that barbiturates, even in anesthetic doses, exert any specific direct action on the cerebral vasculature; changes in cerebral circulation induced by them are secondary to some of their other effects. In barbiturate intoxication or anesthesia mean arterial blood pressure (253, 378, 387) and cerebral metabolic rate (85, 170, 253, 254, 328, 378, 387, 397) are reduced. Both these changes tend to lower cerebral blood flow, the former by reducing the driving pressure, the latter by raising cerebrovascular tone through the previously discussed chemical mechanisms which regulate cerebral blood flow to metabolic demand. On the other hand, barbiturates also depress respiratory exchange as indicated by the low oxygen contents (253, 254, 378, 387) and pH (387, 397) and elevated pCO_2 (387, 397) of the arterial blood, and these chemical changes, particularly the carbon dioxide retention, have cerebral vasodilator effects which may be sufficiently great to overcome the opposing influences and increase the cerebral blood flow (387). Furthermore, even when blood flow is reduced, it never falls as greatly as the cerebral metabolic rate so that cerebral oxygen supply is always more than adequate. The decreased cerebral oxygen consumption in barbiturate anesthesia, and probably also in other types of anesthesia, is, therefore, clearly not secondary to circulatory insufficiency and inadequate oxygen supply. It reflects instead the reduced demand for oxidative energy attending the depression of functional activity, which, in view of the findings of Larrabee and his coworkers (222, 223), may be secondary to the inhibition by anesthetic agents of synaptic transmission and neuronal interaction.

Recent studies of local cerebral blood flow indicate that the changes in circulation during barbiturate anesthesia are not uniformly distributed throughout the brain (220, 362). In cats under light thiopental anesthesia, blood flow was significantly reduced from the levels existing during consciousness in less than half of the 28 cerebral structures examined; all others showed no change. All significant changes were observed in gray structures and none in white matter. The greatest reductions occurred in the primary sensory areas of the cerebral cortex, for example, those subserving visual, auditory, and somatosensory functions, which during consciousness have the highest perfusion rates of all cortical areas and, except for the inferior colliculus, of all structures in the brain. The net result is that differences in blood flow among the various cortical areas, so prominent during consciousness, are eliminated by thiopental anesthesia, and cerebral cortical blood flow becomes uniform at a lower level. Since changes in local blood flow may represent secondary readjustments to local changes in metabolic demands, then these results suggest that a major effect of thiopental anesthesia is a reduction in functional and metabolic activities of the primary sensory cortical areas. Whether this effect is the cause or the result of the depression of sensory functions in the anesthetized state remains, of course, undetermined.

Although the barbiturates are hardly representative, it is likely that most general anesthetics influence the cerebral circulation similarly. With the possible exception of ether, which appears to have specific cerebral vasodilator actions (92, 94, 194, 332, 335, 338, 340, 399), there is little evidence that any of them have any greater direct action on the cerebral circulation than the barbiturates. Any influence they may have is also probably chiefly secondary to their effects on blood pressure, cerebral metabolic rate, and the respiratory gas tensions in the blood.

Local anesthetics. The effects of the systemic administration of the local anesthetic, procaine hydrochloride (Procaine hydrochloride, U.S.P.; Novocaine®; *p*-aminobenzoyl-diethylaminoethanol hydrochloride), on the cerebral circulation have been studied in man by Scheinberg and his coworkers (323). Intravenous infusions of 0.75 g over a period of 20 min failed to alter arterial blood pressure, cerebral blood flow, or cerebral oxygen consumption. A slight rise in cerebrovascular resistance suggested a minor increase in the tone of the cerebral vessels. Since these observations were made in patients whose cerebral vessels were normal, they do not necessarily describe the action of procaine when cerebrovascular tone is increased as, for example, following cerebral embolism. There have been reports of rapid alleviation of the neurological disturbances following cerebral gas embolism by intravenous procaine administration (40), and local application of procaine or cocaine abolishes the slight pial vasoconstrictor effect of cervical sympathetic stimulation (103). It is conceivable that the cerebral circulatory effects observed by Scheinberg *et al.* (323) were negligible because of a failure to achieve adequate blood levels since procaine is rapidly inactivated during such administration; several of the subjects, however, developed subjective symptoms, and the dosage rate exceeded that generally required to produce analgesia, indicating that such was not the case.

Narcotics. Narcotic drugs, both natural and synthetic, appear to exert only minor influence on the cerebral circulation, and their effects, when they occur, are probably not direct but secondary to their actions on other functions, as, for example, pulmonary ventilation. The alkaloids of opium, morphine and codeine, have been described as capable of dilating cerebral vessels (337), as probably reducing cerebral blood flow (335), and as having little or no effect (47). In cats morphine has been observed to exert only negligible effects on pial arteries (94) except when blood pressure falls, and then only slight vasodilatation occurs. With thermoelectric techniques in cats morphine was found to increase blood flow in the medulla (340) but to have no effects in the hypothalamus (332). Abreu and his coworkers (1), in quantitative studies in man by means of the nitrous oxide technique, found no significant changes in cerebral circulation or metabolism 20 minutes after the intramuscular administration of 10 mg of morphine sulfate. In similar studies in both normal pregnant women and preeclamptic patients, McCall and Taylor (252) administered 20 to 30 mg doses subcutaneously and measured their effects one hour after injection. Statistical analysis of their data indicates that morphine caused a significant ($p < 0.05$) rise in cerebral blood flow, reduction in cerebrovascular resistance, and a slight fall in mean arterial blood pressure. Since morphine, if anything, raises intracranial pressure (184, 189), the reduction in vascular resistance must represent a true relaxation in cerebrovascular tone. However, even though statistically significant, the changes in cerebral circulation produced by morphine in the doses and routes of administration employed in these studies are too slight to have any pharmacological importance. The synthetic narcotic, methadone hydrochloride (Methadone hydrochloride, U.S.P.; Amidone hydrochloride; *dl*-2-dimethylamino-4,4-diphenylheptanone-5-hydrochloride), administered intramuscularly in 5 mg doses, is also without any notable effect on cerebral circulation and metabolism in man (2).

Morphine and the synthetic narcotic, meperidine [Meperidine (Pethidine) hydrochloride, U.S.P.; Demerol hydrochloride®; Dolantin; ethyl-1-methyl-4-phenylpiperadine-4-carboxylate hydrochloride], are known to cause considerable increases in cerebrospinal fluid pressure (184, 189). Keats and Mithoefer (184) have observed that the rise in cerebrospinal fluid pressure following a 10 mg intravenous dose of morphine sulfate coincides in time with a fall in pulmonary ventilation and alveolar oxygen tension and an increase in alveolar pCO_2. It is prevented or removed by hyperventilation. The same dose of the semi-synthetic congener and antagonist of morphine, nalorphine (Nalorphine hydrochloride, U.S.P.; N-allylnormorphine hydrochloride), when administered alone, produces the same respiratory and cerebrospinal fluid pressure changes as caused by morphine alone. When administered after morphine, however, it reverses the morphine-induced changes to the levels existing prior to any drug administration; when given first, it blocks the effects of a subsequent dose of morphine. Also, after nalorphine has prevented or counteracted the effects of morphine, hyperventilation has negligible effects on cerebrospinal fluid pressure. The antagonism of nalorphine toward the respiratory depression induced by morphine has been frequently observed (75, 382). As Keats and Mithoefer (184) point out, these findings indicate

that cerebrospinal fluid pressure increases following morphine administration because of a rise in arterial pCO_2 secondary to a depression of respiration. The rise in intracranial pressure reflects the cerebral vasodilatation and augmentation of blood flow caused by the increased blood pCO_2 (397). The failure of morphine to cause any appreciable rise in cerebral blood flow in the nitrous oxide studies previously cited (1, 252) does not necessarily refute this evidence in view of the difference in routes of administration and dosage. Had pulmonary ventilation, alveolar or arterial respiratory gas tensions, and cerebrospinal fluid pressures been measured in the nitrous oxide studies, they too would probably have been unaltered. Indeed, in the study by McCall and Taylor (252) in which data on blood gas contents were presented, there is no indication of respiratory depression. On the basis of present evidence it appears that morphine and other similar narcotics have no significant direct action on the cerebral circulation, but as a consequence of the respiratory depression and carbon dioxide retention which frequently attends their administration, cerebral blood vessels may be dilated and blood flow increased.

Stone and his coworkers (373) have found the respiratory effects of morphine to be clinically useful in the treatment of hemorrhagic shock. Because of the low arterial blood pressure and a hypocapnia and respiratory alkalosis resulting from an unexplained hyperventilation, cerebral blood flow in that condition was significantly decreased (373). The intravenous injection of 8–10 mg of morphine sulfate in these cases was found to depress respiration, raise arterial pCO_2, and restore the cerebral blood flow to normal levels. Dramatic subjective improvement accompanied the restoration of cerebral blood flow.

Ethyl alcohol. Peripheral vasodilatation, particularly in the skin, is one of the prominent effects of moderate doses of ethyl alcohol (52). Evidence of a similar action on cerebral vessels was obtained by Thomas (379), who found intracarotid or intravenous doses of ethyl alcohol to dilate temporarily the pial vessels of the anesthetized cat or rabbit; Sohler *et al.* (360), however, found only negligible effects in the cat and monkey. In man cerebral arteriovenous oxygen difference and cerebrospinal fluid pressure have been reported to be unaltered by intravenous injections of intoxicating amounts of alcohol (239); the finding of a low arteriovenous oxygen difference during naturally occurring acute alcoholic intoxication has been attributed to a depression of cerebral metabolic rate rather than to an increase in cerebral blood flow (136). In quantitative studies in man employing the nitrous oxide method, Battey (16, 17), Fazekas (82), Hine (171), and their respective coworkers have clearly demonstrated that intravenously administered ethyl alcohol in sufficient amounts to raise the blood alcohol level as high as 200 mg% and cause the symptoms of mild inebriation is without significant effects on cerebral blood flow, metabolic rate, and vascular resistance. Even when the alcohol was given in combination with a sufficient dose of chlorpromazine to cause tranquilization and hypotension, cerebral blood flow and oxygen consumption remained unchanged (82). A reduction in cerebrovascular resistance like that occurring with chlorpromazine alone balanced the effect of the hypotension, but it was probably not a direct effect of either drug but rather a non-specific relax-

ation of cerebrovascular tone which generally accompanies any acute reduction of arterial blood pressure (99, 197, 212, 353).

In contrast with the effects of mild inebriating doses of alcohol, severe alcoholic intoxication is associated with marked alterations in cerebral circulation and metabolism. In patients admitted to the hospital in coma with an average blood alcohol level of 320 mg%, Battey *et al.* (16) found the cerebral oxygen consumption to be profoundly reduced. Cerebral blood flow, however, was considerably elevated because of a reduction in cerebrovascular resistance; arterial blood pressure was unchanged. Following recovery all these functions reverted to normal. A low cerebral metabolic rate is characteristic of all types of coma (85, 191), but the fact that it was in these cases accompanied not by a proportionate readjustment in the cerebral circulation but rather by changes in the opposite direction suggests the action of strong cerebral vasodilator influences. The cerebral vasodilatation may not, however, have resulted from a direct action of alcohol on the cerebral vessels. In the intoxicated state, there was evidence of respiratory depression and acidosis of sufficient degree to cause the observed changes in the cerebral circulation. Apparently the effects of acutely administered alcohol on the cerebral circulation are seen only when the amounts are great enough to depress the central nervous system and then are probably secondary to the effects of the respiratory depression. In chronic alcoholism complicated by delirium tremens, there is a reduction in cerebral metabolic rate and a proportionate decrease in cerebral blood flow (17).

Tetraethylthiuram disulphide (Disulfiram; Antabuse®), an agent which causes hypersensitivity to alcohol and has been employed in the treatment of chronic alcoholism, has been reported to cause a 30% decrease in cerebral blood flow and a somewhat more moderate fall in cerebral oxygen consumption when administered in daily 0.5 to 1 g doses over a four-day period (171). The mechanisms of these effects are unclear. When followed by a small dose of alcohol which alone has only negligible effects, cerebral blood flow is restored to normal, but cerebral metabolic rate is depressed even further. The blood flow change occurs despite a marked blood pressure fall because of a considerable relaxation in cerebrovascular tone. It appears as though prior treatment with antabuse endows normally small, negligible doses of alcohol with the effectiveness of large doses as regards the effects on cerebral circulation and metabolism. Since the antabuse-alcohol reaction is characterized by an elevation of acetaldehyde levels in the body, the enhancement of the action of alcohol by antabuse suggests that it is not alcohol but its intermediate metabolite, acetaldehyde, which is ultimately responsible for the effects.

Methyl alcohol. The effects of methyl alcohol are quite different. In patients with acute methanol intoxication, Battey and his associates (17, 18) found profound and proportionate decreases in both cerebral blood flow and metabolic rate. These changes were not completely irreversible, for in those patients who recovered, these functions tended to return toward normal.

Hypnotics, sedatives, analgesics, and anticonvulsants. The opiates and synthetic narcotics have been considered separately. The effects of anesthetic doses of bar-

biturates have also been previously discussed. In semi-narcotic doses like those employed in narcosynthesis or in sedative doses, thiopental, amytal, and phenobarbital are without effects on cerebral circulatory functions in man (205, 253). Bromides administered intravenously exert no obvious influence on pial vascular diameters (361). Indeed, there is no evidence that any of the common hypnotic or sedative drugs in doses less than required to produce unconsciousness have any significant effects on cerebral circulation and metabolism.

Few studies have been reported on the effects of the non-narcotic analgesic and antipyretic drugs. Acetanilid (Acetanilid, U.S.P.; Antifebrin®; Monoacetylaniline) has been found to cause negligible change in the caliber of the pial vessels (360, 361). It is unlikely that any of these agents in their usual therapeutic doses influence the cerebral circulation.

Kennedy and his coworkers (187) have studied the effects of the chronic administration of therapeutic doses of the anticonvulsant agent, diphenylhydantoin [Diphenylhydantoin Sodium (Phenytoin Sodium), U.S.P.; Dilantin Sodium®], in epileptic children. Unlike the results obtained in adult epileptics (123, 143), cerebral blood flow during the interseizure period was significantly reduced in these children before treatment. Effective anticonvulsant therapy with diphenylhydantoin restored the cerebral circulation to normal. The mechanism of the effect is obscure.

2. Central nervous system excitants. Convulsant drugs. Early qualitative observations on the effects of convulsant drugs have been contradictory. Strychnine has been reported to be a cerebral vasodilator because of increases in the diameters of the superficial cortical vessels following its topical application (98) and a vasoconstrictor because of a reduction in brain volume following its intravenous administration (213). Finesinger and Cobb (93) found no consistent effects of convulsant doses of absinth, homocamfin (Cyclosal; Hexeton; 5-isopropyl-3-methyl-2-cyclohexen-1-one), monobromated camphor (Camphor Monobromated, N.F.; 3-bromocamphor) and picrotoxin (Picrotoxin, U.S.P.) on the pial arteries, but Gibbs (121), employing the thermoelectric flow recorder, found with comparable doses of the same agents increases in blood flow in the parietal cortex before and especially during the convulsions followed by a fall during the postconvulsive period to less than the control level. Pentamethylenetetrazol [Pentylenetetrazol (Pentamethylenetetrazol) U.S.P.; Metrazol®; Cardiazol; Leptazol; 1,5-pentamethylenetetrazol] has been reported to reduce arterial inflow and venous outflow and to cause a severe and prolonged cerebral anemia in association with its convulsant action in the anesthetized rabbit (226), to dilate pial vessels independently of changes in blood pressure, respiration, or convulsive activity in the anesthetized cat and monkey (107), and to have negligible effects on the pial vessels of normal unanesthetized animals (360). The discrepancies in these results probably reflect the contamination of the true drug action by numerous other factors, such as the type and depth of anesthesia, the blood respiratory gas tensions, the arterial blood pressure, the timing of the observation with respect to the convulsions, as well as the unreliability of some of the methods employed.

The actions of convulsant drugs on the cerebral circulation are probably best

described by the studies of Schmidt and his coworkers (73, 339), who employed the bubble-flow meter technique in lightly anesthetized monkeys. Cerebral blood flow and oxygen consumption invariably rose during the convulsions produced by intravenous or intracarotid injections of Metrazol, picrotoxin, and nikethamide (Nikethamide, U.S.P.; Coramine®; N,N-diethylnicotinamide). Following the convulsions cerebral blood flow, metabolic rate, and functional activity, as judged by reflex activity, were all markedly reduced. When no convulsions occurred, the same or even larger doses failed to alter blood flow or metabolic rate, indicating that the blood flow changes resulted from the convulsant activity and not the direct action of the drugs on the cerebral blood vessels. Geiger and Magnes (118) have observed similar increases in cerebral blood flow and oxygen consumption during the convulsions produced by strychnine as well as Metrazol.

The increase in cerebral blood flow elicited by these drugs is apparently mediated by the chemical effects of the increased cerebral metabolic rate during the convulsions. Polarographic studies with the oxygen electrode have demonstrated a fall in cerebral tissue pO_2 during convulsions produced by these drugs or other means (65, 66). A fall in cerebral tissue pH which precedes the increase in blood flow has also been observed during Metrazol convulsions (181). In the absence of convulsions, there is no increase in cerebral metabolic rate (339), no fall in tissue pO_2 (65), and, therefore, no rise in cerebral blood flow (339).

The increase in cerebral blood flow, when it occurs, is less than proportional to the increased metabolic demand (339). For this reason cerebral pO_2 falls and may reach remarkably low levels during convulsions (65). The therapeutic use of analeptic drugs for stimulation of a depressed central nervous system may, therefore, be quite hazardous. If cerebral metabolic demand is stimulated beyond the ability of the circulation to meet it, then the relative cerebral anoxia which follows may cause even further depression. This is probably the basis of the secondary depression of cerebral functional activity, oxygen consumption, and blood flow which Schmidt *et al.* (339) observed following the convulsions produced by analeptic drugs. If the nervous tissues are already depressed because of a tissue anoxia, and particularly if it is the result of a primary circulatory insufficiency, as, for example, in secondary shock, then the secondary depression may be expected to be all the greater. Therefore, since it is unlikely that analeptic drugs can stimulate the nervous system without increasing its metabolic rate (339), their clinical use in such cases is probably contraindicated. On the other hand, when the cause of the depression is not tissue ischemia or anoxia but drug intoxication as, for example, in barbiturate poisoning, then the nervous tissues may be able to withstand the temporary reduction in oxygen tension which attends the stimulant action of the analeptic drugs. They may then be helpful if used cautiously and only in conjunction with effective measures to maintain systemic circulatory and respiratory functions so that cerebral blood flow and oxygen supply do not fall too far behind the metabolic demand.

Ehrmantraut and his coworkers (78) have studied the effects of the analeptic drug, methylphenidate hydrochloride (Ritalin®), on the cerebral circulation in man by means of the nitrous oxide method. In intravenous doses of 10–30 mg,

it failed to alter any of the cerebral circulatory or metabolic functions when given alone or following sedative doses of promazine although it was reported to reverse the clinically depressant effects of the latter.

Xanthines. The xanthine derivatives, caffeine (1,3,7-trimethylxanthine) and theophylline (1,3-dimethylxanthine), are often employed clinically for their central nervous stimulant action. On the basis of early qualitative studies in animals, they have also been considered to be cerebral vasodilators (337, 399), but the numerous reports of such action have been neither impressive nor consistent. Thus, intravenous or local administration of caffeine in less than convulsant doses has been reported to dilate pial arteries in cats under amytal anesthesia, but when the vessels are already dilated by ether anesthesia, intravenous caffeine causes a mild temporary constriction often followed by a dilatation (92). Convulsant doses of caffeine have also been reported to cause an initial pial arterial constriction followed by a dilatation during the convulsion (93); corresponding changes in parietal cortical blood flow, as indicated by the thermoelectric flow recorder, have been reported to accompany convulsant doses of caffeine in the anesthetized cat (121). Most animal studies, however, employing thermoelectric techniques have indicated that caffeine administered intravenously in less than convulsant doses increases cerebral blood flow (289, 338, 340, 341). Various soluble preparations of theophylline (281) have been found to increase internal carotid blood flow in the dog even more so than caffeine; of the various compounds added to theophylline to render it water-soluble, isopropanolamine and diethanolamine were without effect, but ethylene diamine also increased the flow (281). Blood flow changes in the internal carotid artery of the dog may, however, reflect more the effects in the extracranial than in the cerebral circulation because of the extensive anastomoses between them (15). In fact, Schmidt and Hendrix (338) obtained evidence by means of thermocouple methods of far greater increases in extracranial than in intracranial blood flow following intravenous or intracarotid injections of caffeine. However, caffeine has been observed to increase carotid inflow to the isolated cerebral circulation of the rabbit (338) where the anatomical problem is not so great. In quantitative studies in the monkey by means of the bubble-flow meter technique, Dumke and Schmidt (73) found intravenous administration of caffeine to cause only slight and inconstant increases in cerebral blood flow; the effects of theophylline ethylenediamine (Aminophylline®) were even less impressive. When injected directly into the carotid artery, however, both raised cerebral blood flow approximately 60%. The fact that increased cerebral blood flow following xanthine administration in animals has often been observed in the presence of a fall in arterial blood pressure (281, 289, 338) and a rise in cerebrospinal fluid pressure (92, 289) suggests that cerebral vasodilatation occurs. Indeed, the rise in cerebrospinal fluid pressure is itself secondary to the cerebral vasodilatation and increased blood flow and also to an enlargement of brain volume which has been reported to follow caffeine administration in dogs and cats (213).

The results of studies in man have been altogether different. The intravenous administration of clinically therapeutic doses of caffeine sodium benzoate was

found by Gibbs and his associates (124) to lower internal jugular venous blood flow as indicated by the thermoelectric flow recorder. Similar effects in response to both caffeine and theophylline have been repeatedly observed in quantitative studies employing the nitrous oxide technique. Wechsler *et al.* (388) found the intravenous administration of Aminophylline in the usual therapeutic dose, 0.5 g, to raise cerebral vascular resistance and to lower the cerebral blood flow approximately 25%. Arterial blood pressure and cerebral metabolic rate were unaltered although in a few cases who responded to the drug with anxiety, tachycardia, and palpitation cerebral oxygen consumption was markedly elevated. The fall in internal jugular oxygen content which resulted from the combination of a reduced blood flow and undiminished metabolic rate was so great as to suggest to these workers the occurrence of a true cerebral anoxia. Arterial pCO_2 was also reduced significantly in these studies because of an associated hyperventilation, but the change was insufficient to explain the degree of cerebral vasoconstriction which must, therefore, be attributed to a direct action of the drug. Similar results have been obtained with Aminophylline in patients with cardiac failure with and without Cheyne-Stokes respiration (265), in patients with hypertension headaches (272), and in elderly normotensive and hypertensive persons (86). Almost the same effects have been observed with comparable intravenous doses of caffeine sodium benzoate in patients with brain tumor (350) or hypertension headaches (272); although a significant rise in blood pressure in these studies prevented as great a reduction in cerebral blood flow, the degree of cerebral vasoconstriction was comparable to that observed with Aminophylline (265, 272, 388). As has been observed in other studies in man (68, 144, 237), cerebrospinal fluid pressure in the patients with hypertension headaches (272) was reduced by both drugs, and the degree of reduction correlated well with the depression in cerebral blood flow and with the relief of headache. Symptomatic improvement was dramatic with both drugs, particularly Aminophylline. Since reduction in cerebrospinal fluid pressure alone by other means does not accomplish such improvement in hypertension headaches (349), the beneficial effect of the xanthines may result from their direct cerebral vasoconstrictor action and its consequent relief of vascular distention.

The results of animal studies notwithstanding, it is clear that Aminophylline and caffeine, so often employed clinically for cerebral vasodilatation, are, in fact, potent cerebral vasoconstrictors when administered in the usual manner and dosage in man. Furthermore, their excitant action on the central nervous system is not related to a stimulation of cerebral metabolic rate. Moyer *et al.* (265) have suggested that they arrest Cheyne-Stokes respiration by stimulating the respiratory center either directly or secondarily through the elevation in medullary pCO_2 resulting from the reduction in cerebral blood flow. Recently, however, Moyer and his associates (270) have found the newly introduced soluble salt of theophylline, parephylline (Soluphylline®; R-3588; diethylaminoethyl theophylline hydrochloride), to have negligible effects on cerebral hemodynamics and cerebrospinal fluid pressure in hypertensive patients when ad-

ministered intravenously in the usual therapeutic dose, 0.5 g. Also unlike the effects of the other xanthines, it caused a 25% increase in cerebral oxygen consumption. Since this drug is equally capable of relieving Cheyne-Stokes respiration without reducing cerebral blood flow, Moyer and his coworkers (270) have concluded that its mode of action, as well as that of the other xanthines, is by direct stimulation of the respiratory center rather than by effects secondary to an altered cerebral circulation. However, the alternative hypothesis has by no means been excluded, for, in view of the accelerated metabolic rate without a concomitant increase in cerebral blood flow, there still remains the possibility of a relative ischemia, anoxia, and/or carbon dioxide accumulation in the respiratory center.

3. Psychotropic drugs. Considerable interest has recently been aroused by a number of drugs which produce profound alterations in psychological functions (193). Some, the so-called psychotomimetic drugs, cause disturbances in mental processes which simulate those observed in naturally occurring psychoses. Others, the psychotherapeutic drugs, are reputed to cause a unique type of sedation, popularly called tranquilization, and have proved useful in the treatment of psychiatric disease. These two groups of drugs do not necessarily represent two chemically homogeneous classes of compounds; indeed, many of them are chemically unrelated to one another. However, because they alter mental functions, they presumably act upon the central nervous system, and since their actions are presently considered by many as unique from those of other pharmacological agents, they are considered here apart from any of the other centrally acting drugs.

Psychotomimetic drugs. Mescaline (3,4,5-trimethoxyphenylethylamine), the active alkaloid of mescal, is known for its ability to cause psychic aberrations and vivid visual hallucinations in man (148, 172, 173). Its effects on cerebral circulation and metabolism have been studied by Ecker and Polis (77) in the unanesthetized rhesus monkey by means of the nitrous oxide method. In doses of 40 mg/kg of body weight, approximately ten times the amount required to produce psychotomimetic symptoms in man, mescaline more than doubled the cerebral blood flow. An approximately proportionate rise in cerebral oxygen consumption lacked statistical significance in the small series studied, but when combined with an observed significant increase in cerebral carbohydrate utilization, it suggests an acceleration of cerebral metabolic rate by mescaline. The effects of mescaline on cerebral circulatory and metabolic functions are, therefore, similar to those of epinephrine (206) which it resembles chemically. Since data on arterial blood pressure and cerebrovascular resistance, as well as other pertinent factors, were not presented in the report (77), the mechanism of the cerebral blood flow rise is not entirely clear. To some extent, it undoubtedy represents the chemical adjustment of the cerebral circulation to the increased metabolic rate. The effects of *d*-lysergic acid diethylamide (LSD-25), the partially synthesized derivative of ergot which in extremely minute doses produces similar psychic and perceptual disturbances (173, 303, 372), have been studied in normal and schizophrenic man (365). Although the doses employed, 100–120

μg administered intravenously, were sufficient to produce the characteristic LSD-25 psychosis as well as a slight pressor effect and hemoconcentration, there were no detectable changes in cerebral circulation and metabolism in either group. In the isolated unanesthetized cat head (encéphale isolé), Ingvar and Söderberg (177) have found LSD-25 to increase cerebral blood flow, but the doses required were more than twenty times those employed in man.

Psychotherapeutic drugs. The effects of acute doses of the phenothiazine derivatives, chlorpromazine [Chlorpromazine hydrochloride, U.S.P.: Thorazine hydrochloride®; Largactil®; 2-chloro-10-(3-dimethylaminopropyl) phenothiazine hydrochloride] and promazine (Sparine®), two currently popular tranquilizing drugs, have been studied in man. In intramuscular or intravenous doses sufficient to produce sedative and even soporific effects, these drugs are without any noteworthy actions on cerebral circulatory and metabolic functions (5, 78, 82, 262). When given intravenously, chlorpromazine frequently depresses mean arterial blood pressure (5, 82, 262), and then secondary to the hypotension cerebral blood flow may be slightly reduced (262). Usually, however, there is a concomitant relaxation of cerebrovascular tone which compensates for the effects of the hypotension and maintains the cerebral blood flow at the control level (5, 82). The reduction in cerebrovascular resistance is not attributable to a cerebral vasodilator action of the drug but is a non-specific response to an acute fall in arterial blood pressure (99, 197, 212). The combination of tranquilizing or anti-emetic doses of chlorpromazine and intoxicating doses of ethyl alcohol is no more effective in altering cerebral circulation than either drug alone (82). Similarly, promazine and the analeptic, methylphenidate, both individually and in combination, have no effect on cerebral hemodynamics and metabolism (78). The Rauwolfia alkaloid, reserpine (Serpasil®), employed clinically for its antihypertensive properties as well as for its tranquilizing action, has also been found to be devoid of any actions on cerebral blood flow or metabolic rate. No effects were observed following the daily oral administration of 4 mg for at least a month until maximum blood pressure depression and moderate sedation occurred (208, 210) or after its acute intravenous administration in doses sufficient to lower arterial blood pressure approximately 20% (154). The effects of the hypotension were balanced by a reduction in cerebrovascular resistance maintaining a constancy of blood flow.

The psychological and mental changes induced by psychotropic drugs, including the production of psychotic symptoms or their relief by sedation and tranquilization, are, therefore, like those associated with barbiturate sedation (205) or schizophrenia (205); they are all without effect on the circulation and metabolic rate of the brain as a whole. The possibility of local circulatory and metabolic changes in individual structures of the brain too small to be detected in studies of the brain as a whole has, of course, not been excluded.

D. Autonomic Drugs

1. Sympathomimetic drugs. Of the various sympathomimetic drugs, the naturally occurring adrenal medullary amines have been most extensively studied

as regards their actions on the cerebral circulation. Most investigations have employed the natural adrenal medullary hormone. This preparation, for example, Epinephrine, U.S.P. (Adrenaline, B.P.), contains appreciable amounts of *l*-norepinephrine (11, 134, 380), a pressor amine with remarkably different pharmacological actions from those of pure epinephrine [Synthetic epinephrine; Suprarenin®; *l*-β-(3,4-dihydroxyphenyl)-α-methylaminoethanol] on numerous circulatory and metabolic functions (12, 21, 71, 133, 135, 244, 255) including those of the brain (206, 345). Despite the quantities of *l*-norepinephrine contained in it, however, natural or U.S.P. grade epinephrine has not been found to elicit either cerebral (345) or general (134) hemodynamic and metabolic responses distinguishable from those of pure *l*-epinephrine. The latter two preparations will, therefore, be considered together, but pure *l*-norepinephrine will be discussed separately. Although it was not always stated, it has been assumed that the natural impure preparation of epinephrine was employed in all but the most recent studies of the cerebral circulation because of the probable unavailability of the pure form. When it is clear that synthetic epinephrine was employed, as in some recent quantitative studies in man (206, 345), it will be so specified in the following discussion; otherwise it is to be assumed that the natural or U.S.P. grade of epinephrine was used.

Epinephrine. Animal studies on the effects of epinephrine on the cerebral circulation have yielded conflicting results. Topical application of epinephrine to the brain surface has occasionally been reported to exert no effect on superficial cerebral vessels (98), but most studies have found it to constrict the pial arteries (100, 104, 109, 399). Intracarotid injection has been reported in some studies to constrict pial vessels (109, 399) and decrease blood flow in the arterial supply of the presumably isolated cerebral circulation (33, 73, 185); in others, it caused pial vasodilatation (104), increased blood flow in various areas of the brain studied by locally placed thermocouples (289, 338), and a rise in blood flow in the isolated cerebral arterial supply (338). Following intravenous administration it has been reported to dilate (100, 104, 109), constrict (100), or have no effect (98) on pial vessels, to increase brain volume (98, 213) and cerebrospinal fluid pressure (289), to raise (289, 340), lower (91), or cause an increase followed by a decrease (332) in cerebral or spinal cord blood flow as indicated by thermocouples in the tissues, and to increase the arterial inflow to the isolated cerebral circulation (33, 73, 185, 339). To some extent this remarkable variability in results can be explained by differences in dosage and means of administration and their effects on blood pressure. Generally, when blood pressure was unchanged, most often seen following topical application or the intra-arterial injection of small doses, the action of epinephrine was to constrict cerebral vessels and reduce blood flow (33, 73, 100, 104, 109, 185, 213, 399). Increases in blood pressure, which usually occurred with intravenous administration, were associated with opposite effects (33, 73, 100, 104, 109, 185, 213, 339, 399), and then often as the blood pressure returned toward normal, it was accompanied by a secondary vasoconstriction (73, 332, 399). The significance of the blood pressure change is even more apparent in those studies in which it was experi-

mentally controlled. Fog (100) observed that intravenous injections of epinephrine invariably constricted pial arteries when blood pressure was artificially maintained constant and dilated them when it was allowed to rise; Finesinger and Putnam (95) noted comparable effects on the pial arteries and blood flow of the perfused cat or monkey brain when epinephrine was added to the perfusate. These animal studies suggest that epinephrine has a weak cerebral vasoconstrictor action which is readily overcome by the passive dilatation of the vessels or, perhaps, other effects associated with a rise in systemic blood pressure. That its vasoconstrictor action in the brain is weaker than in extracranial vascular beds is indicated by the fact that in the latter areas vasoconstriction always follows epinephrine administration, regardless of changes in arterial blood pressure (95, 338).

Studies in unanesthetized man have failed to demonstrate any cerebral vasoconstrictor action of epinephrine. By means of the thermoelectric flow recorder inserted in the internal jugular vein, Gibbs *et al.* (124) obtained qualitative evidence of marked and parallel rises in cerebral blood flow and arterial blood pressure following intravenous pressor doses of epinephrine. However, smaller doses which failed to raise arterial blood pressure or even lowered it also caused definite though lesser increases in blood flow indicating that cerebral vasodilatation had occurred. Similar results have been obtained in quantitative human studies employing the nitrous oxide method. The continuous intravenous infusion of synthetic epinephrine in sufficient amounts to cause a sustained 20% rise in mean arterial blood pressure has been found by King and his coworkers (206) to cause approximately proportionate increases in cerebral blood flow and oxygen consumption without any change in cerebrovascular resistance. There is, therefore, no evidence of any cerebral vascular constriction or dilatation under these conditions. The possibility that chemical vasodilator effects of the increased metabolic rate may have obscured a vasoconstrictor action of the drug is excluded by changes in oxygen content and pCO_2 of the cerebral venous blood which indicate that the cerebral blood flow was more than adequate to prevent the accumulation of vasodilator products of metabolism. However, the fact that cerebrovascular resistance did not fall is evidence of a slight increase in cerebrovascular tone, sufficient at least to prevent passive dilatation by the elevated systemic blood pressure. Sensenbach and coworkers (345) have studied in man the comparative effects of intramuscular injections of synthetic *l*-epinephrine and U.S.P. epinephrine in oil. In doses between 0.6 and 1.4 mg, both preparations yielded identical results, a very slight but significant decrease in mean arterial blood pressure and no changes whatsoever in cerebral hemodynamics or metabolism. The discrepancy between their results and those of King *et al.* (206), as regards the effects on hemodynamic functions, they attributed to the differences in dose and mode of administration. However, for obscure reasons, they declined to explain the difference in cerebral metabolic effects on the same basis and instead interpreted their findings as evidence that "cerebral metabolism normally functions at nearly its maximum rate". This interpretation is no more justified than a similar one regarding blood pressure which was also not

elevated in their studies. The obvious explanation lies in the difference in the levels of circulating epinephrine following the two modes of administration. In low concentrations epinephrine is without effect; in high concentrations, sufficient, for example, to raise blood pressure approximately 20%, it increases the cerebral metabolic rate, a finding consistent with its known calorigenic actions (146).

Most of the evidence supports the following summary concerning the action of epinephrine on the cerebral circulation. In animals it appears to have a slight direct cerebral vasoconstrictor effect, but this action is so weak that it is readily overcome either by the passive dilatation secondary to a rise in systemic blood pressure (399) or the chemical vasodilator effects of an increased cerebral metabolic rate which occurs with pressor doses (206). Therefore, when blood pressure is unchanged, cerebral blood flow is also unchanged or slightly reduced; when blood pressure is increased, cerebral blood flow follows it passively. In man there is little evidence of any noteworthy direct action and none to indicate a constrictor effect on the cerebral vessels. Less than pressor doses of epinephrine probably have little or no effect on cerebral circulation and metabolism (345) although there is some contrary qualitative evidence to indicate cerebral vasodilatation and increased blood flow following its intravenous administration (124). With pressor doses, however, cerebral blood flow is increased proportionately to the systemic blood pressure; cerebrovascular resistance remains unchanged (124, 206). The compensatory cerebral vasoconstriction usually accompanying a rise in blood pressure (99) is probably prevented by the effects of the increased cerebral metabolic rate (206).

l-Norepinephrine [Levarterenol Bitartrate, U.S.P.; *l*-Arterenol; *l*-Noradrenaline; Levophed®; *l*-2-amino-1-(3,4-dihydroxyphenyl)-ethanol]: Unlike the studies of epinephrine, those of *l*-norepinephrine have been few but clear and consistent. In normotensive man, pressor doses of *l*-arterenol, whether administered intramuscularly in oil (345) or by continuous intravenous infusion (206, 268), constrict cerebral vessels and raise the cerebrovascular resistance more greatly than the mean arterial blood pressure resulting in a moderate reduction in the blood flow to the brain. Cerebral metabolism is unaffected. These cerebral hemodynamic changes under conditions in which cardiac output is negligibly affected (135) suggests that in normotensive individuals *l*-norepinephrine redistributes the output of the heart in a manner less favorable to the brain. If the same situation were to obtain in hypotension in which cerebral blood flow is already reduced (87, 97, 260, 267, 268, 373), then, despite its pressor effect, administration of the drug could be detrimental in those clinical hypotensive states like secondary shock in which its therapeutic use has been recommended (31, 218, 236, 257, 269). Actually, however, it appears to have the reverse effect in hypotension. In man during the hypotension induced by ganglionic blocking agents, restoration of the blood pressure by *l*-norepinephrine infusion does raise cerebrovascular resistance also, but disproportionately less than arterial blood pressure so that cerebral blood flow increases toward normal levels (267, 268). Also in experimental hemorrhagic shock in dogs, it has been found to increase

both blood flow and oxygen tension of the brain during its pressor action (113); simultaneously, coronary and adrenal blood flow are also increased, renal blood flow is reduced and that of the liver unchanged.

The differential effects of *l*-norepinephrine on the cerebral circulation in the normal and hypotensive states cannot be explained simply by its pressor action since it raises blood pressure in both instances; neither can they be attributed to a lesser cerebral vasoconstrictor action during hypotension. The explanation lies in a difference in the mechanisms of the pressor response and its quantitative relationship to the change in cerebrovascular resistance. In the normal state the vasoconstrictor effect of the drug on most vascular beds is antagonized to some extent by the response of the pressoreceptor reflexes to the rise in blood pressure (135, 206, 345). The cerebral vessels do not appear to be under the influence of these reflexes (337, 399) and are, therefore, more greatly constricted than the over-all circulatory bed. Since cardiac output is not increased (135), cerebrovascular resistance is raised disproportionately more than arterial blood pressure, and cerebral blood flow falls. During hypotension induced by ganglionic blockade, however, the antagonistic action of the pressoreceptor reflexes in the peripheral vascular beds is interrupted. Constriction of the cerebral vasculature by the drug is then no greater than elsewhere, indeed less, because of the opposition of the chemical homeostatic mechanisms. These are already more actively tending to produce cerebral vasodilatation in response to the reduction in blood flow by the hypotension (97, 260, 267, 268). Such mechanisms are not operating effectively in most other vascular beds because, unlike the cerebral vasculature, they have already been excessively dilated by the ganglionic blockade. *l*-Norepinephrine then increases total peripheral vascular resistance and, therefore, arterial blood pressure to a greater degree than the cerebrovascular resistance, thus raising the cerebral blood flow.

The mechanism of action during the hypotension arising from secondary shock is less clear because of a paucity of data. Elevation of cerebral blood flow by pressor doses of *l*-norepinephrine has been reported in dogs in hemorrhagic shock (113). It is likely that this occurs when the pressor response results not only from peripheral vasoconstriction but also from a rise in cardiac output which *l*-norepinephrine has been observed to cause in certain stages of hemorrhagic shock in dogs (111, 113, 131). The cardiac output may also be preferentially redistributed in favor of the brain and heart (113).

Miscellaneous sympathomimetic drugs. The synthetic vasopressor amine, Metaraminol Bitartrate, N.N.D. [Aramine Bitartrate®; *l*-1-(*m*-hydroxyphenyl)-2-amino-1-propanol hydrogen *d*-tartrate], has effects on the cerebral circulation in normotensive and hypotensive man which are almost indistinguishable from those of equivalent pressor doses of *l*-norepinephrine (268). On the other hand, *Mephentermine Sulfate, U.S.P.* (Wyamine Sulfate®; N,α,α-trimethylphenethylamine sulfate), another synthetic sympathomimetic amine, when infused intravenously in normal man in doses sufficient to cause a moderate rise in arterial blood pressure, markedly raises the cerebral metabolic rate but apparently has

only a minimal acceleratory effect on cerebral blood flow and none on the vascular resistance (302). Its actions, therefore, resemble somewhat those of epinephrine.

Qualitative evidence of increases in cerebral cortical blood flow following intravenous injections of pressor doses of Phenylephrine Hydrochloride, U.S.P. [Neo-Synephrine®; *l*-1-(*m*-hydroxyphenyl)-2-methylaminoethanol hydrochloride] has been obtained in anesthetized dogs (167). Similar effects following intravenous (289) or intracarotid (338) administration of ephedrine (Ephedrine Sulfate, U.S.P.) have been reported in cats even at times when extracranial blood flow was simultaneously reduced (338). These responses do not necessarily indicate a cerebral vasodilator action of these drugs; they may reflect only a passive response of the cerebral circulation to a rise in systemic blood pressure and/or the effects of an increased cerebral metabolic rate. In dogs in shock Hydroxyamphetamine Hydrobromide, U.S.P. (Paredrine® Hydrobromide; *p*-hydroxy-α-methylphenethylamine hydrobromide) appears to have no effect on the cerebral circulation, whether or not systemic blood pressure is raised (112).

Amphetamine (Amphetamine Sulfate, U.S.P.: Benzedrine Sulfate®, N.N.R.; *dl*-α-methylphenethylamine sulfate) is also without notable effect on the cerebral circulation. In the anesthetized monkey, intra-arterial injections have been observed to reduce blood flow moderately at times when arterial blood pressure is unchanged, indicating some degree of cerebral vasoconstriction (73); intravenous doses as high as 5 mg were without consistent effects on both cerebral blood flow and metabolism (339). In man, no effects on cerebral circulatory and metabolic functions have been observed following the intravenous administration of 20 mg of amphetamine sulfate to normal subjects in whom it raised arterial blood pressure (3) or to patients in a depressed state of consciousness (350).

2. Parasympathomimetic drugs. Although the cerebral circulation is probably devoid of any significant parasympathetic nervous control, the choline esters are apparently capable of dilating cerebral vessels (337, 338, 399). Intravenous injections of acetylcholine in cats have been observed to dilate pial vessels (398), increase brain volume (213), and raise cerebrospinal fluid pressure (289). Generally an associated fall in blood pressure occurs which temporarily lowers the cerebral blood flow despite the cerebral vasodilatation (289, 398, 399). However, as indicated by thermocouple techniques (242, 289, 332, 340, 341, 399), the fall in blood flow is transient; it may rise to considerable levels when the blood pressure returns to normal. Following intracarotid injections, acetylcholine increases blood flow in the parietal cortex of the cat and rabbit and in the isolated cerebral arterial supply of the latter, even during a transient, moderate fall in arterial blood pressure (338). Similar actions have been ascribed to acetyl-β-methylcholine (Methacholine Chloride, U.S.P.; Mecholyl Chloride®). Injected intravenously it has been reported to cause a slightly less, but more prolonged, increase in blood flow in the parietal cortex of the cat than does acetylcholine (289). When injected intra-arterially, methacholine appears to be the

more potent cerebral vasodilator (338). Both drugs are more effective in increasing extracerebral than intracranial blood flow (338). In quantitative studies in the monkey Dumke and Schmidt (73) confirmed the cerebral vasodilator properties of methacholine; injected intra-arterially in 0.1 μg doses, it invariably caused a moderate increase in cerebral blood flow simultaneously with a slight depression of arterial blood pressure. The effects were brief, however, complete recovery occurring within three minutes.

The choline esters are, therefore, capable of dilating cerebral vessels as they do other vascular beds. Their action here, too, can be blocked by atropine (289, 338). Since the cerebral vasodilatation results from their direct action and is not simply a secondary adjustment of the cerebral circulation to the hypotension, they cause an actual increase in cerebral blood flow. However, because of the transient nature of their action (73, 289, 338), their effects are of limited usefulness and importance.

There are few reliable data on the effects of other types of parasympathomimetic drugs. Pilocarpine (Pilocarpine Nitrate, U.S.P.) has been reported to cause a negligible increase in blood flow in the cat brain perfused at constant pressure (95) and to raise cerebrospinal fluid pressure despite a fall in systemic blood pressure (183). Information on the effects of the cholinesterase inhibitors is even more scanty, but since parasympathetic nervous control of the cerebral circulation does not seem to be functionally important (337, 338, 399), specific actions on their part are unlikely. They probably do exert some influence on the cerebral circulation but secondarily to their general systemic effects, particularly those on arterial blood pressure.

3. Autonomic blocking agents. Although the cerebral vessels respond to the exogenous administration of chemical agents which normally mediate autonomic nervous functions, there is little evidence of any physiologically significant tonic autonomic influences on the cerebral circulation (191, 337, 338, 399). There is, therefore, little reason to expect any primary cerebral circulatory effects of autonomic blocking agents, but since they do profoundly alter systemic circulatory hemodynamics, they may secondarily influence the cerebral circulation. Furthermore, some of these drugs have other actions in addition to autonomic blockade. All modes of action of these drugs as they pertain to the cerebral circulation will be considered here, and their inclusion in this section does not necessarily indicate that autonomic blockade is the mechanism of their action upon the cerebral circulation. They may be included here simply because this action best identifies their pharmacological class or governs their clinical use.

a. Adrenergic blocking agents. Ergot alkaloids. The natural ergot alkaloids have in addition to their adrenolytic properties the ability to stimulate smooth muscle and constrict blood vessels, but despite these actions, there is no convincing evidence that in reasonable doses they exert any influence on the cerebral circulation. Ergotamine tartrate (Ergotamine Tartrate, U.S.P.; Gynergen®) has been found to prevent the minor degree of pial arterial constriction produced by electrical stimulation of the cervical sympathetic nerves in cats (103); alone it has only slight and variable effects on pial vessels while

constricting those of the dura and skin (299). Large doses of ergotoxine, a naturally occurring mixture of ergocornine, ergocristine, and ergocryptine, have been reported to reduce brain volume presumably by cerebral vasoconstriction but to reverse the normally observed cerebral vasoconstrictor effects of cervical sympathetic stimulation or small doses of epinephrine (213). Blood flow studies by means of thermocouples placed in brain tissue have yielded variable results. Intravenously administered ergotoxine in the cat has been observed to increase hypothalamic blood flow along with systemic blood pressure (332). Intracarotid injections of ergotamine were found by Schmidt and Hendrix (338) to have variable effects in both parietal cortex and extracranial muscle of the cat which seemed to be related to the dose; small doses increased, and large doses decreased the blood flow in both areas. Since no striking changes in blood pressure occurred, the results were interpreted as evidence of cerebral vasodilatation and vasoconstriction, respectively. The changes in the extracranial tissues were usually more marked than in the brain. In similar experiments in the rabbit, ergotamine had no noteworthy effects (242, 338). In man Lennox and his coworkers (230) obtained by means of a thermoelectric flow recorder in the internal jugular vein qualitative evidence that therapeutic doses of ergotamine tartrate increase cerebral blood flow. The only quantitative studies of the natural ergot alkaloids are the bubble-flow meter experiments of Dumke and Schmidt (73) in the anesthetized monkey. Small intra-arterial doses of ergotamine tartrate were without any effect; 0.1 mg injected intra-arterially markedly reduced both cerebral blood flow and arterial blood pressure, the former somewhat more profoundly suggesting a slight degree of cerebral vasoconstriction. It is apparent that no consistent action on the cerebral vessels can be attributed to the natural ergot alkaloids. They may, perhaps, dilate in small doses and constrict in large doses, but cerebral blood flow usually follows the change in systemic blood pressure (399).

It is unlikely that the efficacy of ergotamine in the relief of migraine headache is related to its sympathocolytic properties or to its action on the intracranial circulation. Graham and Wolff (142) found therapeutic doses of ergotamine tartrate to constrict the extracranial arteries which were distended during a migraine attack and to reduce the amplitude of the pulsations within them. The retinal veins were also slightly constricted, but the retinal arteries which are derived like many of the cerebral arteries from the internal carotid artery were unaffected. Twenty to twenty-five per cent elevations of the cerebrospinal fluid pressure were caused irregularly by the drug in both normal subjects and in patients during a migraine episode. The termination of the headache by ergotamine did not correlate with any of the observed changes other than the constriction and reduced pulsations in the extracranial arteries. On the basis of these and similar findings, Wolff and his associates (400) have suggested that the headache of migraine results from the distention of the branches of the external carotid artery, all extracerebral vessels in man, and that ergotamine relieves the headache by constricting them and reducing the pulsations within them.

Studies on the effects of the dihydrogenated ergot alkaloids have led to more consistent results. Hafkenschiel *et al.* have determined the effects of intramuscular dihydroergocornine (DHO-180) in 0.3 to 0.5 mg doses on the cerebral hemodynamics and metabolism of normotensive subjects (149) and patients with essential hypertension (150). In both groups it caused a significant depression of arterial blood pressure, but cerebral blood flow was maintained almost unchanged because of a simultaneous reduction in cerebrovascular resistance. Cerebral oxygen consumption was unaltered in both groups. In a few patients studied by Abreu and his coworkers (2), there were suggestions of similar actions by dihydroergotamine.

The dihydrogenated derivatives of ergot are effective hypotensive agents by virtue of their ability to cause widespread vasodilatation (132, 149, 150, 278, 395). Because these effects occur following doses which are inadequate to cause adrenergic blockade, they have been attributed to a central depressant action of these drugs (13). The cerebral vessels are also dilated so that, despite the hypotension, cerebral blood flow is unimpaired. However, since the cerebral vessels are not under any demonstrable tonically active neurogenic influence, at least, none mediated via the stellate ganglion and cervical sympathetics (160, 315), it is unlikely that the mechanism of the cerebrovascular dilatation is the same as in other vascular beds. Taeschler and coworkers (377), who found evidence of a dilatation in the vertebral arterial inflow channels to the cat brain following Hydergine® (equal parts mixture of the methanesulfonates of dihydroergocornine, dihydroergocristine, and dihydroergocryptine) administration, attributed the response to either a direct action on cerebral vascular smooth muscle or a centrally mediated depressant effect on cerebrovascular tone. On the basis of the results obtained in man (2, 149, 150), it is unnecessary to invoke such mechanisms to explain the effects of the dihydrogenated ergot alkaloids on the cerebral circulation. They are not substantially different from those observed during reductions in arterial blood pressure achieved by means which are hardly likely to have direct effects on cerebral vessels, namely, differential spinal block (197), high spinal anesthesia (212), and thoracolumbar sympathectomy (353). The results of these procedures were almost identical to those obtained with dihydroergocornine (149, 150), except for a small reduction in cerebral blood flow observed following differential spinal block which was probably secondary to an associated hypocapnia presumably caused by hyperventilation. The cerebrovascular relaxation produced by the dihydrogenated ergot alkaloids may then well be a non-specific response to the hypotension mediated by the chemical mechanisms for cerebral homeostasis.

Imidazoline derivatives (Tolazoline and Phentolamine). In addition to their moderately effective sympathicolytic actions, these drugs are capable of producing direct peripheral vasodilatation (278). Their administration, even in doses insufficient to cause adrenergic blockade, results in hypotension and increased blood flow in a number of tissues, particularly the skin and muscles (4, 147, 221, 306, 383). There has been evidence of similar effects in the brain. Dilatation of pial vessels in cats (80) and retinal vessels in man (43) have been

observed following tolazoline (Tolazoline Hydrochloride, U.S.P.; Priscoline® Hydrochloride; Priscol® Hydrochloride; 2-benzyl-2-imidazoline hydrochloride) administration, and although there have also been negative findings (156), beneficial clinical effects of tolazoline in the treatment of vascular disease associated with signs of symptoms of cerebral ischemia have been reported (305, 306, 359). In patients with mitral stenosis, Dewar *et al.* (70) found the intravenous administration of 20–30 mg of tolazoline to raise cerebral blood flow 25% despite a slight but distinct fall in arterial blood pressure. The reduction in cerebrovascular resistance was, therefore, too great to represent simply a non-specific response to the hypotension; it indicated additional cerebral vasodilator effects which these investigators attributed to a histamine-like action of the drug (70). However, in similar studies, Scheinberg (319), Clarke (46), and their respective coworkers observed no significant changes in cerebral circulatory and metabolic functions following the same or even larger intravenous doses of tolazoline in patients with and without cerebral vascular disease. In fact, cerebral blood flow tended to be reduced. In view of the discrepancy in the results of such otherwise similar studies, it is unlikely that the action of tolazoline on the cerebral circulation is of sufficient prominence to be of clinical importance. Phentolamine [Phentolamine Hydrochloride, U.S.P.; Regitine® Hydrochloride, N.N.R.; C-7337; 2-(N′-*p*-tolyl-N′-*m*-hydroxyphenylaminoethyl) imidazoline hydrochloride] does not appear to have any more decisive effects on the cerebral circulation (26).

Dibenzyline. The β-haloalkylamines are more potent and specific adrenergic blocking agents than those previously considered (278). When one of them, Dibenzyline (phenoxybenzamine; N-phenoxyisopropyl,N-benzyl-β-chloroethylamine), was injected intravenously into normotensive subjects or hypertensive patients in doses which accomplish complete adrenergic blockade, arterial blood pressure was reduced, but the response of the cerebral circulation was no different from that occurring in any other type of induced hypotension (271). With moderate reductions of arterial blood pressure, cerebrovascular tone was reduced sufficiently to maintain a normal cerebral blood flow; with severe depression of blood pressure, relaxation of cerebrovascular tone was inadequate, and a fall in blood flow ensued. There was no evidence of any specific action on the cerebral circulation not attributable to the effects of a fall in arterial blood pressure. Indeed, since the cerebral vessels are apparently devoid of resting sympathetic nervous tone (160, 315), none was to be expected.

b. Drugs which block post-ganglionic cholinergic nervous functions. Experimental data on the responses of the cerebral circulation to drugs which inhibit structures innervated by post-ganglionic cholinergic nerves are scanty. In cats, atropine sulfate has been reported to block the cerebral vasodilator effect of acetylcholine administraton (289) and to prevent the slight vasodilatation produced by stimulation of the facial nerve near the geniculate ganglion (103). Since neither nervous mechanisms nor acetylcholine have been clearly implicated in the normal regulation of the cerebral circulation, these observations are probably of negligible relevance to the cerebral circulatory actions of atropine

alone. A cerebral vasodilator action has been attributed to atropine because it has been observed to raise cerebrospinal fluid pressure (183) and to increase the diameters of superficial cortical vessels (348) in animals, but there is no reliable evidence that atropine and other drugs in its class have any actions which significantly alter the circulation through the brain.

c. Ganglionic blocking agents. The cerebral circulatory effects of a wide variety of ganglionic blocking agents have been extensively studied, particularly in man. Among them have been hexamethonium [C6; hexamethylenebis(trimethylammonium) chloride or bromide] (59, 60, 69, 96, 97, 176, 209, 210, 260, 261, 267, 268, 293, 374), trimethaphan [Arfonad®; *d*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylenethiophanium *d*-camphor sulfonate] (267, 268), pendiomide [N,N,N′N′-3-pentamethyl-N-N′-diethyl-3-azopentylene-1,5-diammonium dibromide] (27, 28, 267, 268), and tetraethylammonium chloride [Etamon® Chloride, TEA Chloride] (29). A detailed discussion of each of them is unnecessary since all of them influence the cerebral circulation only indirectly and secondarily to their effects on arterial blood pressure. The changes induced in cerebral hemodynamics are dependent only on the degree of hypotension achieved, regardless of the particular drug or dose employed (268). With progressive reduction in arterial blood pressure, there is a parallel compensatory decrease in cerebrovascular resistance which over a wide range of blood pressure serves to maintain an adequate cerebral blood flow in the face of the hypotension. In many of the reported studies (29, 59, 69, 293, 374), mean arterial blood pressure was reduced 30 to 40% without a significant fall in cerebral blood flow or signs of cerebral hypoxia. Moyer (267, 268), Morris (260), and their respective coworkers found that significant reductions in cerebral blood flow and oxygen consumption and signs of cerebral hypoxia appeared in normotensive subjects when their mean arterial blood pressure was reduced to 55 to 60 mm Hg; infusions of pressor agents, such as norepinephrine or Aramine, then raised blood pressure and cerebral blood flow back toward normal levels. By means of a combination of hexamethonium and head-up tilting, Finnerty *et al.* (97) were able to lower arterial blood pressure so far that a cerebral blood flow rate adequate to maintain consciousness could no longer be maintained, and fainting occurred. The level of mean arterial blood pressure at which consciousness was lost varied between 29 and 89 mm Hg, depending on the degree of vascular disease. Normotensive subjects withstood lower levels of arterial blood pressure; in patients with postural hypotension or malignant hypertension, in whom the tolerance is less or the resting blood pressure is higher, the critical point occurred at a higher level. In all cases, however, consciousness was lost at approximately the same level of cerebral blood flow, approximately 30 to 35 ml/100 g of brain tissue per minute. In similar drug studies, Finnerty *et al.* (96) obtained evidence that compensatory changes in the cerebrovascular resistance can maintain the cerebral blood flow above the critical level until the cardiac output fails; the additional fall in arterial blood pressure at this point overwhelms the compensatory mechanisms and leads to cerebral ischemia.

The studies cited above were performed in more or less normal man (97, 260,

267, 268), anesthetized man (176), and patients with hypertension or vascular disease (27, 28, 29, 60, 69, 96, 97, 209, 210, 293); except for the differences in blood pressure levels at which cerebral ischemia occurred, the results were similar in all groups. The ganglionic blocking agents do alter the cerebral circulation but only secondarily to their effects on blood pressure. With moderate depressions of arterial blood pressure there is a compensatory reduction in cerebrovascular resistance which is adequate to maintain the cerebral blood flow. With more severe degrees of hypotension the compensatory mechanisms, which are probably chemical, may be inadequate, and signs of cerebral ischemia and unconsciousness may occur. Contrary evidence obtained in anesthetized dogs indicating that cerebral blood falls in direct proportion to the degree of hypotension induced by hexamethonium without any compensatory reduction in cerebrovascular tone is unconvincing (277). Their cerebral circulatory effects are, therefore, non-specific; they are like those observed during the hypotension induced by other means, for example, differential spinal sympathetic block (197) or high spinal anesthesia (212).

d. Nicotine and related drugs. Relatively little is known concerning the action of nicotine and other drugs of its class on cerebral circulatory and metabolic functions. Keller (185) has reported that lobeline in doses employed to produce respiratory stimulation increases internal carotid arterial blood flow in dogs. Since it is difficult to separate the cerebral from the extracerebral circulations in this animal, the relationship of this effect to cerebral blood flow is in doubt. Recently, Wechsler (386) has studied the effects of intravenous injections of 8 to 10 mg of nicotine base (administered as nicotine bitartrate) in normal human subjects by means of the nitrous oxide method and found them to stimulate the cerebral oxygen consumption approximately 30%. Probably as an adjustment to the increased metabolic rate, cerebrovascular resistance was decreased and cerebral blood flow increased despite the antagonistic vasoconstrictor effect of an associated hyperventilation and hypocapnia. Anxiety and nausea were prominent features of the response. The smoking of three cigarettes consecutively was without effect. The mechanisms of action are unclear, but the following possibilities must be considered. Drugs of the nicotine group stimulate the carotid and aortic chemoreceptors (137), and the central nervous stimulation with its consequent changes in cerebral blood flow may be secondary to an activation of these reflexes. Nicotine is also known to cause a release of epinephrine (137) which in sufficiently large doses produces very similar effects (206). Equally possible is a direct stimulation of the central nervous system by the drug.

e. Neuromuscular blocking agents. The effects of neuromuscular blocking agents on the cerebral circulation remain largely undetermined. A few qualitative studies in animals indicate that in doses which produce hypotension, these agents lower blood flow in the central nervous system. In artificially ventilated rabbits, spinal cord blood flow, as indicated by a thermocouple in the tissue, appeared to follow the changes in blood pressure following the administration of *d*-Tubocurarine Chloride, U.S.P. (91). A similar parallel relationship between

blood pressure and blood flow in the internal carotid and occipital arteries has been observed in dogs rendered hypotensive by a combination of *d*-tubocurarine and hexamethonium (277). Paralyzing doses of dihydro-β-erythroidine hydrobromide have been found to cause profound reductions in cortical pO_2, presumably because of a fall in cerebral blood flow (307). There are to our knowledge no reports of studies more reliable or quantitative than these and none with doses approximating those clinically employed in man. In view of the scarcity of data, a discussion of the possible mechanisms of action is futile.

E. Miscellaneous Vasodilator Drugs

A number of drugs have in common the ability to cause widespread arteriolar and/or capillary dilatation by direct action on the vessel walls. The cerebral vessels participate in the over-all response. These compounds have little else in common; indeed they are almost entirely dissimilar as regards their chemical structures and other pharmacological actions. They are considered together in this section only because of similarities in their modes of action on the circulation in general and on that of the brain in particular.

1. Histamine. There is ample evidence that histamine [2-(4-imidazolyl) ethylamine] is a potent cerebral vasodilator. Following its administration to anesthetized animals, all visible pial and cortical vessels are dilated (95, 110, 348, 399). When ether anesthesia is employed, the cerebral vessels may already be dilated, and then histamine sometimes causes a slight pial vascular narrowing; this phenomenon does not occur with barbiturate anesthesia (110, 399). It does not reflect a vasoconstrictor action of histamine under these conditions but rather a secondary passive response of the already dilated cerebral vessels to the fall in hydrostatic pressure within them when histamine lowers systemic blood pressure (110, 399). As a result of the cerebral vasodilatation, histamine increases brain volume (213) and cerebrospinal fluid pressure (41, 110, 289, 298).

The cerebrovascular dilatation is not always attended by an increased cerebral blood flow. In the monkey or cat brain perfused at constant pressure, histamine almost invariably causes an increase in blood flow which coincides with the pial arterial dilatation (95). Normally, however, a fall in arterial blood pressure occurs which may counteract the effects of the cerebral vasodilatation. Immediately following intravenous histamine injections, cerebral blood flow, as indicated by thermocouple techniques, has been observed to decline together with systemic blood pressure; the initial fall is followed by an increased blood flow which continues for some time after the blood pressure has returned to the pre-injection level, an indication of the persistence of the cerebral vasodilatation (185, 289, 373). During continuous intravenous infusions the systemic blood pressure remains depressed and along with it the cerebral blood flow (399). The same effect is obtained by injections of histamine repeated before the systemic blood pressure has recovered from the previous dose (399). Following termination of the infusion or after the last injection, when the blood pressure returns to normal, cerebral blood flow rises above the control level. Intracarotid injections of hista-

mine cause similar effects. Schmidt and Hendrix (338), by means of thermocouples placed in both the parietal cortex and an extracranial muscle in cats, found extracranial blood flow invariably elevated following such administration and always more so than that of the brain; cerebral blood flow was frequently not increased at all or actually decreased when the arterial blood pressure was depressed. On the other hand, in studies in the monkey by means of the quantitative bubble-flow meter technique, Dumke and Schmidt (73) found following intracarotid injections of histamine in doses too minute to alter arterial blood pressure an approximately 40% increase in total cerebral blood flow. The response, however, was transitory, persisting for less than three minutes.

The same relationship between systemic blood pressure and histamine effects on the cerebral circulation appears to hold in man. Gibbs *et al.* (124), by means of a thermoelectric flow recorder inserted in the internal jugular vein, obtained qualitative evidence of a substantially increased cerebral blood flow independent of arterial blood pressure changes following a single, intravenous injection of 0.5 mg of histamine phosphate. Blood flow rose promptly after the injection despite a slight transient fall in blood pressure, continued to rise gradually as the blood pressure regained and exceeded the normal level, and remained elevated for a period of 10 to 15 minutes, even after blood pressure had returned to its resting level. With continuous intravenous infusions of a dilute histamine phosphate solution at a dosage rate (0.5–1.0 ml/min of a 1:10,000 solution) which only negligibly altered arterial blood pressure, Weiss and Lennox (390) observed changes in cerebral arteriovenous oxygen difference which were inconsistent, inconclusive and considerably less than occurred concurrently in the extracerebral and forearm vascular beds. In quantitative studies in man, Shenkin (350) and Alman *et al.* (8) found no significant changes in the mean values for cerebral blood flow and metabolic rate during continuous intravenous infusions of histamine adjusted to lower mean arterial blood pressure between roughly 10 and 60% in the former studies and 4 and 50% in the latter. The mean values for cerebrovascular resistance were decreased in both studies and only in proportion to the fall in blood pressure so that blood flow remained unchanged. However, in Shenkin's studies (350) in which relatively normal subjects were employed, there was an excellent and highly significant correlation between individual decreases in arterial blood pressure and changes in cerebral blood flow. With small decreases in mean arterial blood pressure, cerebral blood flow increased; with moderate depressions of blood pressure, blood flow was unchanged; when blood pressure was markedly reduced, cerebral blood flow decreased. These observations indicate that in man, as in animals, the response of the cerebral circulation to histamine varies with the change in blood pressure. This relationship was not apparent in the studies of Alman and coworkers (8), perhaps, because their subjects were elderly, hypertensive, and probably also arteriosclerotic. Such patients have been reported to exhibit lowered cerebrovascular responses to histamine, as indicated by the degree of rise in cerebrospinal fluid pressure following its administration (41).

Histamine is, therefore, a cerebral vasodilator drug in both man and animals,

but it may not always increase cerebral blood flow because of its hypotensive effect. Its vasodilator action on the cerebral circulation is considerably less potent than on extracerebral (338, 390) and peripheral vascular beds (390). Therefore, whenever it does raise cerebral blood flow, it must be because cardiac output is increased as well, an action of histamine which has also been described (391). Because of the transient nature of its action, it is probably of little practical value in the therapy of cerebral vascular insufficiency.

The cerebral circulatory effects of histamine have been implicated in one of its unpleasant side effects, headache, which has been attributed to a dilatation and distention of the intracranial arteries and the stretching of their walls and surrounding tissues, particularly those of the pia and dura (45, 117, 298, 400). The headache following histamine injection occurs only after the initially lowered arterial blood pressure and elevated cerebrospinal fluid pressure have returned to normal (298). It is likely that at this point the walls of the still dilated intracranial vessels are further stretched as a consequence of the altered balance of the hydrostatic forces operating upon them. This explains why the headache is relieved by: 1) positive radial acceleration (217), which lowers arterial blood pressure; 2) artificial elevation of the intracranial pressure (343); 3) continued histamine administration (298), which accomplishes both of the other effects. The fact that the headache is abolished by raising the cerebrospinal fluid pressure is evidence of its intracranial origin. It also distinguishes it from that of migraine which is not so relieved (343, 400) and which has been attributed to a similar mechanism operating on the walls of the extracranial branches of the external carotid artery (142, 343, 376, 400). That they may not be entirely independent, however, is indicated by the finding of Von Storch (385) that patients with migraine have a lower threshold for the induction of headache by histamine than do normal subjects. The explanation of this relationship may be, as suggested by the observations of Schumacher and Wolff (343), on the basis of some contribution by the extracranial arteries to the histamine headache.

2. Nitrites. The chief pharmacological actions of the nitrites are the relaxation of smooth muscle and a generalized vasodilatation, particularly of the finer blood vessels (137). The cerebral vessels participate in the response. The inhalation of amyl nitrite (isoamyl nitrite) or the administration of nitrite solutions has been observed in animals to dilate all visible cortical and pial vascular channels, arteries, veins, and minute vessels alike (348, 398, 399). As a consequence of the cerebral vasodilatation, cerebrospinal fluid pressure is raised (137, 289), and, despite an often severe drop in systemic blood pressure, cerebral blood flow, as indicated by thermoelectric techniques, is increased (124, 185, 242, 289, 332, 338). In the cat Schmidt and Hendrix (338) found the inhalation of amyl nitrite to cause a greater rise in blood flow in the parietal cortex than in the extracranial muscle tissues; intra-arterial injections of glyceryl trinitrate (Nitroglycerin; Trinitrin) raised them both equally. The cerebral vasodilator effects of nitrite were second only to those of carbon dioxide. When the effects of a fall in arterial blood pressure are avoided, as, for example, in the artifically perfused cat brain, cerebral blood flow may be elevated as much as 70% by

glyceryl trinitrate (95). In quantitative studies in the monkey by means of the bubble-flow meter method, Dumke and Schmidt (73) found following intra-arterial injections of 0.5 to 1.0 μg of glyceryl trinitrate an approximately 40% rise in cerebral blood flow despite a mild fall in blood pressure.

The acceleration of cerebral blood flow by nitrites is, however, extremely transient disappearing almost entirely in less than three minutes (73, 124, 289), and often it is followed by an abrupt fall in blood flow below the level existing prior to the drug administration (124). For example, with prolonged amyl nitrite inhalation the effects of hypotension finally overcome those of the vasodilatation, and cerebral blood flow is depressed (289); cerebral tissue pO_2 may then fall markedly (307). The same effects are undoubtedly responsible for the syncope that often attends the assumption of the erect position following nitrite administration.

3. Papaverine. Papaverine (6,7-dimethoxy-1-veratrylisoquinoline), one of the benzylisoquinoline alkaloids derived from opium, has no narcotic properties; its chief pharmacological action is the relaxation of smooth muscle, the mechanism by which it effectively dilates blood vessels, particularly the larger arteries (137). This vasodilator effect is clearly demonstrable in the brain. Papaverine administration in animals is followed by a dilatation of the superficial cortical vessels (348) and an increase in cerebral cortical (242) and internal carotid (341) blood flow as indicated by thermoelectric devices. In the perfused dog brain papaverine has been observed to cause cerebral vasodilatation (32). There have been several studies on the quantitative effects of papaverine on human cerebral circulation by means of the nitrous oxide technique. In a few patients with impaired cerebral circulation, Shenkin (350) found a moderate reduction in cerebrovascular resistance following the intravenous administration of 60 mg of papaverine hydrochloride; however, because of a proportionate fall in mean arterial blood pressure, cerebral blood flow was not significantly changed. On the other hand, in toxemias of pregnancy, in which there are also cerebral circulatory disturbances, for example, elevations in mean arterial blood pressure and cerebrovascular resistance and a reduction in cerebral blood flow (248), McCall *et al.* (250) found that the injection of 120 mg intravenously or 180 mg intramuscularly significantly altered these functions and restored them to the normal level. In patients with no cerebral circulatory disorders, Jayne *et al.* (182) also found intravenous doses of 0.2 g papaverine to reduce the cerebral vascular resistance so that, despite a fall in arterial blood pressure, cerebral blood flow was raised approximately 13%. Cerebral metabolic rate was unchanged The absence of changes in cerebral blood flow in the studies by Shenkin (350) may, perhaps, reflect the considerably smaller doses he employed. Indeed, Russek and Zohman (311), in a large series of cases, found orally administered papaverine to be of distinct benefit in the treatment of vascular encephalopathy associated with hypertension or glomerulonephritis, but the dosage required was three to four times the usual therapeutic amount.

4. Nicotinic acid. A prominent side effect of the vitamin, nicotinic acid (Nicotinic Acid, U.S.P.; Niacin; pyridine-3-carboxylic acid), is a direct dilator action

on blood vessels, particularly noticeable in the blush areas of the skin. Aring and his coworkers (9) have reported that simultaneously with the cutaneous flush produced by the intravenous administration of nicotinic acid, there is in man an increase in intracranial blood flow as well. However, because of communications between the extracranial and cerebral vascular beds, the plethysmographic method employed by them might well have been demonstrating the events in the skin rather than in the brain. Other studies have failed to indicate any actions of nicotinic acid on the cerebral circulation. Roseman *et al.* (307) found it to have no effect on cortical oxygen tension in cats. In man Loman *et al.* (240) observed no significant changes in the retinal vessels, cerebrospinal fluid pressure, or cerebral arteriovenous oxygen difference following intravenous or intra-arterial injections of nicotinic acid in doses which caused considerable rises in blood flow in the arm. Scheinberg (316) also observed no significant effects on cerebral blood flow, vascular resistance, or oxygen consumption following the intravenous infusion of large, flushing doses, 0.3–0.8 g, of nicotinic acid in man. He did find evidence that the facial vasodilatation tended to cause more extracerebral contamination of the cerebral venous blood sampled from the superior bulb of the internal jugular vein. Although such contamination undoubtedly lowered the reliability of the nitrous oxide method which he employed in these studies, it was not sufficient to alter the validity of his conclusions. There appears to be, therefore, no pharmacological basis for the use of nicotinic acid as a cerebral vasodilator.

F. Miscellaneous Antihypertensive Drugs

Several groups of drugs quite distinct from one another pharmacologically and chemically are currently being employed in the treatment of hypertension because of their ability to lower arterial blood pressure. The mechanisms of their action are varied; none acts by peripheral autonomic blockade. They all apparently fail to produce any direct effects or, indeed, any changes at all in the cerebral circulation which cannot be attributed to its secondary readjustment to a fall in systemic blood pressure. In this respect, they are similar to each other and to many of the autonomic blocking agents.

1. Rauwolfia alkaloids. The effects of reserpine have been previously discussed in detail in regard to its tranquilizing action. It has been found to be without significant effects on cerebral blood flow or metabolic rate in man (154, 208, 210); when it lowers blood pressure, cerebrovascular resistance is reduced proportionately.

2. Veratrum alkaloids. The veratrum alkaloids are potent anti-hypertensive agents. The mechanisms of their action are not completely understood, but it is believed that they lower arterial blood pressure chiefly by reflex vasodilatation (67, 137, 180, 215). Since cerebrovascular tone is not under any demonstrable reflex neurogenic control, specific cerebral circulatory effects of these drugs are hardly to be expected, and, indeed, there has been no evidence to the contrary. In patients in whom arterial blood pressure and cerebrovascular resistance are already elevated by the disease state, for example, essential hypertension,

malignant hypertension with encephalopathy, or toxemia of pregnancy, intravenous injections of hypotensive doses of protoveratrine (Protoveratrines A and B, N.N.D.; Veralba®) (58), alkavervir (Alkavervir, N.N.R.; Veriloid®) (266), and *Veratrum viride* (Veratrum Viride, N.F.) (249), respectively, tend to lower these functions toward normal. A new derivative of *Veratrum viride*, cryptenamine (Cryptenamine Acetates, N.N.R.; Unitensen® Acetates), has recently been found to do the same in toxemia of pregnancy (251). Cerebral blood flow, which is initially normal in these states, is not changed by the drug administration indicating that the cerebral vessels dilate sufficiently to compensate for the fall in blood pressure. Cerebral blood flow is similarly maintained when *Veratrum viride* is administered intravenously in uncomplicated pregnancy although in these cases arterial blood pressure and cerebrovascular resistance are initially normal and are reduced by the drug to less than normal levels (249). Intramuscular injections of protoveratrine, in contrast to the results obtained with intravenous administration, have been reported to cause a moderate lowering of cerebral blood flow in essential hypertension (58); the reduction in arterial blood pressure was greater and more sustained following the intramuscular injections and apparently was sufficient to exceed the compensatory capacity of the cerebral chemical homeostatic mechanisms. Except for the unexplained finding by McCall *et al.* (251) of a stimulation of cerebral oxygen consumption by cryptenamine in patients with nonconvulsive toxemia of pregnancy, all previously cited studies (58, 249, 266) indicate that the veratrum alkaloids have no significant effects on human cerebral metabolic rate.

In general, the actions of the veratrum alkaloids on cerebral circulatory and metabolic functions do not appear to be anything other than the expected secondary effects of the reduction in mean arterial blood pressure.

3. Hydralazine. Hydralazine (Hydralazine Hydrochloride, N.N.R.; Apresoline® Hydrochloride; 1-hydrazinophthalazine), another agent currently employed in the treatment of hypertension, has been studied in man as regards its cerebral circulatory effects. The mechanism of its hypotensive effect is not entirely understood; it is believed to result chiefly from a peripheral vasodilatation secondary to a central suppression of efferent sympathetic vasopressor impulses (114, 137). There may also be some degree of adrenergic (115, 137, 263) and/or ganglionic blockade (114, 342) involved. None of these actions which are mediated through the autonomic nervous system is likely to be exerted on the cerebral vessels, but a direct peripheral vasodilator action has also been suggested (375). In man, hydralazine does not appear to have any notable specific vasodilator action on the cerebral blood vessels. It has been given in hypotensive doses by intramuscular injection in normal pregnancy (249), toxemia of pregnancy (249), and essential hypertension (152) and by continual oral administration either alone (207) or in combination with reserpine (210) in hypertensive arteriosclerotic disease; in all cases the same effects were observed, moderate reductions in arterial blood pressure and cerebrovascular resistance and no change in cerebral blood flow. Except for one report of increases in normal and toxemic pregnancies (249), hydralazine has not been found to alter the oxygen consumption of the brain (152, 207, 210).

Although the drug does apparently cause a significant relaxation of cerebrovascular tone, it is no greater than that occurring in response to a fall in arterial blood pressure achieved by means which almost certainly do not influence the cerebral vessels directly (197, 212, 353).

G. Hormones and Related Drugs

1. Thyroid hormone. Although the thyroid hormone has no apparent effect on the oxygen consumption of the mature adult brain, alterations in its blood level result in changes in cerebral hemodynamics (317, 325, 353, 367). In hyperthyroid patients, Scheinberg (317) found the cerebral circulatory and metabolic functions to be normal, but in adult myxedema he and his associates (325) observed parallel depressions in cardiac output and cerebral blood flow, a rise in cerebrovascular resistance, and a lowering of the cerebral metabolic rate. On the other hand, Sokoloff *et al.* (367) found a significantly higher cerebral blood flow and lower cerebrovascular resistance in hyperthyroid patients than in normal subjects of comparable age. Following treatment these functions tended to return to normal; cerebral oxygen consumption was normal before and unchanged after treatment. Since the cerebrovascular resistance correlated significantly with the arterial hemoglobin concentration, these workers (367) suggested that the anemia present in their patients may have been responsible for the cerebral hemodynamic changes. In the most extensive studies to date, Sensenbach *et al.* (344), on the basis of comparative values before and after treatment, have confirmed that hyperthryoidism is associated with a rise in cerebral blood flow and a reduction in cerebrovascular resistance, that in myxedema changes in the opposite direction occur, and that in both cases restoration of the euthyroid state by effective therapy results in a return of the cerebral circulatory functions to normal. Cerebral oxygen consumption and glucose utilization are normal in both diseases and are unchanged by treatment. Himwich *et al.* (168) obtained qualitative evidence of similar circulatory changes in juvenile hypothyroidism, for example, cretinism; following thyroid medication cerebral blood flow, as indicated by thermoelectric needle in the internal jugular vein, was increased.

Apparently then the cerebral circulatory changes associated with altered thyroid function parallel those occurring in cardiac output (274, 325) and in blood flow to most other organs and tissues (79, 274, 309, 370, 371). However, unlike the situation in other tissues, the metabolic rate of the brain is unchanged so that it is not metabolism which is responsible for the cerebral circulatory changes. The studies of Sensenbach *et al.* (344) have excluded anemia as the cause; nor were there in any of the aforementioned studies (317, 325, 344, 367) any alterations in blood constituents or other variables which could explain the changes in cerebral hemodynamics. Except for this lack of any other obvious mechanism, however, there is no evidence to suggest a direct action of the thyroid hormone on the cerebral circulation.

2. Insulin. Insulin (Insulin Injection, U.S.P.; Iletin®), in adequate dosage to cause confusion or coma, markedly reduces the cerebral metabolic rate (205). Evidence that it has no significant effects on the cerebral circulation was first obtained qualitatively in man by means of the thermoelectric flow recorder (166)

and the plethysmographic technique (90) and quantitatively in the monkey by means of the bubble-flow meter technique (339). In their classical study in man by means of the nitrous oxide method, Kety *et al.* (205) have clearly demonstrated that the administration of insulin, even in doses large enough to produce coma and depress markedly the cerebral metabolic rate, has no effect on any of the cerebral circulatory functions. Similar effects on cerebral blood flow and metabolism occur in irreversible insulin coma and persist until death (84).

With insulin deficiency, as, for example, in uncompensated diabetes, there are significant changes in cerebral circulation (199), but these are attributable not directly to the insulin lack but rather to the associated changes in acid-base balance and blood carbon dioxide tension. These changes have been previously discussed in relation to the actions of acids and bases.

3. Adrenal medullary hormones. The adrenal medullary sympathomimetic amines, epinephrine and *l*-norepinephrine, have profound effects on the cerebral circulation (206, 345). These effects are discussed in the section on autonomic drugs.

4. ACTH and the adrenocortical steroids. Sensenbach *et al.* (346) have investigated the effects of cortisone (Cortisone Acetate Injection, U.S.P.; 11-dehydro-17-hydroxycorticosterone-21-acetate) and the adrenocorticotrophic hormone, ACTH (Corticotropin, U.S.P.; Adrenocorticotrophin; Acthar®), on cerebral circulation and metabolism in man. In a group of miscellaneous patients studied before, during, and after the prolonged daily administration of 100–200 mg of cortisone or 10–200 mg of ACTH, mean arterial blood pressure and cerebrovascular resistance were elevated proportionately by the drugs, and cerebral blood flow and oxygen consumption were unaffected. After the drugs were discontinued, the altered functions tended to return to the pretreatment levels. In similar studies, Schieve *et al.* (326) observed comparable effects of ACTH, except that cerebrovascular resistance rose proportionately more than arterial blood pressure resulting in a slight reduction in blood flow to the brain. The effects of ACTH on cerebral circulatory hemodynamics are apparently slow in developing, for they are not observed after only three or four days of its administration (7). Both ACTH and cortisone, therefore, have similar cerebral circulatory and metabolic effects which are like those seen in Cushing's syndrome (346) and in essential hypertension (195). The mechanism by which they raise cerebrovascular resistance is unknown; it is undoubtedly common to both drugs and, in view of the blood pressure rise, probably operates to some extent on other vascular beds as well.

Desoxycorticosterone (Δ^4-pregnene-3,20-dion-21-ol), administered intravenously as the water-soluble glucoside, has been found by Bentinck *et al.* (23) to have no effects on cerebral blood flow and oxygen consumption in man. They reported however, that it caused the release of a sugar, believed to be galactose (23, 140), from the brain. The latter observations were not confirmed by Schieve and Wilson (327) nor by the previous workers themselves (138) in subsequent investigations.

The effects of adrenalectomy have also been studied. Functional changes per-

sisting after this procedure probably reflect mainly the consequences of adrenocortical insufficiency, but the effects of adrenomedullary lack cannot be excluded. Bergen and coworkers (24, 25) have reported marked reductions in cerebral blood flow and oxygen consumption in totally adrenalectomized rats. Both functions were rapidly restored to normal by adrenal cortical extract (Adrenal Cortical Injection, U.S.P.), pregnenolone (Arthenolone; Enolone; Δ^5-pregnen-3β-ol-20-one), or cortisone; desoxycorticosterone was without effect. Since it is unlikely that valid measurements of the cerebral functions could be made with the techniques employed in these studies, the significance of these results is obscure. In human subjects with essential hypertension, whose mean arterial blood pressure and cerebrovascular resistance were elevated by the disease, Hafkenschiel *et al.* (153) found 90% adrenalectomy to lower both toward normal. Cerebral blood flow was minimally elevated, and the oxygen consumption was unchanged. Similar but more pronounced effects were observed when adrenalectomy was combined with sympathectomy (153). The patients, however, had been on presumably adequate adrenocortical replacement therapy following operation, and since it is highly questionable whether adrenomedullary deficiency could have caused such hemodynamic changes, the basis of the effects observed in these studies is not obvious.

5. Gonadal steroids and related compounds. Gordan and Adams (139) have found in young adult patients suffering from preadolescent eunuchoidism markedly high values for cerebral blood flow and oxygen consumption approximating those observed by Kennedy and Sokoloff (188) in prepubertal children. The possibility that these changes might be secondary to the high gonadotropin levels present in such patients is refuted by almost identical findings in preadolescent hypopituitarism in which circulating gonadotropin is reduced (138, 139). Gordan and his associates (138, 139) suggest instead that they are the result of a deficiency of gonadal steroids which, they believe, normally provide a "braking" action on the metabolic rate and, consequently, on the blood flow of the brain. They further suggest that it is the increased secretion of such steroids at that period of life that is responsible for the rapid fall in cerebral blood flow and oxygen consumption at puberty (139, 188, 192). Indeed, a number of steroids with the androstene nucleus have been observed to inhibit cerebral oxygen consumption *in vitro* (140). Recently, a progesterone derivative, 21-hydroxypregnane-3,20-dione sodium hemisuccinate (hydroxydione, Viadril®), has been reported to reduce cerebral blood flow and oxygen consumption and to induce anesthesia in man (138, 141). Studies on the effects of castration in adult human males have, however, led to contrary results (138). Prior to castration, acute intravenous administration of 250 mg potassium testosterone sulfate in a few patients appeared to lower cerebral blood flow and metabolic rate, but castration also seemed to do the same (138). Furthermore, after castration, desoxycorticosterone or testosterone had, if any effect at all, an accelerative one on cerebral circulation and metabolism. These results are far from clear. Further investigation in this area is required before the actions of the gonadal steroids on cerebral circulatory and metabolic functions, if any, are clarified.

6. Anterior pituitary hormones. The actions of the adrenocorticotrophic hormone (ACTH) on the cerebral circulation have been described together with those of the adrenocortical hormones. Except for the finding by Gordan and his associates (138, 139) of markedly elevated cerebral circulatory and metabolic rates in preadolescent hypopituitarism, there are little quantitative data on the effects of other hormones of this gland. Baruk *et al.* (14) have reported that topical or subcutaneous administration of *anterior pituitary extract* has no effect on the superficial vessels of the exposed rabbit cortex; intravenous injections cause vasoconstriction and a reduction in brain volume. Whether these changes reflect the actions of ACTH, which raises cerebrovascular resistance in human subjects (326, 346), or some other component of the extract is unknown.

7. Posterior pituitary hormones. The results of studies on the effects of hormones of the posterior pituitary lobe on the cerebral circulation have been variable (399). On the basis of direct observation in animals, both posterior pituitary extract (Posterior pituitary Injection, U.S.P.; Pituitrin®) and vasopressin (Vasopressin Injection, U.S.P.; Pitressin®; β-hypophamine), applied locally or injected intravenously, have been reported to exert no effect on pial vessels (98), to constrict them (95), to dilate them (104), or to do both (104, 398, 399). Where both effects have been observed, usually either constriction (398) or dilatation (104) has been considered to be the more prominent effect. Generally, these drugs elevate cerebrospinal fluid pressure (104, 289), suggesting some degree of cerebral vasodilatation and/or increased blood flow. However, pitressin alters water transport in the kidney, as manifested by its antidiuretic effects, and one cannot with certainty exclude a similar direct action on the rate of spinal fluid formation which might also alter the pressure in the subarachnoid space. In fact, pituitrin has been reported to increase the permeability of the blood-brain barrier (37, 53).

The observed effects on blood flow have been no more consistent. Blood flow in the internal carotid artery of the dog was decreased by pituitrin despite a rise in arterial blood pressure, evidence of a cerebral vasoconstrictor response (341). Similar results were obtained with pitressin in the monkey and cat brain perfused at constant pressure (95). In all these experimental preparations, however, complete isolation of the cerebral circulation is unlikely, and the results may well have reflected effects in the extracerebral tissues. Indeed, posterior pituitary extracts have been found to constrict blood vessels (104) and reduce blood flow (338) in the extracranial tissues.

Probably of greater significance are the results of studies by means of thermocouples inserted in brain tissue. With such a technique Norcross (289) obtained evidence of parallel increases in parietal cortical blood flow and arterial blood pressure following intravenous injections of posterior pituitary extract in cats. Schmidt *et al.* observed a similar increase in blood flow in the medulla (340) but no changes in the hypothalamus (332) after intravenous pituitrin administration in cats. After intra-arterial injections of either pituitrin or pitressin, Schmidt and Hendrix (338) observed increases in parietal cortical blood flow in the rabbit and in the cat, even though arterial blood pressure was unchanged, and extra-

cranial blood flow was decreased. On the other hand, in quantitative studies in the monkey by means of the bubble-flow meter method, the intra-arterial injection of 0.1 unit of pituitrin was found by Dumke and Schmidt (73) to cause immediate, marked, parallel decreases in cerebral blood flow and arterial blood pressure; the effects were only transient, however.

The results of these studies suggest that the effects of posterior pituitary hormones on cerebral circulation may depend on the concomitant changes in arterial blood pressure. Most evidences of cerebral vasodilatation or increased blood flow have been obtained during a rise in blood pressure and decreased blood flow during a fall. Sokoloff and Wagner (366) have attempted by continuous intravenous infusions of pitressin to achieve in normal man an appreciable, sustained pressor response, during which they could quantitatively measure the cerebral hemodynamic response by means of the nitrous oxide method. In a couple of cases they have succeeded in raising the arterial blood pressure approximately 10%. A proportionate rise in cerebrovascular resistance occurred which maintained the cerebral blood flow more or less constant; cerebral oxygen consumption was also unaffected. Whether the rise in cerebrovascular resistance is a reflection of a secondary readjustment of the cerebral vessels to the rise in blood pressure or an equal vasoconstrictor action of the drug on the cerebral as on other vascular beds cannot be determined from their preliminary results. They do indicate, however, that the action of pitressin on the cerebral circulation is minimal.

V. SUMMARY

The outstanding impression obtained from an over-all view of the action of drugs on the cerebral circulation is the great resistance of the cerebral blood flow to change. Both physiologically and pharmacologically, the cerebral blood flow is rarely altered by as much as a factor of two, even by changes in blood tensions of the respiratory gases, the agents with the most potent effects on the cerebral circulation. This stability reflects the relative constancy of the cerebral metabolic rate and is achieved by a combination of mechanisms operating on the two determinants of cerebral blood flow. First, pressoreceptor reflexes, including those with receptors in the internal carotid artery, a major source of supply to the brain, operate to maintain a more or less constant blood pressure head for the cerebral circulation without involving the cerebral vessels in the adjustments necessary to accomplish this. Secondly, cerebrovascular resistance is altered by chemical products of metabolism in a manner serving to maintain homeostasis as regards their concentrations in brain tissue. To some extent cerebrovascular resistance is also influenced by changes in intracranial pressure in a direction tending to maintain a constancy of cerebral blood flow.

The net result is that blood flow to the brain is less readily changed by drugs than it is in other tissues. Those most effective are physiological agents which are already operating when drug therapy directed at the cerebral circulation is desired. There is, therefore, no spectacularly clinically useful drug available for such purposes, but for the same reasons drugs employed for other types of therapy rarely have seriously deleterious effects on the cerebral circulation, except under the most extreme conditions.

REFERENCES

1. Abreu, B. E., Elliott, H. W., Sutherland, V. C., Margolis, L. and Simon, A.: Effect of morphine sulfate on cerebral blood flow and metabolism in man. Fed. Proc. 8: 270, 1949.
2. Abreu, B. E., Liddle, G. W., Burks, A. L., Simon, A., Sutherland, V. and Gordan, G. S.: Effects of amphetamine, dihydroergotamine, and methadon on human cerebral blood flow and oxygen uptake. Fed. Proc. 7: 201, 1948.
3. Abreu, B. E., Liddle, G. W., Burks, A. L., Sutherland, V., Elliott, H. W., Simon, A. and Margolis, L.. Influence of amphetamine sulfate on cerebral metabolism and blood flow in man . J. Amer. pharm. Ass., Sci. Ed. 38: 186-188, 1949.
4. Ahlquist, R. P., Huggins, R. A. and Woodbury, R. A.: The pharmacology of benzyl-imidazoline (priscol). J. Pharmacol. 89: 271-288, 1947.
5. Aikawa, T., Goto, Y., Tazaki, Y., Hamaya, S. and Makino, K.: The effects of chlorpromazine on cerebral circulation and metabolism. Keio J. Med. 5: 205-213, 1956.
6. Alman, R. W., Bessman, A. N., Hayes, G. J. and Fazekas, J. F.: Influence of cerebrospinal fluid upon cerebral blood-flow determination. J. Lab. clin. Med. 39: 753-756, 1952.
7. Alman, R. W. and Fazekas, J. F.: Effects of ACTH on cerebral blood flow and oxygen consumption. Arch. Neurol. Psychiat., Chicago 65: 680-682, 1951.
8. Alman, R. W., Rosenberg, M. and Fazekas, J. F.: Effects of histamine on cerebral hemodynamics and metabolism. Arch. Neurol. Psychiat., Chicago 67: 354-356, 1952.
9. Aring, C. D., Ryder, H. W., Roseman, E., Rosenbaum, M. and Ferris, E. B., Jr.: Effect of nicotinic acid and related substances on the intracranial blood flow of man. Arch. Neurol. Psychiat., Chicago 46: 649-653, 1941.
10. Ashton, N., Ward, B. and Serpell, G.: Effects of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Brit. J. Ophthal. 38: 397-432, 1954.
11. Auerbach, M. E. and Angell, E.: The determination of arterenol in epinephrine. Science 109: 537-538, 1949.
12. Barcroft, H. and Konzett, H.: On the actions of noradrenaline and isopropyl noradrenaline on the arterial blood pressure, heart rate, and muscle blood flow in man. J. Physiol. 110: 194-204, 1949.
13. Barcroft, H., Konzett, H. and Swan, J. C.: Observations on the action of the hydrogenated alkaloids of the ergotoxine group on the circulation in man. J. Physiol. 112: 273-291, 1951.
14. Baruk, H., David, M., Racine, M., Vallancien and Borenstein, P.: Étude expérimentale de l'action du lobe antérieur d'hypophyse sur la circulation cérébrale et sur l'oedème cérébral acétylcholinique. Ann. méd.-psychol. 1: 163-165, 1947.
15. Batson, O. V.: Anatomical problems concerned in the study of cerebral blood flow. Fed. Proc. 3: 139-144, 1944.
16. Battey, L. L., Heyman, A. and Patterson, J. L., Jr.: Effects of ethyl alcohol on cerebral blood flow and metabolism. J. Amer. med. Ass. 152: 6-10, 1953.
17. Battey, L. L., Patterson, J. L. and Heyman, A. H.: Effects of methyl and ethyl alcohol on cerebral blood flow and oxygen consumption. Amer. J. Med. 13: 105, 1952.
18. Battey, L. L., Patterson, J. L. and Heyman, A.: Effects of methyl alcohol on cerebral blood flow and metabolism. Observations during and after acute intoxication. Arch. Neurol. Psychiat., Chicago 76: 253-256, 1956.
19. Beale, H. D.: Delirium and coma precipitated by oxygen in bronchial asthma complicated by respiratory acidosis. New Engl. J. Med. 244: 710-714, 1951.
20. Bean, J. W.: Effects of oxygen at increased pressure. Physiol. Rev. 25: 1-147, 1945.
21. Bearn, A. G., Billing, B. H. and Sherlock, S.: The effect of adrenalin and noradrenalin on hepatic blood flow and splanchnic carbohydrate metabolism in man. J. Physiol. 115: 430-441, 1951.
22. Bennett, S., Bassett, D. L. and Beecher, H. K.: Influence of anesthesia (ether, cyclopropane, sodium evipal) on the circulation under normal and shock conditions. J. clin. Invest. 23: 181-208, 1944.
23. Bentinck, R. C., Gordan, G. S., Adams, J. E., Arnstein, L. H. and Leake, T. B.: Effect of desoxycorticosterone glucoside upon cerebral blood flow and metabolism of human subjects. J. clin. Invest. 30: 200-205, 1951.
24. Bergen, J. R., Hunt, C. and Hoagland, H.: Blood flow and oxygen consumption of brain in relation to adrenal cortical action. Fed. Proc. 11: 12, 1952.
25. Bergen, J. R., Hunt, C. A. and Hoagland, H.: Effects of adrenalectomy and replacement therapy on brain circulation, oxygen consumption and the electrocorticogram. Amer. J. Physiol. 175: 327-332, 1953.
26. Bernsmeier, A.: Die chemische Blockierung des adrenergischen Systems am Menschen. Acta neuroveg. Suppl. V: 1-142, 1954.
27. Bernsmeier, A., Sack, H. and Siemons, K.: Der cerebrale Kreislauf bei der Behandlung des Hirndrucks mit ganglienblockierenden Substansen. Nervenarst 24: 390-392, 1953.
28. Bernsmeier, A. and Siemons, K.: Der Hirnkreislauf bei der gesteuerten experimentellen Hypotension (Hypotension controllée). Schweiz. med. Wschr. 83: 210-212, 1953.
29. Bessman, A. N., Alman, R. W. and Fazekas, J. F.: Effect of acute hypotension on cerebral hemodynamics and metabolism of elderly patients. Arch. intern. Med. 89: 893-898, 1952.
30. Binet, L., Cachera, R., Fauvert, R. and Strumza, M. V.: Anoxémie et circulation cérébrale. C. R. Soc. Biol., Paris 126: 166-169, 1937.
31. Blumgart, H. L.: Treatment of acute myocardial infarction with particular reference to shock. J. Amer. med. Ass. 154: 107-111, 1954.
32. Bouckaert, J. and Jourdan, F.: Influences de la caféine, de la papavérine et du chlorure de baryum sur les vaisseaux cérébraux. C. R. Soc. Biol., Paris 120: 257-259, 1935.
33. Bouckaert, J. J. and Jourdan, F.: Recherches sur la physiologie et la pharmacodynamie des vaisseaux cérébraux: IV. Influence de l'adrénaline. Arch. int. Pharmacodyn. 54: 109-128, 1936.

34. Bouckaert, J. J. and Jourdan, F.: La circulation cérébrale. J. Physiol., Paris 41: 69A–112A, 1949.
35. Britton, S. W., Corey, E. L. and Stewart, G. A.: Effects of high acceleratory forces and their alleviation. Amer. J. Physiol. 146: 33–51, 1946.
36. Britton, S. W., Pertzoff, V. A., French, C. R. and Kline, R. F.: Circulatory and cerebral changes and protective aids during exposure to acceleratory forces. Amer. J. Physiol. 150: 7–26, 1947.
37. Broman, T.: On the problem of the blood-brain and blood-spinal fluid barriers. (Translated from Swedish.) Nord. med. Tidskr. 15: 205–213, 1938.
38. Broman, T. and Olson, O.: The tolerance of cerebral blood vessels to a contrast medium of the diodrast group. Acta radiol., Stockh. 30: 326–342, 1948.
39. Bronk, D. W. and Gesell, R.: The regulation of respiration. X. Effects of carbon dioxide, sodium bicarbonate and sodium carbonate on the carotid and femoral flow of blood. Amer. J. Physiol. 82: 170–180, 1927.
40. Cadenat and Monsaingeon: Embolie gaseuse du cerveau. Heureuse action de la novocainisation intraveineuse. Mém. Acad. Chir. 72: 355–359, 1946.
41. Cameron, D. E. and Rosen, S. R.: The reactivity of intracranial vessels in the aged. Amer. J. med. Sci. 201: 871–876, 1941.
42. Cannon, J. L.: The estimation of the cerebral blood flow from the arterial carbon dioxide tension. II. Applications in aviation medicine. Project No. NM 001 059.06.08, U. S. Naval School of Aviation Medicine, Pensacola, Fla. August 1, 1952.
43. Cholst, M. R., Schilback, H. F., Handelsman, M. B. and Levitt, L. M.: The response of the retinal vessels to priscoline in various vascular conditions. Amer. J. Ophthal. 35: 191–195, 1952.
44. Chorobski, J. and Penfield, W.: Cerebral vasodilator nerves and their pathway from the medulla oblongata. Arch. Neurol. Psychiat., Chicago 28: 1257–1289, 1932.
45. Clark, D., Hough, H. and Wolff, H. G.: Experimental studies on headache: observations on histamine headache. Res. Publ. Ass. nerv. ment. Dis. 15: 417–436, 1934.
46. Clarke, E., Jones, N. C. H. and Logethetopoulos, J.: The action of tolazoline hydrochloride on cerebral blood-flow in cerebral thrombosis. Lancet 2: 567–569, 1954.
47. Cobb, S.: Cerebral circulation. Res. Publ. Ass. nerv. ment. Dis. 18: 719–752, 1938.
48. Cobb, S. and Finesinger, J. E.: Cerebral circulation XIX. The vagal pathway of the vasodilator impulses. Arch. Neurol. Psychiat., Chicago 28: 1243–1256, 1932.
49. Cobb, S. and Fremont-Smith, F.: The cerebral circulation. XVI. Changes in the human retinal circulation and in the pressure of the cerebrospinal fluid during inhalation of a mixture of carbon dioxide and oxygen. Arch. Neurol. Psychiat., Chicago 26: 731–736, 1931.
50. Cobb, S. and Lennox, W. G.: Cerebral circulation—intrinsic control and clinical phenomena. Fed. Proc. 3: 151–158, 1944.
51. Comroe, J. H., Bahnson, E. R. and Coates, E. O.: Mental changes occurring in chronically anoxemic patients during oxygen therapy. J. Amer. med. Ass. 143: 1044–1048, 1950.
52. Cook, E. N. and Brown, G. E.: The vasodilating effects of ethyl alcohol in peripheral arteries. Proc. Mayo Clin. 7: 449–452, 1932.
53. Cooke, B. T., Hurst, E. W. and Swan, C.: Routes of entry into the nervous system of viruses introduced into the blood-stream. Experiments with the viruses of pseudorabies, herpes, and infectious myxomatosis. Aust. J. exp. Biol. med. Sci. 20: 129–138, 1942.
54. Courtice, F. C.: The effect of raised intracranial pressure on the cerebral blood flow. J. Neurol. Psychiat., Chicago 3: 293–305, 1940.
55. Courtice, F. C.: The gaseous tensions in the brain. J. Physiol. 100: 193–197, 1941.
56. Courtice, F. C.: The effect of oxygen lack on the cerebral circulation. J. Physiol. 100: 198–211, 1941.
57. Cow, D.: Some reactions of surviving arteries. J. Physiol. 42: 125–143, 1911.
58. Crumpton, C. W., Klingensmith, W. C., Keffer, N. J. and Hafkenschiel, J. H.: Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. Fed. Proc. 10: 32, 1951.
59. Crumpton, C. W. and Murphy, Q. R.: Effects of hexamethonium bromide upon hemodynamics of cerebral and coronary circulation in hypertension. J. clin. Invest. 31: 622, 1952.
60. Crumpton, C. W., Rowe, G. G., Capps, R. C., Whitmore, J. J. and Murphy, Q. R.: The effect of hexamethonium upon cerebral blood flow in patients with premalignant and malignant hypertension. Circulation 2: 106–109, 1955.
61. Cusick, P. L., Benson, O. O. and Boothby, W. M.: Effect of anoxia and of high concentrations of oxygen on the retinal vessels. Proc. Mayo Clin. 15: 500–502, 1940.
62. Dameshek, W., Myerson, A. and Loman, J.: The effects of sodium amytal on the metabolism. Amer. J. Psychiat. 91: 113–135, 1934.
63. Davies, C. E. and MacKinnon, J.: Neurological effects of oxygen in chronic cor pulmonale. Lancet 2: 883–885, 1949.
64. Davies, P. W., Grenell, R. G. and Bronk, D. W.: The time course of *in vivo* oxygen consumption of cerebral cortex following electrical stimulation. Fed. Proc. 7: 25, 1948.
65. Davies, P. W. and Rémond, A.: Oxygen consumption of the cerebral cortex of the cat during metrasole convulsions. Res. Publ. Ass. nerv. ment. Dis. 26: 205–217, 1946.
66. Davis, E. W., McCulloch, W. S. and Roseman, E.: Rapid changes in the oxygen tension of cerebral cortex during induced convulsions. Amer. J. Psychiat. 100: 825–839, 1944.
67. Dawes, G. S. and Comroe, J. H., Jr.: Chemoreflexes from the heart and lungs. Physiol. Rev. 34: 167–201, 1954.
68. Denker, P. G.: The effect of caffeine on the cerebrospinal fluid pressure. Amer. J. med. Sci. 181: 675–681, 1931.
Sèze, S. de, see 348.

69. DEWAR, H. A., OWEN, S. G. AND JENKINS, A. R.: Effect of hexamethonium bromide on the cerebral circulation in hypertension. Brit. med. J. 2: 1017–1018, 1953.
70. DEWAR, H. A., OWEN, S. G. AND JENKINS, A. R.: Influence of tolazoline hydrochloride (priscol) on cerebral blood flow in patients with mitral stenosis. Lancet 1: 867–870, 1953.
71. DISALVO, R. J., BLOOM, W. L., BRUST, A. A., FERGUSON, R. W. AND FERRIS, E. B.: A comparison of the metabolic and circulatory effects of epinephrine, nor-epinephrine and insulin hypoglycemia with observations on the influence of autonomic blocking agents. J. clin. Invest. 35: 568–577, 1956.
72. DRIPPS, R. D. AND COMROE, J. H., JR.: The respiratory and circulatory response of normal men to inhalation of 7.6 and 10.4 percent CO_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2 and maximal voluntary hyperventilation. Amer. J. Physiol. 149: 43–51, 1947.
73. DUMKE, P. R. AND SCHMIDT, C. F.: Quantitative measurements of cerebral blood flow in the macaque monkey. Amer. J. Physiol. 138: 421–431, 1943.
74. ECHLIN, F. A.: Vasospasm and focal cerebral ischemia. An experimental study. Arch. Neurol. Psychiat., Chicago 47: 77–96, 1942.
75. ECKENHOFF, J. E., ELDER, J. D., JR. AND KING, B. D.: N-Allylnormorphine in treatment of morphine or demerol narcosis. Amer. J. med. Sci. 223: 191–197, 1952.
76. ECKENHOFF, J. E., HAFKENSCHIEL, J. H. AND LANDMESSER, C. M.: The coronary circulation in the dog. Amer. J. Physiol. 148: 582–596, 1947.
77. ECKER, P. G. AND POLIS, B. D.: The action of mescaline on the cerebral metabolism of the rhesus monkey as defined by the oxygen and "glucose" utilization of the intact brain. Naval Air Development Center Report No. NADC-MA-5507, Johnsville, Pa. August 18, 1955.
78. EHRMANTRAUT, W. R., SHEA, J. G., TICKTIN, H. E. AND FAZEKAS, J. F.: Influence of promazine and methylphenidate on cerebral hemodynamics and metabolism. Arch. intern. Med. 100: 66–69, 1957.
79. EICHNA, L. W. AND WILKINS, R. W.: Blood flow to forearm and calf; IV. Thyroid activity: observations on the relation of blood flow to basal metabolic rate. Johns Hopk. Hosp. Bull. 68: 512–521, 1941.
80. ENGEL, D.: Correspondence: cerebral blood vessels and priscol. Brit. med. J. 1: 106, 1953.
81. ETSTEN, B., YORK, G. E. AND HIMWICH, H. E.: Pattern of metabolic depression induced with pentothal sodium. Arch. Neurol. Psychiat., Chicago 56: 171–183, 1946.
82. FAZEKAS, J. F., ALBERT, S. N. AND ALMAN, R. W.: Influence of chlorpromazine and alcohol on cerebral hemodynamics and metabolism. Amer. J. med. Sci. 230: 128–132, 1955.
83. FAZEKAS, J. F., ALMAN, R. W. AND BESSMAN, A. N.: Cerebral physiology of the aged. Amer. J. med. Sci. 223: 245–257, 1952.
84. FAZEKAS, J. F., ALMAN, R. W. AND PARRISH, A. E.: Irreversible post-hypoglycemic comas. Amer. J. med. Sci. 222: 640–643, 1951.
85. FAZEKAS, J. F. AND BESSMAN, A. N.: Coma mechanisms. Amer. J. Med. 15: 804–812, 1953.
86. FAZEKAS, J. F., BESSMAN, A. N., COTSONAS, N. J., JR. AND ALMAN, R. W.: Cerebral hemodynamics in cerebral arteriosclerosis. J. Geront. 8: 137–145, 1953.
87. FAZEKAS, J. F., KLEH, J. AND PARRISH, A. E.: The influence of shock on cerebral hemodynamics and metabolism. Amer. J. med. Sci. 229: 41–45, 1955.
88. FERRIS, E. B., JR.: Objective measurement of relative intracranial blood flow in man with observations concerning the hemodynamics of the craniovertebral system. Arch. Neurol. Psychiat., Chicago 46: 377–401, 1941.
89. FERRIS, E. B., JR., ENGELS, G. L., STEVENS, C. D. AND LOGAN, M.: The validity of internal jugular venous blood in studies of cerebral metabolism and blood flow in man. Amer. J. Physiol. 147: 517–521, 1946.
90. FERRIS, E. B., JR., ROSENBAUM, M., ARING, C. O., RYDER, H. W., ROSEMAN, E. AND HAWKINS, J. R.: Intracranial blood flow in insulin coma. Arch. Neurol. Psychiat., Chicago 46: 509–512, 1941.
91. FIELD, E. J., GRAYSON, J. AND ROGERS, A. F.: Observations on the blood flow in the spinal cord of the rabbit. J. Physiol. 144: 56–70, 1951.
92. FINESINGER, J. E.: Cerebral circulation. XVIII. Effect of caffeine on the cerebral vessels. Arch. Neurol. Psychiat., Chicago 28: 1290–1325, 1932.
93. FINESINGER, J. E. AND COBB, S.: Cerebral circulation. XXVII. Action on the pial arteries of the convulsants, caffeine, absinth, camphor, and picrotoxin. Arch. Neurol. Psychiat., Chicago 30: 980–1002, 1933.
94. FINESINGER, J. E. AND COBB, S.: The cerebral circulation. XXIV. The action of narcotic drugs on the pial vessels. J. Pharmacol. 53: 1–33, 1935.
95. FINESINGER, J. E. AND PUTNAM, T. J.: Cerebral circulation. XXII. Induced variations in volume flow through the brain perfused at constant pressure. Arch. Neurol. Psychiat., Chicago 30: 775–794, 1933.
96. FINNERTY, F. A., GUILLAUDEU, R. L. AND FAZEKAS, J. F.: Cardiac and cerebral hemodynamics in drug induced postural collapse. Circulation Res. 5: 34–39, 1957.
97. FINNERTY, F. A., JR., WITKIN, L. AND FAZEKAS, J. F.: Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. J. clin. Invest. 33: 1227–1232, 1954.
98. FLOREY, H. W.: Microscopical observations on the circulation of the blood in the cerebral cortex. Brain 48: 43–64, 1925.
99. FOG, M.: The relationship between the blood pressure and the tonic regulation of the pial arteries. J. Neurol. Psychiat., Chicago 1: 187–197, 1938.
100. FOG, M.: Cerebral circulation. I. Reaction of pial arteries to epinephrine by direct application and intravenous injection. Arch. Neurol. Psychiat., Chicago 41: 109–118, 1939.
101. FORBES, H. S.: The cerebral circulation: I. Observation and measurement of pial vessels. Arch. Neurol. Psychiat., Chicago 19: 751–761, 1928.

102. Forbes, H. S.: Physiological regulation of cerebral circulation. Arch. Neurol. Psychiat., Chicago 43: 804-814, 1940.
103. Forbes, H. S. and Cobb, S.: Vasomotor control of cerebral vessels. Res. Publ. Ass. nerv. ment. Dis. 18: 201-217, 1938.
104. Forbes, H. S., Finley, K. H. and Nason, G. I.: Cerebral circulation: XXIV. A.—Action of epinephrine on pial vessels. B.—Action of pituitary and pitressin on pial vessels. C.—Vasomotor response in the pia and in the skin. Arch. Neurol. Psychiat., Chicago 30: 957-979, 1933.
105. Forbes, H. S. and Krumbhaar, C. C.: Cerebral circulation. XXI. Action of hydrogen sulphide. Arch. Neurol. Psychiat., Chicago 29: 756-764, 1933.
106. Forbes, H. S. and Nason, G. I.: The cerebral circulation. XLI. Vascular responses to (A) hypertonic solutions and (B) withdrawal of cerebrospinal fluid. Arch. Neurol. Psychiat., Chicago 34: 533-547, 1935.
107. Forbes, H. S. and Nason, G. I.: Effect of metrazol on cerebral vessels. Proc. Soc. exp. Biol., N. Y. 43: 762-765, 1940.
108. Forbes, H. S., Schmidt, C. F. and Nason, G. I.: Evidence of vasodilator innervation in the parietal cortex of the cat. Amer. J. Physiol. 125: 216-219, 1939.
109. Forbes, H. S. and Wolff, H. G.: Cerebral circulation. III. The vasomotor control of cerebral vessels. Arch. Neurol. Psychiat., Chicago 19: 1057-1086, 1928.
110. Forbes, H. S., Wolff, H. G. and Cobb, S.: The cerebral circulation: X. The action of histamine. Amer. J. Physiol. 89: 226-272, 1929.
111. Fowler, N. O. and Franch, R.: Mechanism of pressor response to l-norepinephrine during hemorrhagic shock. Circulation Res. 5: 153-156, 1957.
112. Frank, H. A., Altschule, M. D. and Zamcheck, N.: Traumatic shock. IX. Pressor therapy: the effect of paredrine (p-hydroxy-α-methylphenylethylamine hydrobromide) on the circulation in hemorrhagic shock in dogs. J. clin. Invest. 24: 56-61, 1945.
113. Frank, E. D., Frank, H. A., Jacob, S., Weizel, H. A. E., Korman, H. and Fine, J.: Effect of norepinephrine on circulation of the dog in hemorrhagic shock. Amer. J. Physiol. 186: 74-78, 1956.
114. Freis, E. D. and Finnerty, F. A., Jr.: Suppression of vasomotor reflexes in man following l-hydrazinophthalazine (C-5068). Proc. Soc. exp. Biol., N. Y. 75: 23-24, 1950.
115. Freis, E. D., MacKay, J. C. and Oliver, W. F.: The effects of "sympatholytic" drugs on the cardiovascular responses to epinephrine and norepinephrine in man. Circulation 3: 254-259, 1951.
116. Fremont-Smith, F. and Forbes, H. S.: Intra-ocular and intracranial pressure. Arch. Neurol. Psychiat., Chicago 18: 550-564, 1927.
117. Friedman, A. P., Brenner, C. and Merritt, H. H.: Experimental evidence of the physiologic mechanism of certain types of headache. Arch. Neurol. Psychiat., Chicago 54: 385-388, 1945.
118. Geiger, A. and Magnes, J.: The isolation of the cerebral circulation and the perfusion of the brain in the living cat. Amer. J. Physiol. 149: 517-537, 1947.
119. Gerard, R. W.: Brain metabolism and circulation. Res. Publ. Ass. nerv. ment. Dis. 18: 316-345, 1938.
120. Gellhorn, E. and Kraines, S. H.: Word association as affected by deficient oxygen, excess of carbon dioxide, and hyperpnea. Arch. Neurol. Psychiat., Chicago 38: 491-504, 1937.
121. Gibbs, F. A.: Cerebral blood flow preceding and accompanying experimental convulsions. Arch. Neurol. Psychiat., Chicago 30: 1003-1010, 1933.
122. Gibbs, F. A.: A thermoelectric flow recorder in the form of a needle. Proc. Soc. exp. Biol., N. Y. 31: 141-146, 1933.
123. Gibbs, E. L., Gibbs, F. A., Hayne, R. and Maxwell, R.: Cerebral blood flow in epilepsy. Res. Publ. Ass. nerv. ment. Dis. 26: 131-140, 1947.
124. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G.: The cerebral blood flow in man as influenced by adrenaline, caffein, amyl nitrite, and histamine. Amer. Heart J. 10: 916-924, 1935.
125. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G.: Changes in human cerebral blood flow consequent on alterations in blood gases. Amer. J. Physiol. 111: 557-563, 1935.
126. Gibbs, E. L., Gibbs, F. A., Lennox, W. G. and Nims, L. F.: Regulation of cerebral carbon dioxide. Arch. Neurol. Psychiat., Chicago 47: 879-889, 1942.
127. Gibbs, F. A., Gibbs, E. L., Lennox, W. G. and Nims, L. F.: The value of carbon dioxide in counteracting the effects of low oxygen. J. Aviat. Med. 14: 250-261, 1943.
128. Gibbs, E. L., Lennox, W. G. and Gibbs, F. A.: Bilateral internal jugular blood: comparison of A-V differences, oxygen-dextrose ratios, and respiratory quotients. Amer. J. Psychiat. 102: 184-190, 1945.
129. Gibbs, E. L., Lennox, W. G., Nims, L. F. and Gibbs, F. A.: Arterial and cerebral venous blood; arterial-venous differences in man. J. biol. Chem. 144: 325-332, 1942.
130. Gibbs, F. A., Maxwell, H. and Gibbs, E. L.: Volume flow of blood through human brain. Arch. Neurol. Psychiat., Chicago 57: 137-144, 1947.
131. Gilmore, J. P., Smythe, C. M. and Handford, S. W.: The effect of l-norepinephrine on cardiac output in the anesthetised dog during graded hemorrhage. J. clin. Invest. 33: 884-890, 1954.
132. Goetz, R. H. and Katz, A.: Adrenolytic action of dihydroergocornine in man. Lancet 1: 560-563, 1949.
133. Goldenberg, M.: Adrenal medullary function. Amer. J. Med. 10: 627-641, 1951.
134. Goldenberg, M., Faber, M., Alston, E. J. and Chargaff, E. C.: Evidence for occurrence of nor-epinephrine in adrenal medulla. Science 109: 534-535, 1949.
135. Goldenberg, M., Pines, K. L., Balwin, E. deF., Green, D. G. and Roh, C. E.: The hemodynamic response of man to norepirephrine and epinephrine and its relation to the problem of hypertension. Amer. J. Med. 5: 792-806, 1948.

136. Goldfarb, W., Bowman, K. M. and Wortis, J.: The effect of alcohol on cerebral metabolism. Amer. J. Psychiat. 97: 384–387, 1940.
137. Goodman, L. S. and Gilman A.: The Pharmacological Basis of Therapeutics. Macmillan, New York 1955.
138. Gordan, G. S.: Hormones and metabolism. Influence of steroids on cerebral metabolism in man. In: Recent Progress in Hormone Research, Vol. 12, pp. 153–174. Academic Press, New York 1956.
139. Gordan, G. S. and Adams, J. F.: Cerebral metabolism in the aging process: the steroid factor. In: Hormones and the Aging Process, pp. 299–309. Academic Press, New York 1956.
140. Gordan, G. S., Bentinck, R. C. and Eisenberg, E.: Influence of steroids on cerebral metabolism. Ann. N. Y. Acad. Sci. 54: 575–607, 1951.
141. Gordan, G. S., Guadagni, N., Picchi, J. and Adams, J. E.: Anesthésie stéroïdienne chez l'homme: effets cliniques et cérébro-métaboliques. Pr. méd. 63: 1483–1484, 1955.
142. Graham, J. R. and Wolff, H. G.: Mechanism of migraine headache and action of ergotamine tartrate. Res. Publ. Ass. nerv. ment. Dis., 18: 638–660, 1938.
143. Grant, F. C., Spitz, E. B., Shenkin, H. A., Schmidt, C. F. and Kety, S. S.: The cerebral blood flow and metabolism in idiopathic epilepsy. Trans. Amer. neurol. Ass. 72: 82–86, 1947.
144. Greene, J. A., Paul, W. D. and Feller, A. E.: The action of theophyllin with ethylenediamine on intrathecal and venous pressures in cardiac failure and in bronchial asthma. J. Amer. med. Ass. 109: 1712–1715, 1937.
145. Gregg, D. E. and Shipley, R. E.: Experimental approaches to the study of the cerebral circulation. Fed. Proc. 3: 144–151, 1944.
146. Griffith, F. R., Jr.: Fact and theory regarding the calorigenic action of adrenaline. Physiol. Rev. 31: 151–187, 1951.
147. Grimson, K. S., Reardon, M. J., Marzoni, F. A. and Hendrix, J. P.: The effects of priscol (2-benzyl-4,-5-imidazoline HCl) on peripheral vascular diseases, hypertension, and circulation in patients. Ann. Surg. 127: 968–991, 1948.
148. Guttmann, E.: Artificial psychoses produced by mescaline. J. ment. Sci. 82: 203–221, 1936.
149. Hafkenschiel, J. H., Crumpton, C. W. and Moyer, J. H.: The effect of intramuscular dihydroergocornine on the cerebral circulation in normotensive patients. J. Pharmacol. 98: 144–146, 1950.
150. Hafenschiel, J. H., Crumpton, C. W., Moyer, J. H. and Jeffers, W. A.: The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. clin. Invest. 29: 408–411, 1950.
151. Hafkenschiel, J. H. and Friedland, C. K.: Physiology of the cerebral circulation in essential hypertension: the effects of inhalation of 5% carbon dioxide oxygen mixtures on cerebral hemodynamics and oxygen metabolism. J. Pharmacol. 106: 391–392, 1952.
152. Hafkenschiel, J. H. and Friedland, C. K.: The effects of l-hydrazinophthalazine on cerebral blood flow, vascular resistance, oxygen uptake, and jugular oxygen tension in hypertensive subjects. J. clin. Invest. 32: 655–660, 1953.
153. Hafkenschiel, J. H., Friedland, C. K. and Zintel, H. A.: The blood flow and oxygen consumption of the brain in patients with essential hypertension before and after adrenalectomy. J. clin. Invest. 33: 57–62, 1954.
154. Hafkenschiel, J. H., Sellers, A. M., King, G. A. and Thorner, M. W.: Preliminary observations on the effect of parenteral reserpine on cerebral blood flow, oxygen and glucose metabolism, and electroencephalograms of patients with essential hypertension. Ann. N. Y. Acad. Sci. 61: 78–84, 1955.
155. Hall, F. G.: Carbon dioxide and respiratory regulation at altitude. J. appl. Physiol. 5: 603–606, 1953.
156. Hall, M. N.: A study on the effects of priscoline on patients with psychosis due to cerebral arteriosclerosis. Conn. St. med. J. 15: 385–389, 1951.
157. Hansen, D. B. and Carey, R.: Unpublished observations.
158. Hansen, D. B., Sultzer, M. R., Freygang, W. H. and Sokoloff, L.: Effects of low O_2 and high CO_2 concentrations in inspired air on local cerebral circulation. Fed. Proc. 16: 54, 1957.
159. Hansen, D. B., Sultzer, M. R., Freygang, W. H. and Sokoloff, L.: Unpublished observations.
160. Harmel, M. H., Hafenschiel, J. H., Austin, G. M., Crumpton, C. W. and Kety, S. S.: The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. J. clin. Invest. 28; 415–418, 1949.
161. Henry, J. P., Gauer, O. H., Kety, S. S. and Kramer, K.: Factors maintaining cerebral circulation during gravitational stress. J. clin. Invest. 30; 292–300, 1951.
162. Heyman, A., Patterson, J. L. and Duke, T. W.: Cerebral circulation and metabolism in sickle cell and other chronic anemias, with observations on the effects of oxygen inhalation. J. clin. Invest. 31: 824–828, 1952.
163. Heyman, A., Patterson, J. L., Duke, T. W. and Battey, L. L.: The cerebral circulation and metabolism in arteriosclerotic and hypertensive cerebrovascular disease. New Engl. J. Med. 249: 223–229, 1953.
164. Hickam, J. B., Schieve, J. F. and Wilson, W. P.: The relation between retinal and cerebral vascular reactivity in normal and arteriosclerotic subjects. Circulation 7: 84–87, 1953.
165. Hill, L.: The Physiology and Pathology of the Cerebral Circulation: An Experimental Research. Churchill, London 1896.
166. Himwich, H. E., Bowman, K. M., Daly, C., Fazekas, J. F., Wortis, J. and Goldfarb, W.: Cerebral blood flow and brain metabolism during insulin hypoglycemia. Amer. J. Physiol. 132: 640–647, 1941.
167. Himwich, H. E., Daly, C. and Fazekas, J. F.: Effect of neosynephrine on gaseous exchange of the brain. Proc Soc. exp. Biol., N. Y. 53: 78–79, 1943.
168. Himwich, H. E., Daly, C., Fazekas, J. F. and Herrlich, H. C.: Effect of thyroid medication on brain metabolism of cretins. Amer. J. Psychiat. 98: 489–493, 1942.
169. Himwich, H. E., Fazekas, J., Herrlich, H., Johnson, A. E. and Barach, A. L.: Studies on the effects of

adding carbon dioxide to oxygen-enriched atmospheres in low pressure chambers. II. The oxygen and carbon dioxide tensions of cerebral blood. J. Aviat. Med. 13: 177–181, 1942.

170. Himwich, W. A., Homburger, E., Maresca, R. and Himwich, H. E.: Brain metabolism in man; unanesthetized and in pentothal narcosis. Amer. J. Psychiat. 103: 689–696, 1947.
171. Hine, C. H., Shick, A. F., Margolis, L., Burbridge, T. N. and Simon, A.: Effects of alcohol in small doses and tetraethylthiuramdisulphide (antabus) on the cerebral blood flow and cerebral metabolism. J. Pharmacol. 106: 253–260, 1952.
172. Hoch, P. H.: Experimentally produced psychoses. Amer. J. Psychiat. 107: 607–611, 1951.
173. Hoch, P. H., Cattell, J. P. and Pennes, H. H.: Effects of mescaline and lysergic acid (d-LSD-25). Amer. J. Psychiat. 108: 579–584, 1952.
174. Homburger, E., Himwich, W. A., Etsten, B., York, G., Maresca, R. and Himwich, H. E.: Effect of pentothal anesthesia on canine cerebral cortex. Amer. J. Physiol. 147: 343–345, 1946.
175. Howe, H. S. and McKinley, E.: Cerebral circulation. Arch. Neurol. Psychiat., Chicago 18: 81–86, 1927.
176. Hughes, G.: The investigation of cerebral blood flow during anesthesia with hypotension induced by the use of hexamethonium bromide and posture. Brit. J. Anaesth. 27: 229–243, 1955.
177. Ingvar, D. H. and Söderberg, U.: The effect of LSD-25 upon the cerebral blood flow and EEG in cats. Experientia 12: 427–429, 1956.
178. Irving, L.: Changes in the blood flow through the brain and muscles during the arrest of breathing. Amer. J. Physiol. 122: 207–214, 1938.
179. Irving, L. and Welch, M. S.: The effect of the composition of the inspired air on the circulation through the brain. Quart. J. exp. Physiol. 25: 121–129, 1935.
180. Jarisch, A. and Richter, H.: Die Kreislaufwirkung des Veratrins. Arch. exp. Path. Pharmak. 193: 347–354, 1939.
181. Jasper, H. and Erickson, T. C.: Cerebral blood flow and pH in excessive cortical discharge induced by metrazol and electrical stimulation. J. Neurophysiol. 4: 333–347, 1941.
182. Jayne, H. W., Scheinberg, P., Rich, M. and Belle, M. S.: The effect of intravenous papaverine hydrochloride on the cerebral circulation. J. clin. Invest. 31: 111–114, 1952.
183. Kawaguchi, K.: Effects of pilocarpine and atropine on the pressure and volume of the cerebrospinal fluid, with reference to the blood circulation in the brain. (Translated from Japanese.) Nagoya J. med. Sci. 46: 673–701, 1937.
184. Keats, A. S. and Mithoefer, J. C.: The mechanism of increased intracranial pressure induced by morphine. New Engl. J. Med. 252: 1110–1113, 1955.
185. Keller, C. J.: Die Regelung der Blutversorgung des Gehirnes. Z. ges. Neurol. Psychiat. 167: 281–300, 1939.
186. Kenk, R. and Nall, M. L.: Physiology of the circulation of the brain. An annotated bibliography, 1938–1948. Physiol. Rev. 32 (Suppl. No. 1): 1–437, 1952.
187. Kennedy, C., Anderson, W. and Sokoloff, L.: Cerebral blood flow in epileptic children during the interseizure period. Neurology, 8 (Suppl. No. 1): 100–105, 1958.
188. Kennedy, C. and Sokoloff, L.: An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. J. clin. Invest. 36: 1130–1137, 1957.
189. Kepes, E. R.: Effect of demerol on cerebrospinal fluid pressure. Anesthesiology 13: 281–286, 1952.
190. Kety, S. S.: Quantitative estimation of cerebral blood flow in man. Meth. med. Res. 1: 204–217, 1948. Yearbook Publishers, Chicago.
191. Kety, S. S.: Circulation and metabolism of the human brain in health and disease. Amer. J. Med. 8: 205–217, 1950.
192. Kety, S. S.: Human cerebral blood flow and oxygen consumption as related to aging. J. chronic Dis. 3: 478–486, 1956.
193. Kety, S. S.: The pharmacology of psychotomimetic and psychotherapeutic drugs. Ann. N. Y. Acad. Sci. 66: 417–840, 1957.
194. Kety, S. S.: Unpublished observations.
195. Kety, S. S., Hafkenschiel, J. H., Jeffers, W. A., Leopold, I. H. and Shenkin, H. A.: The blood flow, vascular resistance, and oxygen consumption of the brain in essential hypertension. J. clin. Invest. 27: 511–514, 1948.
196. Kety, S. S., Harmel, M. H., Broomell, H. T. and Rhode, C. B.: The solubility of nitrous oxide in blood and brain. J. biol. Chem. 173: 487–496, 1948.
197. Kety, S. S., King, B. D., Horvath, S. M., Jeffers, W. A. and Hafkenschiel, J. H.: The effects of an acute reduction in blood pressure by means of differential sympathetic block on the cerebral circulation of hypertensive patients. J. clin. Invest. 29: 402–407, 1950.
198. Kety, S. S., Landau, W. M., Freygang, W. H., Rowland, L. P. and Sokoloff, L.: Estimation of regional circulation in the brain by the uptake of an inert gas. Fed. Proc. 14: 85, 1955.
199. Kety, S. S., Polis, B. D., Nadler, C. S. and Schmidt, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. clin. Invest. 27: 500–510, 1948.
200. Kety, S. S. and Schmidt, C. F.: The determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. Amer. J. Physiol. 143: 53–66, 1945.
201. Kety, S. S. and Schmidt, C. F.: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. J. clin. Invest. 25: 107–119, 1946.
202. Kety, S. S. and Schmidt, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. J. clin. Invest. 27: 476–483, 1948.

203. KETY, S. S. AND SCHMIDT, C. F.: The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J. clin. Invest. 27: 484–492, 1948.
204. KETY, S. S., SHENKIN, H. A. AND SCHMIDT, C. F.: The effects of increased intracranial pressure on cerebral circulatory functions in man. J. clin. Invest. 27: 493–499, 1948.
205. KETY, S. S., WOODFORD, R. B., HARMEL, M. H., FREYHAN, F. A., APPEL, K. E. AND SCHMIDT, C. F.: Cerebral blood flow and metabolism in schizophrenia. The effects of barbiturate semi-narcosis, insulin coma and electroshock. Amer. J. Psychiat. 104: 765–770, 1948.
206. KING, B. D., SOKOLOFF, L. AND WECHSLER, R. L.: The effects of l-epinephrine and l-nor-epinephrine upon cerebral circulation and metabolism in man. J. clin. Invest. 31: 273–279, 1952.
207. KLEH, J. AND FAZEKAS, J. F.: The use of apresoline in the hypertensive arteriosclerotic syndrome. Amer. J. med. Sci. 227: 57–64, 1954.
208. KLEH, J. AND FAZEKAS, J. F.: The use of reserpine in the hypertensive arteriosclerotic syndrome. Amer. J. med. Sci. 228: 560–562, 1954.
209. KLEH, J. AND FAZEKAS, J. F.: Cerebral hemodynamic studies on hypertensive atherosclerotic subjects during hexamethonium therapy. Med. Ann. D. C. 23: 480–482, 1954.
210. KLEH, J. AND FAZEKAS, J. F.: Effects of hypotensive agents on subjects with cerebral vascular insufficiency. J. Amer. Geriat. Soc. 4: 18–23, 1956.
211. KLEINERMAN, J. AND HOPKINS, A. L.: Effects of hypothermia on cerebral blood flow and metabolism in dogs. Fed. Proc. 14: 410, 1955.
212. KLEINERMAN, J., SANCETTA, S. M., LYNN, R. B., STAHL, R. AND HACKEL, D. B.: Studies of hemodynamic changes in human beings following induction of high spinal anesthesia. III. The effect on cerebral blood flow, cerebral oxygen consumption and glucose metabolism. J. Lab. clin. Med. 40: 819–820, 1952.
213. KOOPMANS, S.: The function of the blood vessels in the brain. II. The effect of some narcotics, hormones, and drugs. Arch. néerl. Physiol. 24: 250–266, 1939.
214. KRAMER, S.: On the function of the circle of Willis. J. exp. Med. 15: 348–355, 1912.
215. KRAYER, O. AND ACHESON, G. H.: The pharmacology of the veratrum alkaloids. Physiol. Rev. 26: 383–440, 1946.
216. KUBIE, L. S. AND HETLER, D. M.: The cerebral circulation. IV. The action of hypertonic solutions. Part II. A study of the circulation in the cortex by means of color photography. Arch. Neurol. Psychiat., Chicago 20: 749–755, 1928.
217. KUNKLE, E. C., LUND, D. W. AND MAHLER, P. J.: Studies on headache. Analysis of vascular mechanisms in headache by use of the human centrifuge, with observations on pain perception under increased positive G. Arch. Neurol. Psychiat., Chicago 60: 253–269, 1948.
218. KURLAND, G. S. AND MALACH, M.: The clinical use of nor-epinephrine in the treatment of shock accompanying myocardial infarction and other conditions. New Engl. J. Med. 247: 383–389, 1952.
219. LAMBERTSEN, C. J., KOUGH, R. H., COOPER, D. Y., EMMEL, G. L., LOESCHKE, H. H. AND SCHMIDT, C. F.: Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J. appl. Physiol. 5: 471–486, 1953.
220. LANDAU, W. H., FREYGANG, W. H., ROWLAND, L. P., SOKOLOFF, L. AND KETY, S. S.: The local circulation of the living brain; values in the unanesthetized and anesthetized cat. Trans. Amer. neurol. Ass. 80: 125–129, 1955.
221. LANE, M. H., DASTUR, D. K., HANSEN, D. B. AND SOKOLOFF, L.: Rapid continuous measurement of leg blood flow in man: effects of vasodilator drugs. Fed. Proc. 16: 77, 1957.
222. LARRABEE, M. G. AND POSTERNAK, J. M.: Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. J. Neurophysiol. 15: 91–114, 1952.
223. LARRABEE, M. G., RAMOS, J. F. AND BÜLBRING, E.: Effects of anesthetics on oxygen consumption and on synaptic transmission in sympathetic ganglia. J. cell. comp. Physiol. 40: 461–494, 1952.
224. LASSEN, N. A. AND MUNCK, O.: The cerebral blood flow in man determined by the use of radioactive krypton. Acta physiol. scand. 33: 30–49, 1955.
225. LASSEN, N. A., MUNCK, O. AND TOTTEY, E. R.: Mental function and cerebral oxygen consumption in organic dementia. Arch. Neurol. Psychiat., Chicago 77: 126–133, 1957.
226. LEIBEL, B. S. AND HALL, G. E.: Cerebral blood flow changes during insulin and metrazol (pentamethylene tetrazol) shock. Proc. Soc. exp. Biol., N. Y. 38: 894–896, 1938.
227. LENNOX, W. G.: The effect on epileptic seizures of varying the contents of the respired air. J. clin. Invest. 6: 23–24, 1928.
228. LENNOX, W. G.: The cerebral circulation. XIV. The respiratory quotient of the brain and extremities in man. Arch. Neurol. Psychiat., Chicago 26: 719–724, 1931.
229. LENNOX, W. G. AND GIBBS, E. L.: The blood flow in the brain and the leg of man and the changes induced by alteration of blood gases. J. clin. Invest. 11: 1155–1177, 1932.
230. LENNOX, W. G., GIBBS, E. L. AND GIBBS, F. A.: Effect of ergotamine tartrate on the cerebral circulation of man. J. Pharmacol. 53: 113–119, 1935.
231. LENNOX, W. G., GIBBS, F. A. AND GIBBS, E. L.: Relationship of unconsciousness to cerebral blood flow and to anoxemia. Arch. Neurol. Psychiat., Chicago 34: 1001–1013, 1935.
232. LENNOX, W. G., GIBBS, F. A. AND GIBBS, E. L.: The relationship in man of cerebral activity to blood flow and to blood constituents. Res. Publ. Ass. nerv. ment. Dis. 18: 274–297, 1938.
233. LEWIS, B. M., SOKOLOFF, L. AND KETY, S. S.: Use of radioactive krypton to measure rapid changes in cerebral blood flow. Amer. J. Physiol. 183: 638–639, 1955.
234. LEWIS, B. M., SOKOLOFF, L., WECHSLER, R. L., WENTZ, W. B. AND KETY, S. S.: Determination of cerebral blood flow using radioactive krypton. U. S. Naval Air Development Center Report No. NADC-MA-5601, Johnsville, Pa. Feb. 20, 1956.

235. List, C. F., Burge, C. H. and Hodges, F. J.: Intracranial angiography. Radiology 45: 1-14, 1945.
236. Livesay, W. R., and Chapman, D. W.: The treatment of acute hypotensive states with l-nor-epinephrine. Amer. J. med. Sci. 225: 159-171, 1953.
237. Loman, J. and Myerson, A.: The action of certain drugs on the cerebrospinal fluid and on the internal jugular venous and systemic arterial pressure of man. Arch. Neurol. Psychiat., Chicago 27: 1226-1244, 1932.
238. Loman, J. and Myerson, A.: Studies in the dynamics of the human cranio-vertebral cavity. Amer. J. Psychiat. 92: 791-815, 1936.
239. Loman, J. and Myerson, A.: Alcohol and cerebral vasodilatation. New Engl. J. Med. 227: 439-441, 1942.
240. Loman, J., Rinkel, M. and Myerson, A.: The intracranial and peripheral vascular effects of nicotinic acid. Amer. J. med. Sci. 202: 211-216, 1941.
241. Lubin, A. J. and Price, J. C.: Effect of alkalosis and acidosis on cortical electrical activity and blood flow. J. Neurophysiol. 5: 261-268, 1943.
242. Lubsen, N.: Experimental studies on the cerebral circulation of the unanesthetized rabbit. III. The action of ergotamine tartrate and of some vasodilator drugs. Arch. néerl. Physiol. 25: 361-365, 1941.
243. Ludwigs, N. and Schneider, M.: Über den Einfluss des Halssympathicus auf die Gehirndurchblutung. Pflüg. Arch. ges. Physiol. 259: 43-55, 1954.
244. Madison, L. L.: Comparison of the anterior pituitary-adrenal cortical stimulating effect of U.S.P. epinephrine, synthetic l-epinephrine and norepinephrine. J. clin. Invest. 29: 789-791, 1950.
245. Mangold, R.: Stoffwechsel und Kreislauf des menschlichen Gehirns. Schweiz. med. Wschr. 84: 1-23, 1954.
246. Mangold, R., Sokoloff, L., Conner, E. L., Kleinerman, J., Therman, P. G. and Kety, S. S.: The effects of sleep and lack of sleep on the cerebral circulation and metabolism of normal young men. J. clin. Invest. 34: 1092-1100, 1955.
247. Maurer, F. W.: The effects of anoxemia due to carbon monoxide and low oxygen on cerebrospinal fluid pressure. Amer. J. Physiol. 133: 180-188, 1941.
248. McCall, M. L.: Cerebral blood flow and metabolism in toxemias of pregnancy. Surg. Gynec. Obstet. 89: 715-721, 1949.
249. McCall, M. L.: Cerebral circulation and metabolism in toxemia of pregnancy. Observations on the effect of veratrum viride and apresoline (l-hydrasinophthalazine). Amer. J. Obstet. Gynec. 66: 1015-1030, 1953.
250. McCall, M. L., Finch, T. V. and Taylor, H. W.: The cerebral effects of papaverine hydrochloride in toxemia of pregnancy. Amer. J. Obstet. Gynec. 61: 393-398, 1951.
251. McCall, M. L., Sass, D. K., Wagstaff, C. and Cutler, J.: Cryptenamine and cerebral function. The effects of cryptenamine (unitensen) on cerebral circulation and metabolism in toxemia of pregnancy. Obstet. & Gynec. 6: 297-302, 1955.
252. McCall, M. L. and Taylor, H. W.: Effects of morphine sulfate on cerebral circulation and metabolism in normal and toxemic pregnant women. Amer. J. Obstet. Gynec. 64: 1131-1136, 1952.
253. McCall, M. L. and Taylor, H. W.: Effects of barbiturate sedation on the brain in toxemia of pregnancy. J. Amer. med. Ass. 149: 51-54, 1952.
254. McCall, M. L., Taylor, H. W. and Finch, T. V.: The effects of intravenously administered sodium amytal on cerebral circulation and metabolism in toxemia of pregnancy. J. Philad. Gen. Hosp. 3: 110-114, 1952.
255. McChesney, E. W., McAuleff, J. P. and Blumberg, H.: The hyperglycemic action of some analogs of epinephrine. Proc. Soc. exp. Biol., N. Y. 72: 220-223, 1949.
256. McNaughton, F. L.: The innervation of the intracranial blood vessels and dural sinuses. Res. Publ. Ass. nerv. ment. Dis. 18: 178-200, 1938.
257. Miller, A. J., Shifrin, A., Kaplan, B. M., Gold, H., Billings, A. and Katz, L. N.: Arterenol in treatment of shock. J. Amer. med. Ass. 152: 1198-1201, 1953.
258. Mithoefer, J. C.: Increased intracranial pressure in emphysema caused by oxygen inhalation. J. Amer. med. Ass. 149: 1116-1120, 1952.
259. Mithoefer, J. C., Mayer, P. W. and Stocks, J. F.: Effect of carbonic anhydrase inhibition on the cerebral circulation of the anesthetized dog. Fed. Proc. 16: 88-89, 1957.
260. Morris, G. C., Jr., Moyer, J. H., Snyder, H. B. and Haynes, B. W., Jr.: Vascular dynamics in controlled hypotension. Ann. Surg. 138: 706-711, 1953.
261. Morris, G. C., Moyer, J. H., Snyder, H. B. and Haynes, B. W., Jr.: Cerebral hemodynamics in controlled hypotension. Surg. Forum 4: 140-143, 1954.
262. Morris, G., Pontius, R., Herschberger, R. and Moyer, J. H.: Cerebral hemodynamics following administration of chlorpromazine. Fed. Proc. 14: 371-372, 1955.
263. Moyer, J. H., Handley, C. A. and Huggins, R. A.: Some pharmacodynamic effects of l-hydrasinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. J. Pharmacol. 103: 368-376, 1951.
264. Moyer, J. H., Miller, S. I. and Snyder, H.: Effect of increased jugular pressure on cerebral hemodynamics. J. appl. Physiol. 7: 245-247, 1954
265. Moyer, J. H., Miller, S. I., Tashnek, A. B. and Bowman, R.: The effect of theophylline with ethylenediamine (aminophylline) on cerebral hemodynamics in the presence of cardiac failure with and without Cheyne-Stokes respiration. J. clin. Invest. 31: 267-272, 1952.
266. Moyer, J. H., Miller, S. I., Tashnek, A. B., Snyder, H. and Bowman, R. O.: Malignant hypertension and hypertensive encephalopathy. Cerebral hemodynamic studies and therapeutic response to continuous infusion of intravenous veriloid. Amer. J. Med. 14: 175-183, 1953.
267. Moyer, J. H., Morris, G. and Smith, C. P.: Cerebral hemodynamics during controlled hypotension induced by the continuous infusion of ganglionic blocking agents (hexamethonium, pendiomide and arfonad). J. clin. Invest. 33: 1081-1088, 1954.

268. MOYER, J. H., MORRIS, G. AND SNYDER, H.: A comparison of the cerebral hemodynamic responses to aramine and norepinephrine in the normotensive and hypotensive subject. Circulation 10: 265–270, 1954.
269. MOYER, J. H., SKELTON, J. M. AND MILLS, L. C.: Norepinephrine: Effect in normal subjects; use in treatment of shock unresponsive to other measures. Amer. J. Med. 15: 330–343, 1953.
270. MOYER, J. H. AND SNYDER, H. B.: The cerebral hemodynamic response to the xanthine compound, parephyllin (diethylaminoethyl theophylline hydrochloride). Amer. Heart J. 47: 912–918, 1954.
271. MOYER, J. H., SNYDER, H. AND MILLER, S. I.: Cerebral hemodynamic response to blood pressure reduction with phenoxybenzamine (dibenzyline-688A). Amer. J. med. Sci. 228: 563–567, 1954.
272. MOYER, J. H., TASHNEK, A. B., MILLER, S. I., SNYDER, H. AND BOWMAN, R. O.: The effect of theophylline with ethylene diamine (aminophylline) and caffeine on cerebral hemodynamics and cerebrospinal fluid pressure in patients with hypertension headaches. Amer. J. med. Sci. 224: 377–385, 1952.
273. MUNCK, O. AND LASSEN, N. A.: Bilateral cerebral blood flow and oxygen consumption in man by use of Krypton^{85}. Circulation Res. 5: 163–168, 1957.
274. MYERS, J. D., BRANNON, E. S. AND HOLLAND, B. C.: A correlative study of the cardiac output and the hepatic circulation in hyperthyroidism. J. clin. Invest. 29: 1069–1077, 1950.
275. MYERSON, A., HALLORAN, R. D. AND HIRSCH, H. L.: Technique for obtaining blood from the internal jugular vein and internal carotid artery. Arch. Neurol. Psychiat., Chicago 17: 807–808, 1927.
276. NALL, M. L., AND FERGUSON, F. C.: Physiology of the circulation of the brain. An annotated bibliography. Part II. Report literature, 1938–1952. Physiol. Rev. 36 (Suppl. No. 2): 1–148, 1956.
277. NGAI, S. H. AND NELSON, E. C.: Induced hypotension and cerebral blood flow. J. appl. Physiol. 7: 176–179, 1954.
278. NICKERSON, M.: The pharmacology of adrenergic blockade. Pharmacol. Rev. 1: 27–101, 1949.
279. NIELSEN, M. AND SMITH, H.: Studies on the regulation of respiration in acute hypoxia. With an appendix on respiratory control during prolonged hypoxia. Acta physiol. scand. 24: 293–313, 1951.
280. NIMS, L. F., GIBBS, E. L. AND LENNOX, W. G.: Arterial and cerebral venous blood. Changes produced by altering alterial carbon dioxide. J. biol. Chem. 145: 189–195, 1942.
281. NOELL, W.: Über die Wirkung des Theophyllins und der verschiedenen Lösungsvermittler auf die Gehirndurchblutung. Z. ges. exp. Med. 110: 589–600, 1942.
282. NOELL, W.: Über die Durchblutung und die Sauerstoffversorgung des Gehirns. VI. Einfluss der Hypoxämie und Anämie. Pflüg. Arch. ges. Physiol. 247: 553–575, 1944.
283. NOELL, W. AND SCHNEIDER, M.: Die Gehirndurchblutung bei Sauerstoffmangel und bei Übergang von Sauerstoffmangel auf reinen O_2 und auf O_2/CO_2 Gemische. Luftfahrtmedizin 5: 234–250, 1941.
284. NOELL, W. AND SCHNEIDER, M.: Über die Wirkung der Kohlensäure auf Blutdruck und Gehirndurchblutung im Sauerstoffmangel. Luftfahrtmedizin 5: 251–262, 1941.
285. NOELL, W. AND SCHNEIDER, M.: Über den Einfluss der Hyperventilation auf die Gehirndurchblutung. Luftfahrtmedizin 5: 263–266, 1941.
286. NOELL, W. AND SCHNEIDER, M.: Über die Durchblutung und die Sauerstoffversorgung des Gehirns im akuten Sauerstoffmangel. I. Die Gehirndurchblutung. Pflüg. Arch. ges. Physiol. 246: 189–200, 1942.
287. NOELL, W. AND SCHNEIDER, M.: Über die Durchblutung und die Sauerstoffversorgung des Gehirns im akuten Sauerstoffmangel. III. Die arteriovenöse Sauerstoff- und Kohlensäuredifferens. Pflüg. Arch. ges. Physiol. 246: 207–249, 1942.
288. NOELL, W. AND SCHNEIDER, M.: Über die Durchblutung und die Sauerstoffversorgung des Gehirns. IV. Die Rolle der Kohlensäure. Pflüg. Arch. ges. Physiol. 247: 514–527, 1944.
289. NORCROSS, N. C.: Intracerebral blood flow: an experimental study. Arch. Neurol. Psychiat., Chicago 40: 291–299, 1938.
290. NOVACK, P., SHENKIN, H. A., BORTIN, L., GOLUBOFF, B. AND SOFFE, A. M.: The effects of carbon dioxide inhalation upon the cerebral blood flow and cerebral oxygen consumption in vascular disease. J. clin. Invest. 32: 696–702, 1953.
291. NYLIN, G. AND BLÖMER, H.: Studies on distribution of cerebral blood flow with thorium B-labeled erythrocytes. Circulation Res. 3: 79–85, 1955.
292. PAGE, W. F., GERMAN, W. J. AND NIMS, L. F.: The nitrous oxide method for measurement of cerebral blood flow and cerebral gaseous metabolism in dogs. Yale J. Biol. Med. 23: 462–473, 1951.
293. PARRISH, A. E., KLEH, J. AND FAZEKAS, J. F.: Renal and cerebral hemodynamics with hypotension. Amer. J. med. Sci. 233: 35–39, 1957.
294. PATTERSON, J. L., HEYMAN, A., BATTEY, L. L. AND FERGUSON, R. W.: Threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. J. clin. Invest. 34: 1857–1864, 1955.
295. PATTERSON, J. L., HEYMAN, A. AND DUKE, T. W.: Cerebral circulation and metabolism in chronic pulmonary emphysema. With observations on the effects of inhalation of oxygen. Amer. J. Med. 12: 383–387, 1952.
296. PATTERSON, J. L., JR., WAITES, E. J. AND MCPHAUL, M. V.: Differential circulatory effects of carbon dioxide. Cited by PATTERSON *et al.* (294).
297. PATZ, A., EASTHAM, A., HIGGENBOTHAM, D. H. AND KLEH, T.: Oxygen studies in retrolental fibroplasia. II. The production of microscopic changes of retrolental fibroplasia in experimental animals. Amer. J. Ophthal. 36: 1511–1522, 1953.
298. PICKERING, G. W.: Observations on mechanism of headache produced by histamine. Clin. Sci. 1: 77–101, 1933.
299. POOL, J. L. AND NASON, G. I.: Cerebral circulation. XXXV. The comparative effect of ergotamine tartrate on the arteries in the pia, dura, and skin of cats. Arch. Neurol. Psychiat., Chicago 33: 276–282, 1935.
300. RAHN, H. AND FENN, W. O.: A Graphical Analysis of the Respiratory Gas Exchange. The O_2-CO_2 Diagram American Physiological Society, Washington, D. C., 1955.

301. Rein, H.: Vasomotorische Regulationen. Ergebn. Physiol. 32: 28–72, 1931.
302. Richardson, D. W., Ferguson, R. W. and Patterson, J. L.: Effects of mephentermine on cerebral metabolism and circulation. J. Pharmacol. 119: 219–224, 1957.
303. Rinkel, M., DeShon, H. J., Hyde, R. W. and Solomon, H. C.: Experimental schizophrenia-like symptoms. Amer. J. Psychiat. 108: 572–578, 1952.
304. Roberts, K. E., Poppell, J. W., Vanamee, P., Beals, R. and Randall, H. T.: Evaluation of respiratory compensation in metabolic alkalosis. J. clin. Invest. 35: 261–266, 1956.
305. Roch, M. and Roch-Besser, B.: De l'utilité du chlorhydrate de benzyl-imidazoline (priscol) dans les affections cérébrales consécutives à des déficits circulatoires. Schweiz. med. Wschr. 77: 679–680, 1947.
306. Roch-Besser, B.: La benzyl-imidazoline (priscol). Étude pharmacodynamique et applications cliniques. Helv. med. acta 17 (Suppl. 27): 1–175, 1950.
307. Roseman, E., Goodwin, C. W. and McCulloch, W. S.: Rapid changes in cerebral oxygen tension induced by altering the oxygenation and circulation of the blood. J. Neurophysiol. 9: 33–40, 1946.
308. Rossen, R., Kabat, H. and Anderson, J. P.: Acute arrest of cerebral circulation in man. Arch. Neurol. Psychiat., Chicago 50: 510–528, 1943.
309. Rowe, G. G., Huston, J. H., Weinstein, A. B., Tuchman, H., Brown, J. F. and Crumpton, C. W.: The hemodynamics of thyrotoxicosis in man with special reference to coronary blood flow and myocardial oxygen metabolism. J. clin. Invest. 35: 272–276, 1956.
310. Rushmer, R. F., Beckman, E. L. and Lee, D.: Protection of cerebral circulation by the cerebrospinal fluid under the influence of radial acceleration. Amer. J. Physiol. 151: 355–365, 1948.
311. Russek, H. I. and Zohman, B. L.: Papaverine in cerebral angiospasm (vascular encephalopathy). J. Amer. med. Ass. 136: 930–933, 1948.
312. Ryder, H. W., Espey, F. F., Kristoff, F. V. and Evans, J. P.: The measurement of instantaneous changes in cerebral blood flow in human beings by its effect on the cerebrospinal fluid pressure. J. Lab. clin. Med 36: 982, 1950.
313. Ryder, H. W., Espey, F. F., Kristoff, F. V. and Evans, J. P.: Observations on the interrelationships of intracranial pressure and cerebral blood flow. J. Neurosurg. 8: 46–58, 1951.
314. Sapirstein, L. A. and Ogden, E.: Theoretical limitations of the nitrous oxide method for the determination of regional blood flow. Circulation Res. 4: 245–249, 1956.
315. Scheinberg, P.: Cerebral blood flow in vascular disease of the brain, with observations on the effect of stellate ganglion block. Amer. J. med. Sci. 8: 139–147, 1950.
316. Scheinberg, P.: The effect of nicotinic acid on the cerebral circulation with observations on extracerebral contamination of cerebral venous blood in the nitrous oxide procedure for cerebral blood flow. Circulation 1: 1148–1154, 1950.
317. Scheinberg, P.: Cerebral circulation and metabolism in hyperthyroidism. J. clin. Invest. 29: 1010–1013, 1950.
318. Scheinberg, P.: Cerebral blood flow and metabolism in pernicious anemia. Blood 6: 213–227, 1951.
319. Scheinberg, P., Blackburn, I. and Rich, M.: The effects of intravenous priscoline on cerebral circulation and metabolism. J. clin. Invest. 32: 125–129, 1953.
320. Scheinberg, P., Blackburn, I., Rich, M. and Saslaw, M.: Effects of aging on cerebral circulation and metabolism. Arch. Neurol. Psychiat., Chicago 70: 77–85, 1953.
321. Scheinberg, P., Blackburn, I., Saslaw, M., Rich, M. and Baum, G.: Cerebral circulation and metabolism in pulmonary emphysema and fibrosis with observations on the effects of mild exercise. J. clin. Invest. 32: 720–728, 1953.
322. Scheinberg, P. and Jayne, H. W.: Factors influencing cerebral blood flow and metabolism. A review. Circulation 5: 225–236, 1952.
323. Scheinberg, P., Jayne, H. W., Blackburn, L. I. and Rich, M.: Studies of cerebral circulatory functions following intravenous administration of procaine hydrochloride. Arch. Neurol. Psychiat., Chicago 68: 815–818, 1952.
324. Scheinberg, P. and Stead, E. A., Jr.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization and peripheral resistance, with observations on the effect of tilting and anxiety. J. clin. Invest. 28: 1163–1171, 1949.
325. Scheinberg, P., Stead, E. A., Jr., Brannon, E. S. and Warren, J. V.: Correlative observations on cerebral metabolism and cardiac output in myxedema. J. clin. Invest. 29: 1139–1146, 1950.
326. Schieve, J. F., Scheinberg, P. and Wilson, W. P.: The effect of adrenocorticotrophic hormone (ACTH) on cerebral blood flow and metabolism. J. clin. Invest. 30: 1527–1529, 1951.
327. Schieve, J. F. and Wilson, W. P.: Failure of desoxycorticosterone glucoside to alter cerebral venous sugar concentration in man. J. clin. Invest. 31: 984–985, 1952.
328. Schieve, J. F. and Wilson, W. P.: The influence of age, anesthesia and cerebral arteriosclerosis on cerebral vascular activity to carbon dioxide. Amer. J. Med. 15: 171–174, 1953.
329. Schieve, J. F. and Wilson, W. P.: The changes in cerebral vascular resistance of man in experimental alkalosis and acidosis. J. clin. Invest. 32: 33–38, 1953.
330. Schmidt, C. F.: The influence of cerebral blood flow on respiration. I. The respiratory responses to changes in cerebral blood flow. Amer. J. Physiol. 84: 202–222, 1928.
331. Schmidt, C. F.: The influence of cerebral blood flow on respiration. II. The gaseous metabolism of the brain. Amer. J. Physiol. 84: 223–241, 1928.
332. Schmidt, C. F.: The intrinsic regulation of the circulation in the hypothalamus of the cat. Amer. J. Physiol. 110: 137–152, 1934.
333. Schmidt, C. F.: The intrinsic regulation of the circulation in the parietal cortex of the cat. Amer. J. Physiol. 114: 572–585, 1936.

334. SCHMIDT, C. F.: The present status of knowledge concerning the intrinsic control of the cerebral circulation and the effects of functional derangements on it. Fed. Proc. 3: 131-139, 1944.
335. SCHMIDT, C. F.: Recent developments in respiratory physiology related to anesthesia. Anesthesiology 6: 113-123, 1945.
336. SCHMIDT, C. F.: Recent studies of the cerebral circulation. Harvey Lect. Series XLIV: 124-144, 1948-1949.
337. SCHMIDT, C. F.: The Cerebral Circulation in Health and Disease. Charles C. Thomas, Springfield 1950.
338. SCHMIDT, C. F. AND HENDRIX, J. P.: The action of chemical substances on cerebral blood vessels. Res. Publ. Ass. nerv. ment. Dis. 18: 229-276, 1937.
339. SCHMIDT, C. F., KETY, S. S. AND PENNES, H. H.: Gaseous metabolism of the brain of the monkey. Amer. J. Physiol. 143: 33-52, 1945.
340. SCHMIDT, C. F. AND PIERSON, J. C.: The intrinsic regulation of the blood vessels of the medulla oblongata. Amer. J. Physiol. 108: 241-263, 1934.
341. SCHNEIDER, M. AND SCHNEIDER, D.: Untersuchungen über die Regulierung der Gehirndurchblutung. II. Mitteilung. Einwirkung verschiedener Pharmaca auf die Gehirndurchblutung. Arch. exp. Path. Pharmak. 175: 640-664, 1934.
342. SCHROEDER, H. A.: The effect of 1-hydrasinophthalasine in hypertension. Circulation 5: 28-37, 1952.
343. SCHUMACHER, G. A. AND WOLFF, H. G.: Experimental studies on headache. A. Contrast of histamine headache with the headache of migraine and that associated with hypertension. B. Contrast of vascular mechanisms in pre-headache and in headache phenomena of migraine. Arch. Neurol. Psychiat., Chicago 45: 199-214, 1941.
344. SENSENBACH, W., MADISON, L., EISENBERG, S. AND OCHS, L.: The cerebral circulation and metabolism in hyperthyroidism and myxedema. J. clin. Invest. 33: 1434-1440, 1954.
345. SENSENBACH, W., MADISON, L. AND OCHS, L.: A comparison of the effects of l-nor-epinephrine, synthetic l-epinephrine and U.S.P. epinephrine upon cerebral blood flow and metabolism in man. J. clin. Invest. 32: 226-232, 1953.
346. SENSENBACH, W., MADISON, L. AND OCHS, L.: The effect of ACTH and cortisone on cerebral blood flow and metabolism. J. clin. Invest. 32: 372-380, 1953.
347. SEROTA, H. M. AND GERARD, R. W.: Localised thermal changes in cat's brain. J. Neurophysiol. 1: 115-124, 1938.
348. SÈZE, S. DE: De l'anémie cérébrale à la congestion cérébrale. Sem. Hôp. Paris 14: 307-314, 1938.
349. SHELBURNE, S. A., BLAIN, D. AND O'HARE, J. D.: Spinal fluid in hypertension. J. clin. Invest. 11: 489-496, 1932.
350. SHENKIN, H. A.: Effects of various drugs upon cerebral circulation and metabolism in man. J. appl. Physiol. 3: 465-471, 1951.
351. SHENKIN, H. A.: The cerebral circulation in post-operative intracranial hypotension. J. Neurosurg. 10: 48-51, 1953.
352. SHENKIN, H. A., CABIESES, F. AND VAN DEN NOORDT, G.: The effect of bilateral stellate ganglionectomy upon the cerebral circulation of man. J. clin. Invest. 30: 90-93, 1951.
353. SHENKIN, H. A., HAFKENSCHIEL, J. H. AND KETY, S. S.: Effects of sympathectomy on the cerebral circulation of hypertensive patients. Arch. Surg., Chicago 61: 319-324, 1950.
354. SHENKIN, H. A., HARMEL, M. H. AND KETY, S. S.: Dynamic anatomy of the cerebral circulation. Arch. Neurol. Psychiat., Chicago 60: 240-252, 1948.
355. SHENKIN, H. A., SPITZ, E. B., GRANT, F. C. AND KETY, S. S.: The acute effects on the cerebral circulation of the reduction of increased intracranial pressure by means of intravenous glucose or ventricular drainage. J. Neurosurg. 5: 466-470, 1948.
356. SIEKER, H. O. AND HICKAM, J. B.: Normal and impaired retinal vascular reactivity. Circulation 7: 79-83, 1953.
357. SINGER, R. B., DEERING, R. C. AND CLARK, J. K.: The acute effects in man of a rapid intravenous infusion of hypertonic sodium bicarbonate solution. II. Changes in respiration and output of carbon dioxide. J. clin. Invest. 35: 245-253, 1956.
358. SJÖSTRAND, T.: Brain volume, diameter of the blood vessels in the pia mater, and intracranial pressure in acute carbon monoxide poisoning. Acta physiol. scand. 15: 351-361, 1948.
359. SMITH, S. AND TURTON, E. C.: Restoration of speech in severe aphasia by intravenous and oral priscol. Brit. med. J. 2: 891-892, 1951.
360. SOHLER, T. P., LOTHROP, G. N. AND FORBES, H. S.: The pial circulation of normal, non-anesthetized animals. II. The effects of drugs, alcohol, and CO_2. J. Pharmacol. 71: 331-335, 1941.
361. SOHLER, T. P., LOTHROP, G. N. AND WILKINSON, J.: The effects of sedative drugs on the pial vessels. J. Pharmacol. 72: 409-416, 1941.
362. SOKOLOFF, L.: Local blood flow in neural tissue. In: New Research Techniques of Neuroanatomy, pp. 51-61. Charles C. Thomas, Springfield 1957.
363. SOKOLOFF, L., LANDAU, W. M., FREYGANG, W. H., ROWLAND, L. P. AND KETY, S. S.: Normal values for regional blood flow in the cat's brain. Fed. Proc. 14: 142, 1955.
364. SOKOLOFF, L., MANGOLD, R., WECHSLER, R. L., KENNEDY, C. AND KETY, S. S.: The effect of mental arithmetic on cerebral circulation and metabolism. J. clin. Invest. 34: 1101-1108, 1955.
365. SOKOLOFF, L., PERLIN, S., KORNETSKY, C. AND KETY, S. S.: The effects of d-lysergic acid diethylamide on cerebral circulation and over-all metabolism. Ann. N. Y. Acad. Sci. 66: 468-477, 1957.
366. SOKOLOFF, L. AND WAGNER, J.: Unpublished observations.
367. SOKOLOFF, L., WECHSLER, R. L., MANGOLD, R., BALLS, K. AND KETY, S. S.: Cerebral blood flow and oxygen consumption in hyperthyroidism before and after treatment. J. clin. Invest. 32: 202-208, 1953.
368. STADIE, W. C., RIGGS, B. C. AND HAUGAARD, N.: Oxygen poisoning. Amer. J. med. Sci. 207: 84-114, 1944.
369. STECK, I. E. AND GELLHORN, E.: The effect of carbon dioxide inhalation on the peripheral blood flow in the normal and in the sympathectomized patient. Amer. Heart J. 18: 206-212, 1939.

370. Stewart, H. J. and Evans, W. F.: The peripheral blood flow in hyperthyroidism. Amer. Heart J. 20: 715–742, 1940.
371. Stewart, H. J. and Evans, W. F.: Peripheral blood flow in myxedema. Arch. intern. Med. 69: 808–821, 1942.
372. Stoll, W. A.: Lysergäure-diäthylamid, ein Phantasticum aus der Mutterkorngruppe. Schweiz. Arch. Neurol. Psychiat. 60: 279–323, 1947.
373. Stone, H. H., MacKrell, T. N., Brandstater, B. J., Haidak, G. L. and Nemir, P.: The effect of induced hemorrhagic shock on the cerebral circulation and metabolism of man. Surg. Forum 5: 789–794, 1955.
374. Stone, H. H., MacKrell, T. N. and Wechsler, R. L.: The effect on cerebral circulation and metabolism in man of acute reduction in blood pressure by means of intravenous hexamethonium bromide and head-up tilt. Anesthesiology 16: 168–175, 1955.
Storch, T. J. C. von, see 385.
375. Stunkard, A., Wertheimer, L. and Redisch, W.: Studies on hydralazine; evidence for a peripheral site of action. J. clin. Invest. 33: 1047–1053, 1954.
376. Sutherland, A. M. and Wolff, H. G.: Experimental studies in headache: further analysis of the mechanism of headache in migraine, hypertension, and fever. Arch. Neurol. Psychiat., Chicago 44: 929–949, 1940.
377. Taeschler, M., Cerletti, A. and Rothlin, E.: Zur Frage der Hyderginwirkung auf die Gehirnsirkulation. Helv. physiol. acta 10: 120–137, 1952.
378. Taylor, H. W. and McCall, M. L.: The cerebral effects of pentothal sodium in toxemias of pregnancy. J. Philad. Gen. Hosp. 2: 86–89, 1951.
379. Thomas, C. B.: The cerebral circulation. XXXI. Effect of ethyl alcohol on cerebral vessels. Arch. Neurol. Psychiat., Chicago 38: 321–339, 1937.
380. Tullar, B. F.: Separation of l-arterenol from natural U.S.P. epinephrine. Science 109: 536–537, 1949.
381. Turner, J., Lambertsen, C. J., Owen, S. G., Wendel, H. and Chiodi, H.: Effects of .08 and .8 atmospheres of inspired pO_2 upon cerebral hemodynamics at a "constant" alveolar pCO_2 of 43 mm. Hg. Fed. Proc. 16: 130, 1957.
382. Unna, K.: Antagonistic effect of N-allylnormorphine upon morphine. J. Pharmacol. 79: 27–31, 1943.
383. Van Itallie, T. B. and Clarke, C. W., Jr.: The effect of priscoline on peripheral blood flow in normal subjects and patients with peripheral vascular diseases. Circulation 3: 820–829, 1951.
384. Van Middlesworth, L. and Kline, R. F.: Protection against acceleratory forces by carbon dioxide inhalation. Amer. J. Physiol. 152: 22–26, 1948.
385. Von Storch, T. J. C.: Relation of experimental histamine headache to migraine and non-migraine headache. Arch. Neurol. Psychiat., Chicago 44: 316–322, 1940.
386. Wechsler, R. L.: Effects of cigarette smoking and intravenous nicotine on the human brain. Fed. Proc. 17: 169, 1958.
387. Wechsler, R. L., Dripps, R. D. and Kety, S. S.: Blood flow and oxygen consumption of the human brain during anesthesia produced by thiopental. Anesthesiology 12: 308–314, 1951.
388. Wechsler, R. L., Kleiss, L. M. and Kety, S. S.: The effects of intravenously administered aminophylline on cerebral circulation and metabolism in man. J. clin. Invest. 29: 28–30, 1950.
389. Weed, L. H. and Hughson, W.: Intracranial venous pressure and cerebrospinal fluid pressure as affected by intravenous injections of solutions of various concentrations. Amer. J. Physiol. 58: 101–130, 1921.
390. Weiss, S. and Lennox, W. G.: The cerebral circulation. XVII. Cerebral blood flow and the vasomotor response of the minute vessels of the human brain to histamine. Arch. Neurol. Psychiat., Chicago 26: 737–744, 1931.
391. Weiss, S., Robb, G. P. and Ellis, L. B.: The systemic effects of histamine in man, with special reference to the responses of the cardiovascular system. Arch. intern. Med. 49: 360–396, 1932.
392. Wheatley, M. D.: Mechanism of cerebral death with doses of NaCN from which the heart recovers. J. Neuropath. 6: 295–298, 1947.
393. White, J. C., Verlot, M., Silverstone, B. and Beecher, H. K.: Changes in brain volume during anesthesia. The effects of anoxia and hypercapnia. Arch. Surg., Chicago 44: 1–21, 1942.
394. Whittaker, S. R. F. and Winton, F. R.: The apparent viscosity of blood flowing in the isolated hind limb of the dog and its variation with corpuscular concentration. J. Physiol. 78: 339–369, 1933.
395. Wilkins, R. W., Freis, E. D. and Stanton, J. R.: Essential hypertension: laboratory studies in human beings with drugs recently introduced. J. Amer. med. Ass. 140: 261–265, 1949.
396. Williams, D. and Lennox, W. G.: The cerebral blood flow in arterial hypertension, arteriosclerosis, and high intra-cranial pressure. Quart. J. Med. 8: 185–194, 1939.
397. Wilson, W. P., Odom, G. L. and Schieve, J. F.: The effect of carbon dioxide on cerebral blood flow, spinal fluid pressure, and brain volume during Pentothal® Sodium anesthesia. Curr. Res. Anesth. 32: 268–273, 1953.
398. Wolff, H. G.: The cerebral circulation. XIa. The action of acetylcholine. XIb. The action of the posterior lobe of the pituitary gland. XIc. The action of amyl nitrite. Arch. Neurol. Psychiat., Chicago 22: 686–690, 1929.
399. Wolff, H. G.: The cerebral circulation. Physiol. Rev. 16: 545–596, 1936.
400. Wolff, H. G.: Headache and Other Pain. Oxford University Press, New York 1948.
401. Wolff, H. G. and Forbes, H. S.: The cerebral circulation. IV. The action of hypertonic solutions. Arch. Neurol. Psychiat., Chicago 20: 73–83, 1928.
402. Wolff, H. G. and Lennox, W. G.: Cerebral circulation. XII. The effect on pial vessels of variations in the O_2 and CO_2 content of the blood. Arch. Neurol. Psychiat., Chicago 23: 1097–1120, 1930.