JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
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Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932
C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933
D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934
C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races;* April 25, 1935
Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders;* May 15, 1936
R. W. Gerard, *Dynamic Neural Patterns;* April 15, 1937
Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull;* May 5, 1938
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Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates;* May 8, 1941
George Pinkley, *A History of the Human Brain;* May 14, 1942
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Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man;* April 25, 1957
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Charles R. Noback, *The Heritage of the Human Brain;* May 6, 1959
Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization;* May 26, 1960

BRAIN FUNCTION AND THE EVOLUTION OF CEREBRAL VASCULARIZATION

"KNOWLEDGE OF THE ONTOGENY AND PHYLOGENY OF THE VESSELS WITHIN THE BRAIN SUBSTANCE IS STILL SOMEWHAT MEAGER" (E. HORNE CRAIGIE, 1938).

The quoted statement is as valid today as it was in 1938. During the past century a vast amount of effort has been directed toward the study of the evolution of the brain from the lowest forms to the primates. However, little attention has been paid to the phylogeny of the vascular system, without which the human brain could not have attained its present level of differentiation. This neglect of cerebral vascularization as a subject for study is surprising in view of its importance to clinical medicine. "According to reports of the epidemiologic and demographic sections of the World Health Organization, mortality rate from vascular disease of the nervous system holds third place (following heart disease and cancer). This problem has social significance because vascular diseases of the brain frequently disable and make invalids of people who, on the basis of their age, should still be working and still be valuable members of society" (Anonymous, 1959; see also Wright and Luckey, 1955). One of the reasons for the prominent role of the cerebral vascular system in human pathology is the high degree of sensitivity of nervous tissue to lack of oxygen and nutrients. Dysfunction of the central nervous system may result, therefore, from trivial causes such as prolonged erect posture. In this condition the heart may have trouble overcoming gravity and consequently pump an inadequate supply of blood into the brain. Fainting is the well-known result of such temporary anemia of the brain. More serious interference with the flow of blood in the cerebral vessels for even a short time, the time being measured in minutes (Dennis and Kabat, 1939; Bronk, Larrabee, and Gaylor, 1948; Gänshirt and Zylka, 1952; Ten Cate and Horsten, 1954), will cause irreparable damage to nerve cells. Similarly, when at birth the transition from intra-uterine oxygen supply via the maternal circulation to oxygenation of the newborn's blood by his own active respiration does not occur promptly, permanent brain damage and even death may result. Clearly, the human brain could not have reached its complex organization and could not function at the high level it does, if there had not occurred a parallel evolution of its system of supply, namely, the cerebral blood vessels.

The study of this evolution cannot be approached by tracing it through the phyla of the animal kingdom in the order of their taxonomic position beginning with the lower multicellular forms. We shall find instead corresponding levels of morphological and functional differentiation of cerebral vessels in unrelated groups of invertebrates and vertebrates. Consequently we shall consider various types of cerebral vascular systems from the point of view of functional competence, using whatever examples serve best to illustrate consecutive steps in the evolution of cerebral blood supply, irrespective of the level of the phylogenetic order at which they occur.

Extracerebral Blood Supply

As long as the central nervous system is small and primitive, as in many invertebrates, in cephalochordates (*Branchiostoma*), and in cyclostomes (spinal cord of *Petromyzon*), diffusion of oxygen and nutrients from surface vessels is adequate to keep the nerve cells alive and functioning. Also the insect brain, which in some orders reaches a high degree of structural differentiation and functional competence, possesses no intracerebral vessels. However, the insect brain does not depend for its oxygen supply on the hemolymph which surrounds it. The tracheae, fine tubes kept permanently open by chitinous spirals supporting their walls, conduct air into the tissues and even into single cells (Hilton, 1909). The nerve cells are thus aerated by pipes open to the air outside the body. This system is highly efficient, as anyone can attest who has experienced the effects of low oxygen pressure at high altitudes, where insects fly around without signs of discomfort. Also, the mode of providing nutritive materials to the insect brain may not be so inadequate as it would seem if diffusion from extracerebral blood were the only means of supply. There is evidence that glia cells may play an active role in the transport of nutrients to neurons in insects (B. Scharrer, 1939; Pipa, 1961) in a way similar to that which has been suggested for vertebrates (Farquhar and Hartman, 1957; Hartman, 1958). Glia cells as intermediaries between hemolymph and nerve cells may be particularly important in such a case as that of the honeybee which is subject to wide fluctuations of its blood sugar level, the effects of which could well be disastrous if blood came in direct contact with nerve cells. Extracerebral blood supply need not indicate, therefore, a low level of vascular differentiation in all instances; it may, for example, represent one way of maintaining an effective blood-brain barrier.[1] However, the absence of intracerebral blood vessels may have prevented the evolution of insects beyond their present level, since there is a limit to the size that a brain which is nourished from its surface may attain. This may be just as well, because smarter, larger, and more effective insects would probably cause more trouble than man could endure.

[1] The problem of the blood-brain barrier has been extensively studied in vertebrates, particularly man (for references, see Bakay, 1956). Little, if anything, is known about it in invertebrates.

One cannot be sure whether primitive vertebrates the central nervous systems of which do not possess internal vessels remained what they are because their cerebral circulation is poorly developed, or whether the vascular pattern persisted in an underdeveloped stage because it is adequate for the primitive central nervous system of these forms. All vertebrates, except the few cases mentioned, and some invertebrate phyla have "invented" intracerebral vessels which permit growth of the central nervous system. In the course of evolution, an increasingly complex vascular system attempted to keep up with the progressive differentiation of the vertebrate brain and its growing demands. In the most highly developed forms, such as man, the circulatory system of the brain appears to have reached its limits.

Cerebral Arteries and Veins

With the appearance of intracerebral vessels, those on the surface of the brain become trunk lines maintaining a continuous flow of blood which keeps the capillary system supplied at all times. They are divided into arteries which conduct the blood to the intracerebral smaller vessels, and veins which drain the capillary bed. In view of the high degree of sensitivity of nerve cells to lack of oxygen, we are particularly interested in those emergency provisions that assure collateral circulation in case of occlusion of an artery. In the primate brain the internal carotid and the vertebral arteries form a system of anastomoses at the base of the brain (arterial circle of Willis) from which the major arteries originate. These in turn branch out over the surface of the brain, anastomosing and forming a rich network (figs. 1 and 2). It is these surface vessels that have been frequently studied in living animals, either in the exposed brain or through plastic windows inserted into the skull. Many useful and interesting observations have been made in this way, but it must be

FIG. 1. Ventral view of the brain of a rhesus monkey. The surface vessels are injected with colored gelatine. For explanation, see figure 2.

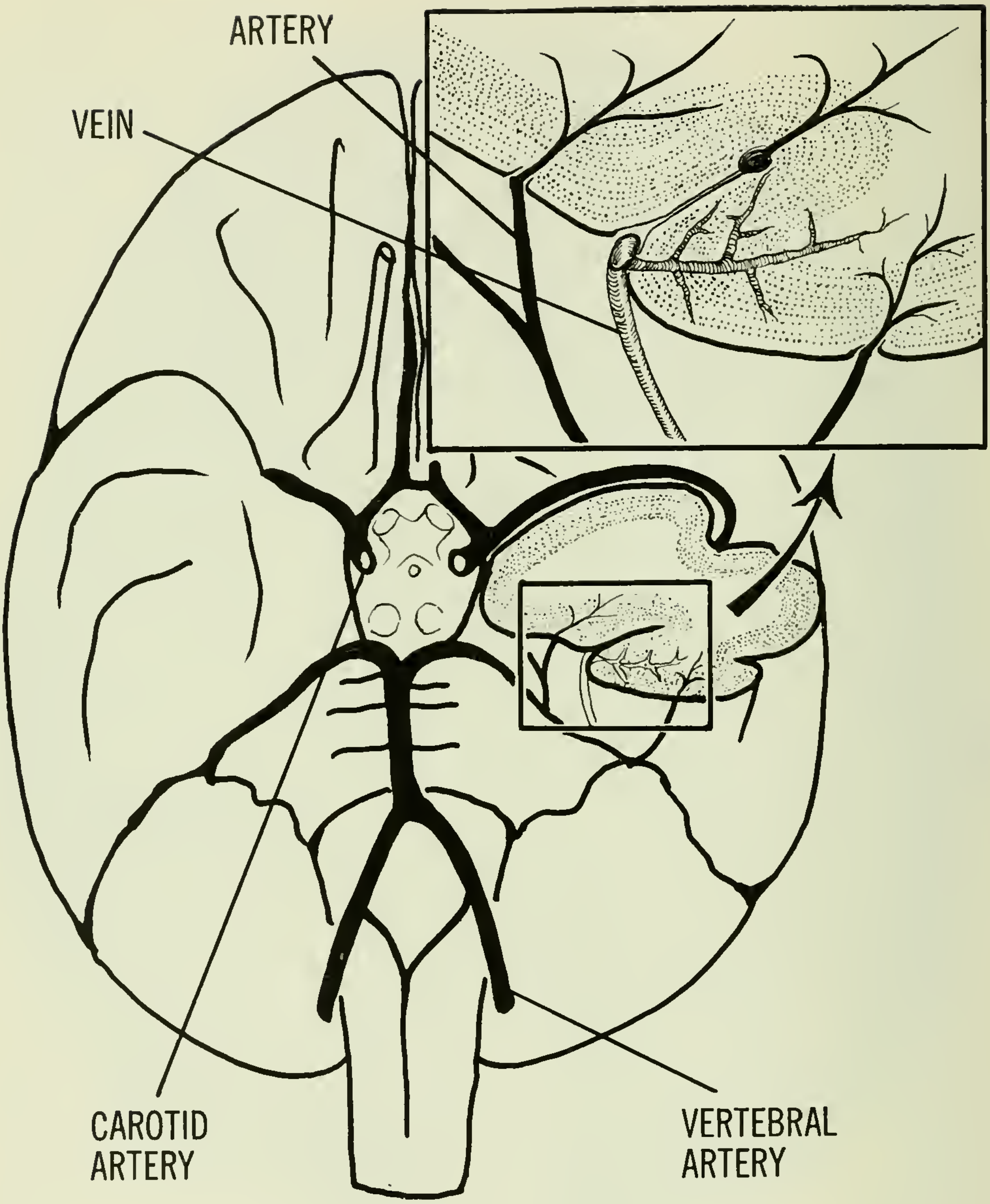

FIG. 2. Same view of monkey brain as is illustrated in figure 1. The anterior pole of the left temporal lobe has been cut off in order to show how blood vessels enter the brain substance. The arrow points to the enlarged picture of the rectangular area of the cut surface.

remembered that they provide only partial information about cerebral circulation. This information is akin to the readings that a public utilities company obtains from measuring the amounts of water, gas, and electricity delivered to a building. Such "data" convey only a general idea of the activities inside a house; what goes on in each room remains unknown.

Once arterial branches enter the nervous tissue, we can no longer observe them in the living animal but must depend on the study of dead tissue and on indirect evidence obtained by a variety of experimental methods. The pitfalls implicit in this approach are well illustrated by the erroneous identification of arteries and veins by Pfeifer (1928, 1930) who, in a series of papers, described the arteries as veins and the veins as arteries in sections of injected brains of various mammals. This error, although it was pointed out (Campbell, 1938; E. Scharrer, 1938), has produced all sorts of wrong conclusions. The correct identification is illustrated in figure 3 of the present paper. The anatomical differences between arteries and veins are probably related to hemodynamic conditions. The blood is injected by the arteries into the capillary bed under high pressure; the smooth curves and mode of branching of the arteries presumably facilitate the flow of blood. By contrast, the blood drains from the capillary bed under low pressure; the smaller venous channels join the larger veins at right angles, like drainage ditches in which the water flows slowly toward larger canals. In lower vertebrates, cerebral vessels have not been studied with respect to their mode of branching, and it is, therefore, not clear whether this feature constitutes merely a functional adaptation in the placental mammals or has evolutionary significance. In marsupials paired arteries and veins branch in like manner (see below).

Abbie (1934) formulated two principles governing the

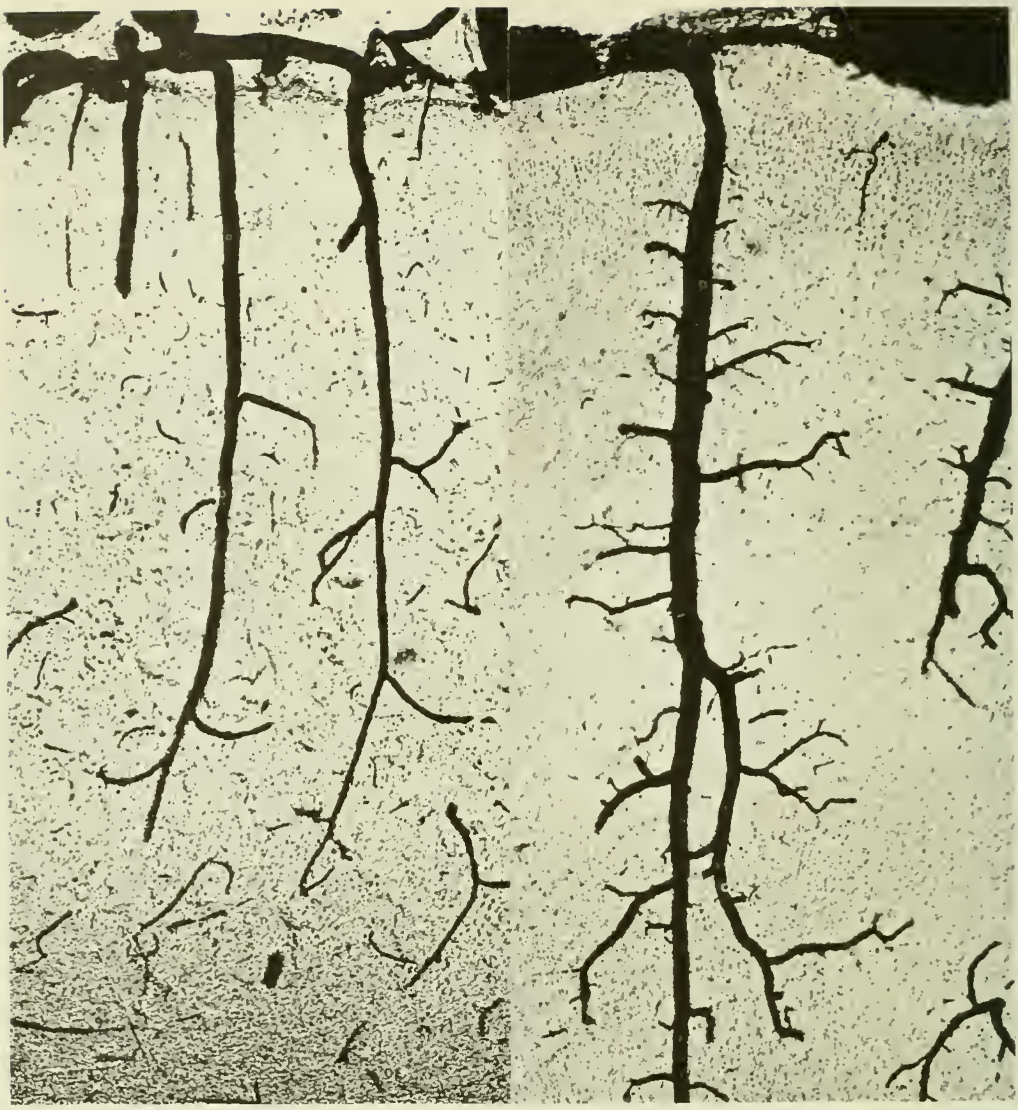

FIG. 3. Injected cat's brain. A. Intracerebral arteries. B. Intracerebral vein. Note the difference in the ramification of the two kinds of blood vessels.

relationship of arteries and cerebral tissue of vertebrates, namely, functional constancy and economy of distribution. Whenever a neural mechanism develops, an artery develops for its supply, and this relationship remains constant throughout evolution. As to the economy of distribution, we shall have more to say in some of the following sections of this paper.

The Ontogenetic Development of the Cerebral Vascular System

Consecutive stages in the differentiation of the cerebral vascular system during embryonic development of higher forms have their parallels in adult patterns of animals of lower phylogenetic order. These may be noted with interest, but conclusions should be drawn cautiously or not at all.

In the early period of development, "*le système vasculaire paraît n'avoir qu'un rapport égal et uniforme avec toutes les parties de la masse nerveuse centrale.*" In later stages, "*on commence à voir sur certains points, aux tubercules quadrijumaux, par exemple, une quantité plus considérable qu'ailleurs de ces vaisseaux,*" as Guyot observed as early as 1829. Since then the development of the cerebral vascular system has been studied by relatively few investigators (see Craigie, 1955; Strong, 1961). It is not only difficult to inject small embryos, but even in successful specimens one cannot be sure of the completeness of the injection. Vessels grow into the nervous tissue as solid strands of cells, becoming patent tubes later when they join up with other vessels. Here procedures of histochemistry may be applied to advantage. For example, the blood vessels of the developing rat brain are (and the fact is uniquely true of them but not of vessels of other organs) rich in alkaline phosphatase, the presence of which may be demonstrated by the method of Gomori (1939). Irrespective of whether or not the vessels are open, they can be traced in their entirety in sections from which the vascular system may be reconstructed as it appears at various stages of its ontogenetic development. As might be expected, the vessels form relatively simple networks in young embryos, similar to those found in more primitive vertebrates, e.g., urodeles. With increasing age, adult patterns begin to emerge, i.e., as nuclei and fiber tracts become more clearly defined, capillary density begins to show differences that reflect progressively the anatomical maturation of the brain (E. Scharrer, 1950).

It has been noted by Klosovskii (1956; see Simonson, 1960, under Bibliographies and Reviews) that the cerebral vessels of placental mammals grow into the embryonic brain tissue in the shape of loops. These are eventually absorbed into the general network, with a few remainders of paired vessels here and there in the adult central nervous system as, for instance, in the cat (Fleischhauer, 1961). The observation of loops in the early development of cerebral blood vessels is of interest in view of the fact that all vessels in the adult brain of marsupial mammals and of a variety of other vertebrates are of the loop type. These are of considerable interest and are discussed, therefore, in some detail in the following sections.

Loops and Networks

Whenever, in the course of evolution, blood vessels started to grow into the central nervous system they had two possibilities of joining up, as illustrated in figure 4. They can fold on themselves, so that each artery becomes paired with a vein and the capillaries end in hairpin-like loops. In this way systems of terminal vessels come about that do not communicate with one another. The brain of the earthworm (*Lumbricus*), the lamprey (*Petromyzon*), and many higher vertebrates shows this kind of vessel. A different type results when they join to form networks which also occur in both invertebrates and vertebrates. Finally, there are some animals that show intermediate types, i.e., networks with terminal loops. Although the difference between the network type and the loop type appears striking to the observer who compares sections of injected brain tissue obtained from animals showing the two types, e.g., opossum and rat, it is not difficult to visualize how the loop type can be converted into a two-

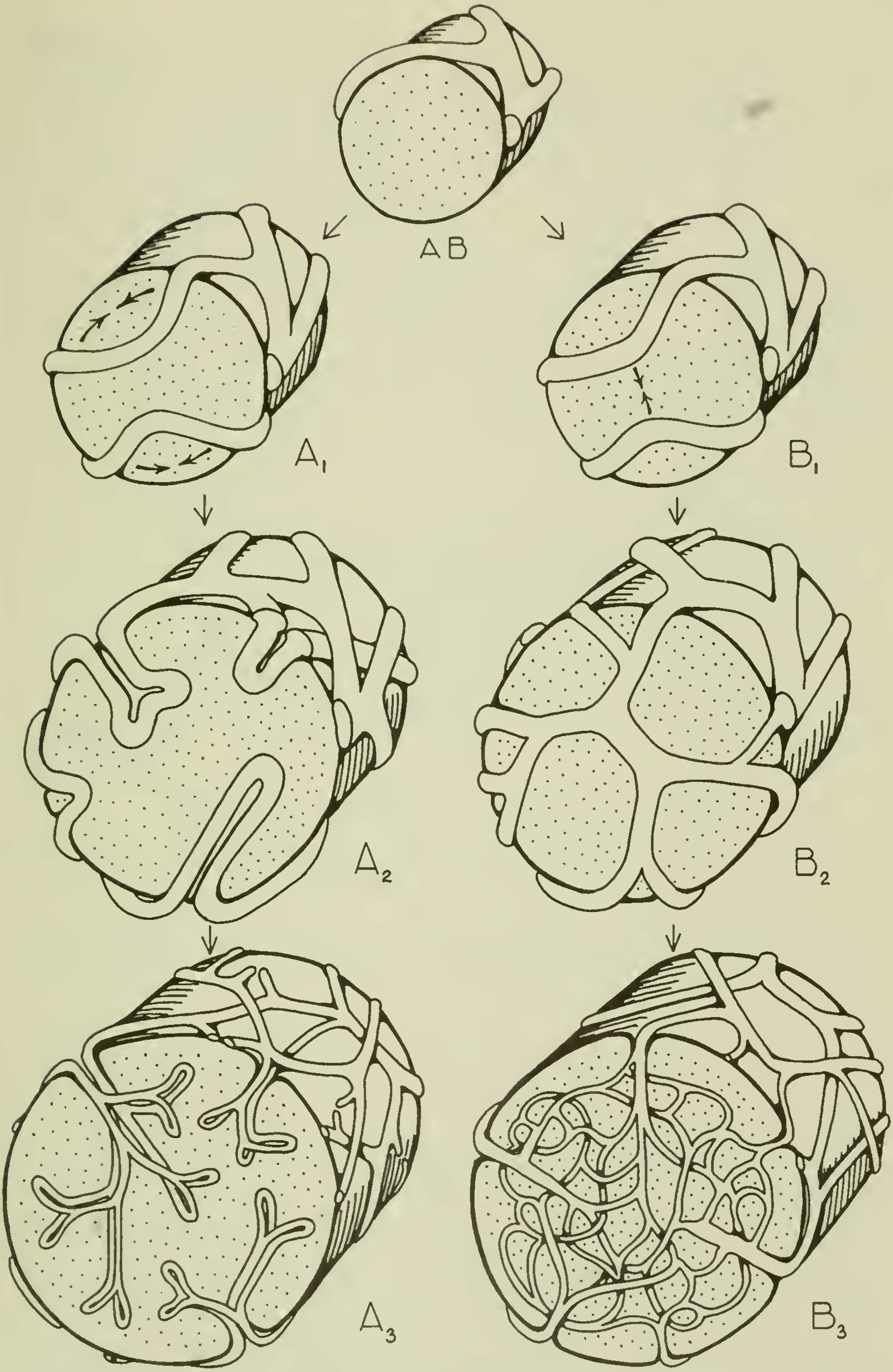

Fig. 4. Blood vessels growing into the nervous tissue may give rise to either terminal loops (A_1, A_2, A_3) or networks (B_1, B_2, B_3).

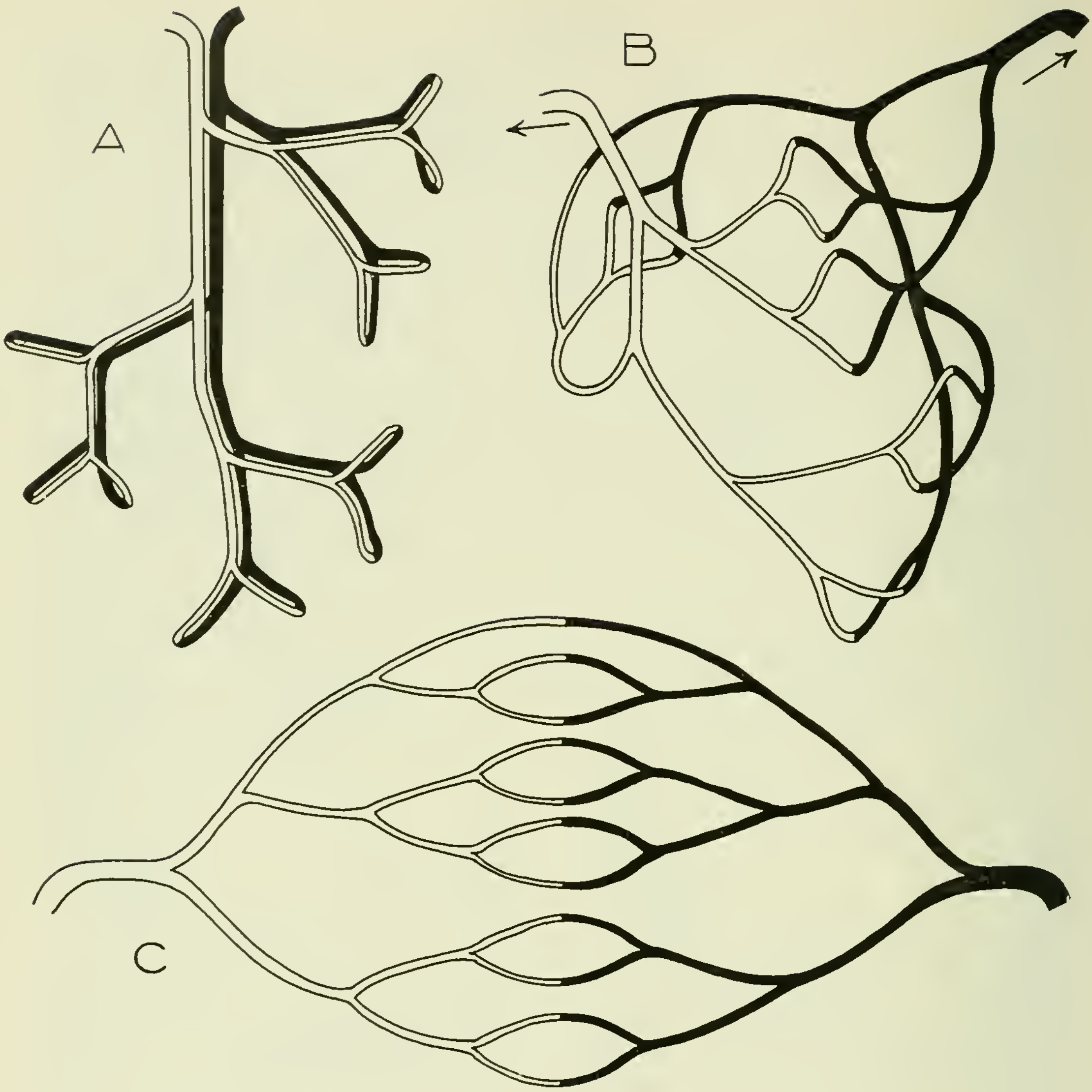

Fig. 5. Diagrams to show the relationship between a system of terminal loops (A) and a network of blood vessels (C).

dimensional network, by pulling artery and vein apart (fig. 5).

The question arises whether, in the course of evolution, loops preceded networks, and the latter therefore represent a more advanced type. It is true that the cerebral vessels of the marsupials, which are more primitive than the placental mammals, are of the loop type and that corresponding relationships obtain in reptiles and amphibians, but in general the occurrence of either type in unrelated groups of invertebrates and vertebrates does not support this concept (E.

Scharrer, 1944c). Before a superior rank to one of the two types is assigned, it might be well to examine their functional potentialities and to define more precisely in which sense the type of cerebral vessel might indicate levels of evolutionary progress.

The Loop Type: The occurrence of vascular loops was first described by Schöbl in the central nervous systems of reptiles (1878) and urodeles (1882). The findings were confirmed by Sterzi (1904) but aroused little interest until Wislocki and Campbell (1937) described the loop type of blood vessels in the brain of the opossum (*Didelphys virginiana*). In addition to further studies by Wislocki (1939), a number of investigators explored the cerebral vascular system of marsupials (E. Scharrer, 1938, 1939a, 1939b, 1940a, 1940b; Craigie, 1938c; Sunderland, 1941) and reexamined a variety of invertebrate and vertebrate brains for the occurrence of these peculiar vessels (Craigie, 1938a, 1938b, 1939, 1940a, 1940b, 1941a, 1941b, 1943; E. Scharrer, 1944b, 1944c).

The brain of the earthworm (*Lumbricus terrestris*) is supplied by paired vessels ending in hairpin loops (fig. 6A). A search among additional representatives of annelids and of invertebrates in general is likely to turn up a number of other groups possessing this type of vessel. Among the most primitive vertebrates, the cyclostomes, *Petromyzon* (Sterzi, 1904; Craigie, 1938a, 1938b, 1955) shows the same type of brain vessels as the earthworm. Actually, the vessels of the lamprey brain are more primitive than those of the earthworm in that they are simple, long, hairpin-shaped loops, which occasionally form a side loop but never branch. The vessels of the earthworm brain are more complex in that they branch as do those of the marsupial brain. Among the amphibians, the urodeles (salamanders, newts, and others), among the reptiles, the lizards, and among the mammals, the marsupials (opossum, kangaroo, and others), belong to

FIG. 6. Terminal capillary loops. A. Brain of the earthworm (*Lumbricus terrestris*). B. Brain of the opossum (*Didelphys virginiana*).

the category of animals with paired cerebral vessels ending in hairpin loops (fig. 6B).

The discovery by Wislocki and Campbell (1937) of the peculiar blood vessels of the opossum brain proved highly rewarding. The availability of a mammal whose brain is supplied by true end-arteries permitted the experimental investigation of a number of problems that had been raised by Cohnheim as early as 1872 in conjunction with observations on the vascular origin of neuropathological lesions. Thus, for instance, the selective vulnerability of the hippocampus, a phylogenetically ancient part of the mammalian brain, in carbon monoxide poisoning which had been related to end-arterial supply (Uchimura, 1928a, 1928b) was shown to have a different etiology (E. Scharrer, 1940b).

The Network Type: The human brain, which is supplied by a capillary network, shares this kind of vascularization with the brains of the squid, the hagfish, the ganoid and teleost fishes, the amphibians (except the urodeles), the reptiles (except the lizards), the birds, and the mammals (except the marsupials). Thus the great majority of the animals, the central nervous systems of which have been examined with respect to vascularity, exhibit the network type. In this arrangement all cerebral and spinal vessels are interconnected with one another by a vast bed of capillaries. It has been said that a red blood cell could enter at the olfactory bulb and thread its way through this type of capillary system to the end of the spinal cord without ever having to emerge and enter a vein. Such a voyage would be impossible in the brain of a marsupial in which an erythrocyte can pass through one vascular tree only, which it must leave via the companion vein of the artery, i.e., at the point where it entered the brain.

Determination of Vessel Type

The phylogenetic development of the cerebral vascular system could have taken place in two ways. Extracerebral vessels could have given rise to intracerebral vessels of the loop type which in higher forms became transformed into vessels of the network type. The alternative is a parallel development of loop and network systems from extracerebral blood vessels (see fig. 4), with the result that either system may be found in representatives of invertebrates and vertebrates unrelated to phylogenetic levels. The latter is what actually happened. The question arises as to what determines the type of blood vessel: Is it a property of the brain tissue which induces the ingrowth of the one or the other type, or are the determining factors inherent in the blood vascular system itself?

The question is difficult to decide by experimental methods in the early stages of development when the central nervous system becomes vascularized. However, one may draw some conclusions from the behavior of regenerating brain vessels which are given an opportunity to grow into brain tissue other than the kind that they normally supply. In experiments in which pieces of dead brain were exchanged between opossums having the loop type of vessels and guinea pigs in which the brain vessels are of the network type, the vessels of the host brain made an attempt to grow into the alien implant. These newly growing vessels were of the host type. Capillary loops, typical for the opossum, grew into implanted guinea pig brain tissue. Capillary networks characteristic of the brain of a placental mammal such as the guinea pig grew into opossum brain implants (E. Scharrer, 1940a). The experiment falls short of proving the thesis that the two existing types of cerebral vessels are the result of factors intrinsic in the vascular system and do not depend on any structural or chemical characteristics of the nervous tissue that they supply. However, the result agrees with the corresponding conclusion one must draw from the comparative survey. If one assumes a determining role of the nervous tissue, one must accept the proposition that the brains of the earthworm, the lamprey, the urodeles, the lizards, and the marsupials have something in common which causes blood vessels to form terminal loops, whereas the brains of all other animals, known to be supplied by networks, would have to have another common denominator on the presence of which depends the differentiation of the network type of vessels. This is most unlikely, and it seems safe to conclude that either one of the two inherent potentialities may be realized. The choice may be more or less accidental. How else could one interpret the fact that, within the cyclostomes, the brain of *Petromyzon* is vascularized by loop vessels, that of *Myxine* by a network?

If this view is correct, it was by chance that among the mammals the marsupial brain acquired loops and that of the placentals networks. Had it happened the other way around and the marsupials chosen the network type, would they have brought forth a *Homo sapiens* and would Dali's "Marsupial Centaurs" depict orthodox mythology? On the other hand, would the placental mammals, in spite of all their other potentialities for higher differentiation, never have developed a brain capable of abstract thought if its blood vessels were of the loop type? Or would the human brain have reached the same level of differentiation, irrespective of the type of vessels supplying it? How do the two types compare in terms of functional competence?

Comparison of Loop and Network Vessels

One look at the terminal vessels of a marsupial brain reveals what appears to be a major defect of this type: if an embolus occludes an artery, the brain area supplied by this particular vessel will be without nourishment and oxygen, because there are no connections with neighboring arteries that could take over by establishing a collateral circulation. That such a situation will indeed arise can be shown experimentally. If one injects *Lycopodium* spores into the carotid artery of an opossum, they will become lodged in the small arterioles cutting off the flow of blood. As a result, the nerve cells surrounding the capillary branches supplied by this arteriole will die (E. Scharrer, 1939a). One might expect that a network will be superior in such an emergency in that the anastomoses among the blood vessels will be utilized to supply the ischemic area. Actually such is not the case (Steegmann and Fuente, 1959). Occlusion of an artery in a network system also results in the death of the nervous tissue in the area supplied by the affected vessel. It appears that the capillary anastomoses are not adequate to supply the ischemic area quickly enough to prevent stasis of the blood and get circulation under way before the nerve cells suffer irreparable damage. This inability of vessels in the human brain to establish collateral circulation is so marked that Cohnheim in 1872 pronounced the doctrine of the brain's being supplied by "end-arteries," without confirming his thesis by the actual observation of such vessels in injected material. The frequent autopsy finding of focal softening of brain tissue following vascular accidents convinced Cohnheim that the blood vessels of the human brain are terminal vessels, each of which supplies a territory of its own. This concept dominated the thinking of neuropathologists until Pfeifer (1928, 1930) showed that cerebral "end-arteries" have no anatomical reality. However, the consequences of the occlusion of an artery supplying a network system are the same as those following an embolism of the terminal artery of a loop system. In this respect, then, man could not be worse off if his brain were supplied by the type of paired vessels that characterize the marsupial brain.

The same conclusion may be reached in a different way. If one exposes opossums to carbon monoxide, one of the most vulnerable structures turns out to be an ancient part of the brain, the so-called hippocampus, or Ammon's horn. This is precisely the same area which in man selectively succumbs to carbon monoxide poisoning. The phenomenon is not completely understood, but there is good evidence that it has a vascular basis (E. Scharrer, 1940b; Nilges, 1944). Again the network type does not prove superior to the loop type in a crisis like the one provoked by a toxic substance such as carbon monoxide.

In fact, the loop type would seem to represent an elegant solution of the problem of uniform and consistent blood supply to nerve cells. If one considers that in a network system blood flowing from the arterial to the venous end of the capillary deteriorates in its content of oxygen and nutrients, one would have to conclude that not all nerve cells lying along a capillary are equally well off. By contrast, in the loop system each pair of capillaries represents a unit operating on the counter current principle which should balance the differences in oxygen and carbon dioxide content at the arterial and venous ends of the two limbs. Such vessels would seem to guarantee the nerve cells a uniform supply throughout their entire length.

All told, the type of vascularization supplying the marsupial brain might have been as adequate as the network type to support the dramatic evolution of the human brain.

Vascular Density and Pattern

Anyone whose attention has not been specifically directed toward capillary types will probably not notice the difference between a section through the medulla oblongata of the injected brain of an opossum and that of a rat. Corresponding cellular areas within the medulla oblongata of the opossum and of the rat will show the same vascular density and pattern, in one case of capillary loops, in the other of networks. Turning now to a discussion of the factors that determine vascular density and patterns in brains of different animals, we shall no longer make separate reference to the two types of blood vessels, because the same principles apply to brains supplied by either type.

The vascular patterns of primitive brains, as, for instance, those of urodeles, are monotonously uniform. In more highly developed types of brains, such as those of teleosts, we find surprisingly variable vascular patterns (fig. 7). Such regional differences presumably evolve in conjunction with cytoarchitectonic differentiation in higher animals. Their study yields

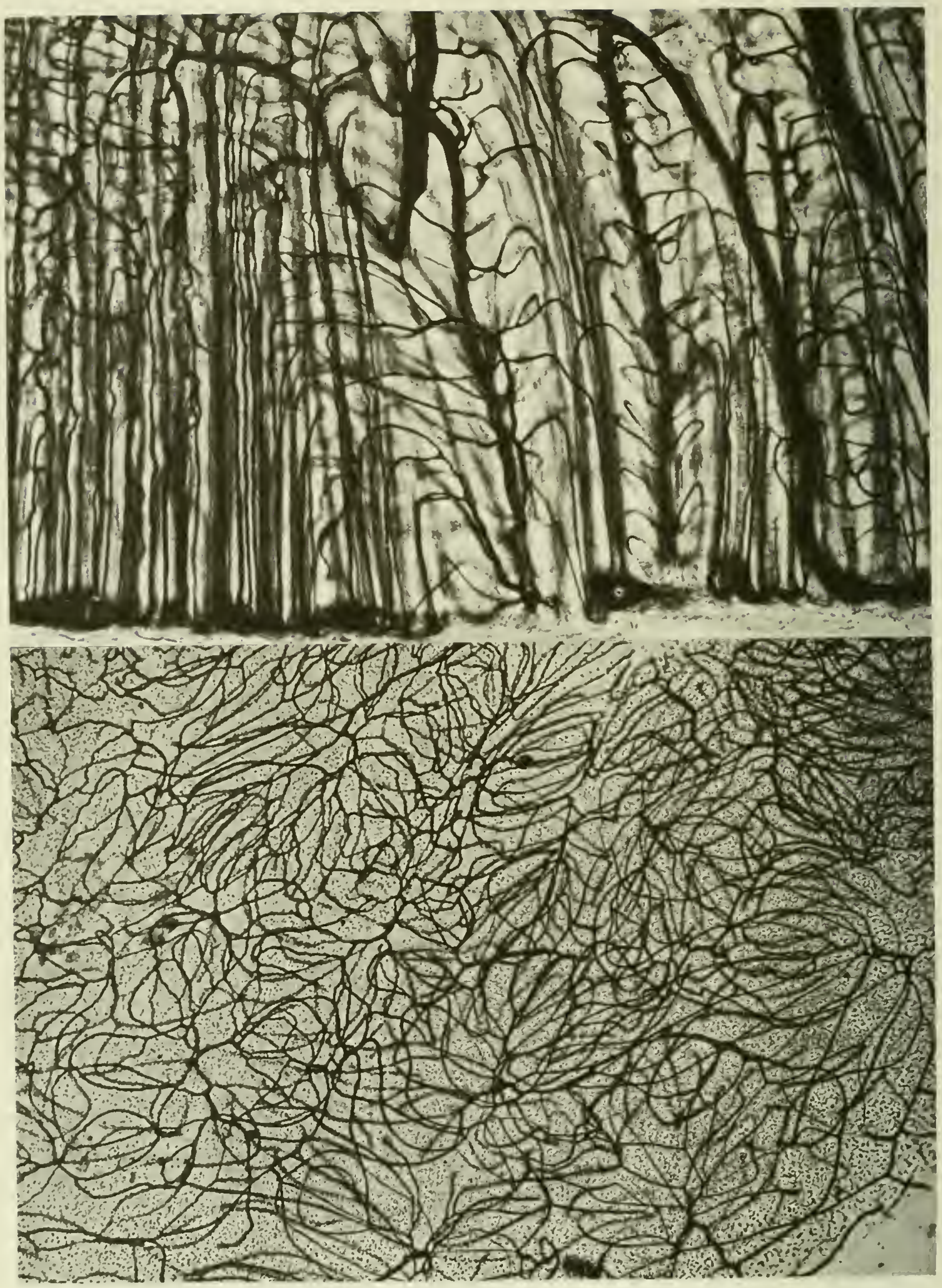

FIG. 7. Examples of the variety of vascular patterns in the brain of a teleost fish (*Tautoga onitis*). A. Lobus inferior. B. Forebrain.

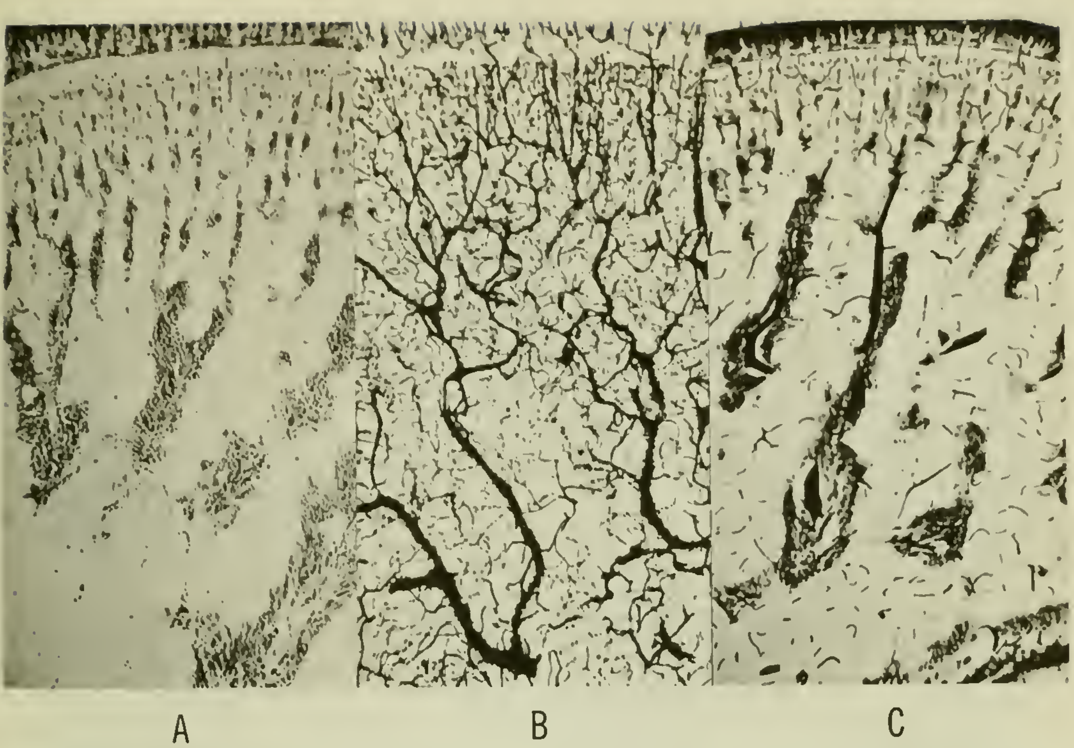

FIG. 8. Optic lobe of brain of squid (*Loligo pelaeii*). A. Pattern of nerve cells (Nissl stain). B. Vascular pattern (India ink-gelatine injection). C. Combination of cell stain and vascular injection.

some useful insights into the functional relationships between blood vessels and nerve cells which are inaccessible to direct methods of analysis (see Billenstien, 1953).

The most striking regional differences concern the density of the blood vessels. It often mirrors the microscopic topography of nuclei and fiber tracts to the extent that they may be accurately identified in sections of brain tissue in which the blood vessels have been injected without the staining of nerve cells or fibers (Pfeifer, 1928, 1930; Altschul, 1939; Dinkhaus, 1942; Craigie, 1920–1943). The question arises, What comes first? Does the cellular arrangement determine the vascular pattern or, conversely, do the cells become so located as to be closest to the vessels from which they receive their sustenance? A comparative survey of vascular versus cellular patterns indicates that either relationship may occur. In the optic lobe of the squid, the nerve cells are arranged along the blood vessels (fig. 8). A similar rela-

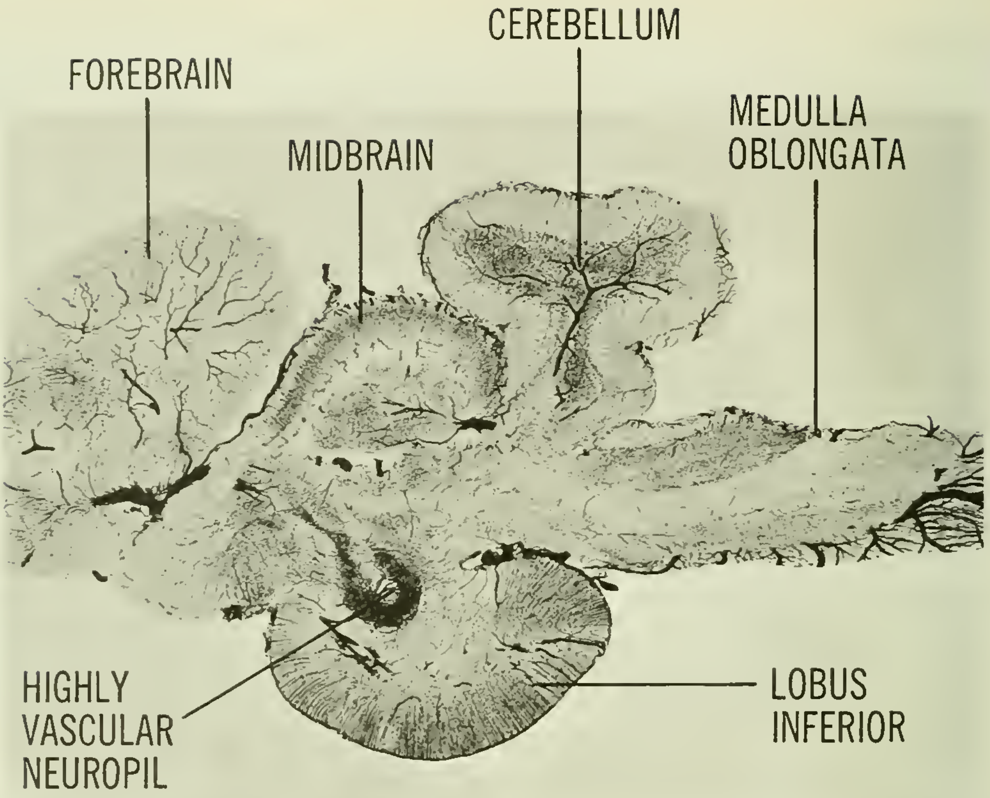

FIG. 9. Sagittal section through the brain of a teleost fish (*Tautoga onitis*) in which the blood vessels had been injected with India ink and gelatine. The varying metabolic requirements of different areas in the brain are reflected in the pattern of vascular density. The most richly supplied area is a neuropil near the center of the brain.

tionship exists in the Nucleus supraopticus accessorius of mammals. However, not many examples can be cited. In general, the organization of the central nervous system in terms of nuclei (i.e., groups of neurons of the same structure, function, and chemistry) and fiber tracts is reflected in corresponding areas of varying vascular density (fig. 9). Areas containing many large cell bodies possess denser capillary beds than those consisting of loosely arranged smaller cells. The latter are better supplied than white matter which consists predominantly of nerve fibers. In terms of metabolic rates these relationships appear reasonable. One would expect that the cell bodies which are centers of protein synthesis would have higher requirements than the fibers, and that areas of crowded large cell bodies will use up more oxygen and nutrients than those in which smaller elements are thinly scattered.

Although this rule holds in a general way, there are exceptions that prove instructive in that they indicate an oversimplification in the explanation stated above. There are occasional areas of densely crowded large nerve cells the vascular bed of which is anything but rich. The Gasserian ganglion of the trigeminal nerve is such an area. The question arises whether factors other than mere size of cell bodies may play a role. It was suggested, and with good reason, that it is not so much the high metabolism of the cell body that requires a rich vascular supply as the turnover at the synapses where impulses are transmitted from one neuron to the next and complex biochemical processes take place (e.g., synthesis and destruction of acetylcholine). This view is supported by the correlation between the presence and absence of synapses on the one hand and the degree of density of the capillary bed on the other. The Gasserian ganglion contains no synapses, and its capillary bed is not so dense as that of the superior cervical ganglion in which cells do synapse. However, even this explanation cannot be generalized without qualifications. If synapses are the decisive factor in determining vascular density, such neuropils as consist largely of synaptic junctions should be highly vascular, even if there are few or no nerve cell bodies included. Such is indeed the case (fig. 9). However, there are exceptions; some neuropils possess relatively few capillaries. Such neuropils have presumably a less active metabolism, as indicated by the smaller number of mitochondria (E. Scharrer, 1944a). The examples may suffice to illustrate the usefulness of quantitative data concerning regional vascularity. They reflect with great sensitivity the differentials in metabolic requirements of adjacent but anatomically distinct areas. We shall presently see how sensitive a measuring device capillary density is.

The Significance of Intercapillary Distance

It has been mentioned above that the central nervous tissue requires a continuous adequate supply of oxygenated blood. Its distribution within the central nervous system seems effectively regulated; each area has its quota of capillaries which is presumably adequate for its normal requirements. Superimposed on the basic anatomical pattern of distribution is a measure of functional control which permits a temporary local increase or decrease of blood flow in accordance with the changing activities of brain centers. However, there are reasons to believe that at no time and in no place can the flow of blood be permitted to cease altogether for even short periods. The thesis is put forward here that it could not stop in a single capillary without consequences to the nerve cells in its immediate neighborhood.

This conclusion is derived from experiments of which the following may serve as an example. The end arteries of the opossum facilitate the experimental occlusion of a small arteriole and its capillaries without interference with those of neighboring vessels, since the capillary loops of different blood vessels do not anastomose with one another. It is easily seen how one can estimate the radius of supply of a single capillary loop, if one determines the extent to which nerve cells die in the neighborhood of a capillary rendered non-functional by the injection of *Lycopodium* spores. The granular layer of the cerebellum of the opossum is particularly favorable for such an experiment on account of its cellular density, because the lines of demarcation between the pericapillary areas in which the cells succumb to anoxemia and those in which they survive are sharp (E. Scharrer, 1939a). The following measurements suggest that there is no margin of safety in the case of such an accident. The distance between capillary loops in the granular layer of the cerebellum averages 50 μ. This is also the width of strips in which the nerve cells have disappeared as a result of experimental emboli. It follows that each capillary supplies the surrounding brain tissue in a radius of about 25 μ, with little if any effective overlap with the area of supply of the neighboring capillaries. Such a marginal ratio of capillaries to nerve cells does not permit the elimination of a single capillary without the loss of nerve cells.

These empirically obtained data were confirmed by different techniques (Opitz and Schneider, 1950; Horstmann, 1960; Thews, 1960; Lierse, 1961) and may well be generally applicable. They have some important applications. There seems to be no reserve of capillaries in the brain as there is, for instance, in muscle. Although it is not clear why marsupials cannot afford such luxury, one may understand why the placental mammals, man in particular, seem to be unable to provide more blood vessels than are absolutely necessary to supply the brain tissue. The human brain, and with it the skull, have about reached the size limit that still permits their passage through the birth canal, although with difficulties for both mother and child. Space within the cranial cavity is at a premium, therefore, and a safer ratio of blood vessels to nerve cells could be accomplished only at the expense of the latter. For the same reason, additional nerve cells would require an expansion of the vascular system for which there is no space in the skull. This circumstance may well set a definite limit to further evolution of the human brain in purely anatomical terms.[1]

Actually, gross anatomical evolution is probably not a

[1] The reasoning of this paragraph does not conflict with the concepts set forth by Hindze (1926) which would indicate, if confirmed, that the gross anatomical study of the circle of Willis, together with the arteries and their branches on the surface of the brain, reveals longer, thicker surface arteries with more branches in human beings of high intelligence than in those of low intelligence. If one accepts the implication that the presumably rich blood supply was related to the high degree of performance of these brains, one must assume, although no data are given by Hindze, that Hrdlička's (1929) finding of a preponderance of large heads among highly intelligent people applied to Hindze's cases, i.e., the heads were probably larger than average and could accommodate a greater number of blood vessels.

conditio sine qua non for further intellectual and ethical evolution. Instead of the installation of additional supply channels, the effective use of existing facilities and the realization of the virtually unlimited potentialities for the progressive differentiation and refinement of intraneuronal connections will be the direction in which the evolution of the human brain can proceed without restraint. Just as the invention of transistors made possible a high degree of electronic performance within limited space and with small expenditure of energy, the miniaturization of synapses and the "invention" of neurohumoral mechanisms with smaller energy requirements than those we know would permit large strides in evolution without a gross anatomical increase of brain mass and, most important, of its supply system. Observations in recent years with electron microscopic techniques indicate that miniaturization exists already in the central nervous system to an unsuspected degree. What was formerly considered as an undifferentiated interstitial matrix filling the assumed spaces between nerve cells, glia cells, and capillaries of the brain ("Nissl's gray") does not exist. Instead there are everywhere richly interdigitating cell processes. Among these are many of very small diameter. We know little about them, but, if they were able to assume functions that are now carried out by larger fibers, the activities of the brain could reach higher levels of complexity and effectiveness without a need for additional space.

Conclusion

This cursory exploration of some aspects of the evolutionary history of cerebral blood supply has afforded us a few unexpected insights in certain areas and has left us unenlightened in others. The discovery of two basic types of cerebral vessels, networks and terminal loops, which appear in invertebrate as well as vertebrate animals irrespective of phylogenetic relationships, has been helpful in the solution of problems that had been sources of fruitless controversies for a long time. Cerebral vascular systems based on either one of these two types may develop complex patterns. Little more can be stated that would apply generally to cerebral vascular systems of all animals. The evolution of each system can be studied profitably only within phyla, e.g., the mollusks or the vertebrates; the latter have been sufficiently explored to permit a comparative study of cerebrovascular evolution. The capacity of man's present cerebral vascular system may well have reached its limits, and the further evolution of the human brain in terms of mere growth may be impossible for this reason. However, much intracranial space is taken up by ancient circuits that could be and probably are right now in the process of being redesigned for more effective use.

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