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Features of the Cerebral Vascular Pattern That Predict Vulnerability to Perfusion or Oxygenation Deficiency: An Anatomic Study

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In an ongoing study of brain microvasculature in humans at autopsy, we had the opportunity to analyze the overall scheme of this vascular supply. The native endothelial membrane enzyme, alkaline phosphatase, is used to precipitate black lead sulfide salt in the vessel wall, rendering the brain microvasculature visible by both light microscopy and microradiography. There are six distinct patterns of intraparenchymal afferent blood supply to the supratentorial brain: short arterioles from a single source (e.g., those in the cortex); short- to intermediate-length arterioles, single source (anterior two-thirds of the corpus callosum); short- to intermediate-length arterioles and arteries, dual source (subcortical U fibers); intermediate-length arterioles and arteries, triple source (extreme/external capsule and claustrum); long arteries and arterioles, single source (centrum semiovale); and large, long muscular arteries, single source (thalamus and basal ganglia). The nature of this arrangement offers some protection to certain regions of the cerebrum from circulatory challenges such as hypotension, while leaving other areas vulnerable. The distal arterioles supplying two of these protected regions, the U-fiber area and the extreme/external capsule and claustrum area, also exhibit the feature of *interdigitation*, which can offer additional collateral potential from one arteriolar territory to the next. Aging, hypertension, diabetes mellitus, and atherosclerosis can have a significant impact on brain microcirculation. The way in which vascular patterns dictate the distribution of these effects is discussed.

The ability to stain the cerebral microvessels and demonstrate the finer points of their patterns in sections and microradiographs has enabled us to resolve some long-standing questions about vascular connections and directions. It has also emphasized the regional differences in blood supply patterns, doing much to explain observed variations in vulnerability to circulatory alterations.

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Human cerebrovascular arrangement is not as uniform as it was once believed to be. There are variations in the sizes of these vessels, their lengths, and the potential for collateral flow from a distant source. The scheme of microvascular supply to the cerebrum theoretically offers protection to various regions against certain circulatory challenges, while leaving other areas vulnerable. In this report we tabulate and illustrate the differences in afferent cerebral vascular patterns and make assumptions about the relative vulnerability of certain areas to anoxia or hypoperfusion.

We have been investigating the brain microvasculature in human autopsy material. A histochemical technique for alkaline phosphatase [1] outlines this vascular architecture while preserving the background neuropil for inspection. The remarkably hardy vascular alkaline phosphatase is well preserved in postmortem brain tissue, and it can withstand the denaturing effects of very dilute cold formalin and the alcohol and other solvents involved in celloidin embedding. When the resulting brain sections are incubated with glycerophosphate and calcium chloride, the enzyme cleaves the substrate, thus beginning the first in a series of histochemical reactions. The final reaction product, black lead sulfide, is precipitated in the

endothelial plasma membrane of small arteries, arterioles, and capillaries, but will not stain most veins, obviating one problem of analysis, namely, discrimination between arteries and veins.

Distal to the circle of Willis the capacity for collateral blood supply diminishes appreciably. The pial-arachnoidal circulation over the surface of the brain is richly interconnected by anastomoses between arteries and arterioles [2], but once arteries and arterioles turn to penetrate the brain parenchyma they are normally "end-arteries" [3]. Flow in these vessels is controlled by some form of internal autoregulation. Diseases that significantly alter the morphology of these incoming vessels clearly leave the brain vulnerable to variations in perfusion pressure, but certain areas are more vulnerable than others, depending on the arrangement of the microvasculature.

Materials and Methods

The brains of 48 patients who died from a variety of causes (none with congenital brain malformations) were obtained at autopsy and serve as the basis of this report. The patients were 43–85 years old (average, 64 years). The brains were removed after a variable postmortem interval of 4–24 hr. They were placed in a refrigerator for 4 hr to attain a suitable consistency for gross cutting. Ten of these brains were also examined by postmortem MR imaging prior to fixation. After a mid-sagittal section divided the cerebrum, the hemispheres were sliced coronally and the corpus callosum sagittally. Large, thick blocks of tissue (up to 5 × 5 × 1 cm) were cut from six separate areas of the cerebrum: frontal lobe, temporal lobe, basal ganglia, thalamus, corpus callosum, and occipital lobe. An average of 7.5% of the brain by weight was processed and inspected, more if disease was identified on MR imaging or at the time of gross cutting.

The tissue blocks were fixed in cold, weak formalin followed by progressively higher concentrations of alcohol prior to celloidin embedding and sectioning at 100, 500, and 1000 μm on a base sledge microtome. The sections were stained histochemically by using the activity of the native nonspecific alkaline phosphatase enzyme present in the endothelium of capillaries, arterioles, and smallest arteries [1, 4]. The final reaction product is brown-black lead sulfide, which makes the microvascular bed of the 100-μm sections suitable for light microscopy after being counterstained with cresyl violet acetate and light green, Congo red, or myelin stain, and then mounted and coverslipped. The presence of the lead precipitate also makes the endothelium relatively opaque to low-energy X-rays. High-resolution contact microradiographs of the 1000- and 500-μm-thick sections were made at 7–10 kVp with the copper anode tube of an ISBR-60 microradiographic unit (Softex Co. Ltd., Tokyo, Japan) using Kodak SO-343 film (Eastman Kodak Co., Rochester, NY). The microradiographs were mounted on glass slides with mounting medium and coverslips and then examined under a light microscope.

Tissue blocks for routine paraffin sections and H and E stain for pathologic studies were also obtained from the opposite side of the brain and, where appropriate, from areas adjacent to the histochemically treated vascular preparations. These sections were studied for vessel wall changes and overall correlation with the findings observed in the alkaline phosphatase preparations. When expedient, trichrome, Holzer, Bielschowsky, and gliofibrillary acidic protein stains were also used on 5-μm sections from the paraffin blocks.

Results

The arteries of the pial-arachnoidal plexus and their larger perforating branches to the cerebrum are negative for alkaline phosphatase. (We have been careful to use *artery* when we mean a thick-walled afferent vessel greater than 100 μm in diameter; *arteriole* defines an afferent vessel with at least one layer of smooth muscle, less than 100 μm in diameter, ultimately supplying the capillary network.) The enzyme first appears in a patchy or streaky fashion in penetrating and intraparenchymal vessels with diameters of approximately 200 to 50 μm; that is, in the smallest arteries and largest arterioles. In this size range, exchange of nutrients begins to occur [4, 5]. The smaller arterioles and the capillary bed are strongly positive for alkaline phosphatase. Usually, venules are alkaline phosphatase–negative; most venules and veins in the choroid plexus and a few in the subependymal region show moderate or patchy staining, but these are easily distinguished as veins by their wall structure [6].

Figure 1 illustrates six distinct patterns of vascular supply to the supratentorial brain, each peculiar to a particular zone. The cortex and the corpus callosum (excluding the splenium) are similar in that they are supplied by short arterioles. There are some features that make the corpus callosum vasculature

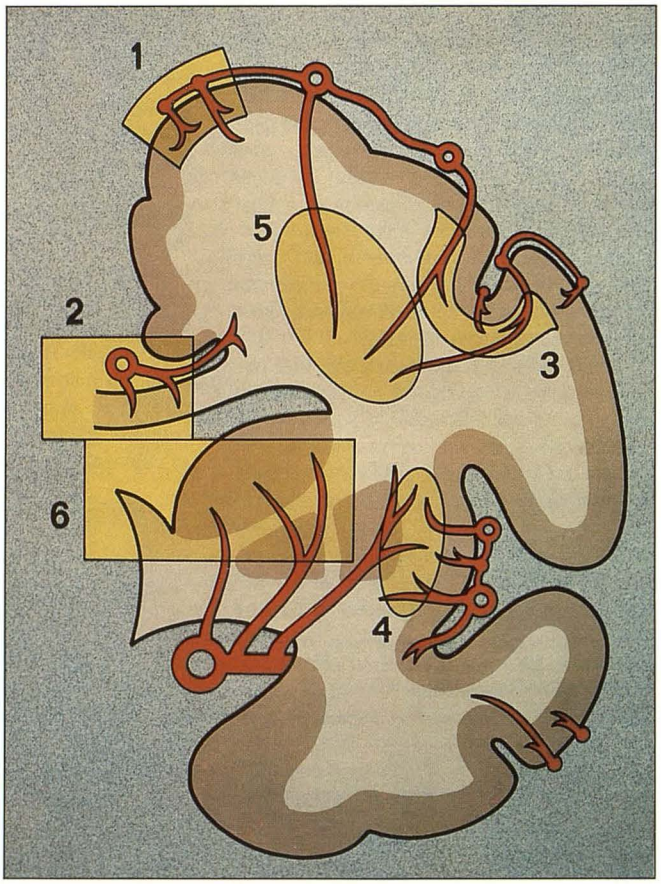

Fig. 1.—Scheme of arteriolar and arterial supply to cerebrum as viewed in coronal plane. 1 = cortex; 2 = corpus callosum; 3 = subcortical U fibers; 4 = external capsule/claustrum/extreme capsule; 5 = centrum semiovale; 6 = basal ganglia and thalamus. Zones 3 and 4 have interdigitating arterioles whose parent vessels arise from different pial arteries, in some instances widely separated. (In zone 3, to cite the most extreme example, arterioles arising from anterior and middle cerebral artery systems might interdigitate with each other.)

unique, as detailed in a previous article [7]. The vascular arrangement of the human cortex (but not detail of deeper areas) has been described by other investigators [4, 8]. In both cortex and corpus callosum there is a single, rather than a dual, blood supply (Figs. 2 and 3) in which the capillary bed is supplied by adjacent arterioles usually arising closely together from the same pial artery. A detailed description of single and dual blood supplies is found in the Discussion section.

The subcortical association bundles (U fibers) are supplied by the terminal twigs of the longest cortical arterioles (Duvernoy type 5) [8] and by the earliest branches of long medullary arteries and arterioles (Duvernoy type 6). Therefore, we classify these vessels as intermediate in length. For a given sector of the U fibers, these two types of afferent vessels usually arise from different points on the brain surface, constituting a dual supply. In the immediate subcortical region their terminal arterioles often appear to interdigitate (Fig. 4).

The external capsule/claustrum/extreme capsule area is supplied by the same two types of vessels as in the U-fiber area, entering the brain through the insular cortex, but additionally by lateral rami of the lateral striate arteries; this constitutes a triple blood supply. The terminal arteriolar territories of these three sources appear to interdigitate (Fig. 5).

The centrum semiovale is supplied from the brain surface by long (20–50 mm) arteries and arterioles having exclusive territories that border smoothly on one another rather than interdigitating. These arteries arise close to each other (single supply) and penetrate to different depths, the longest converging centripetally toward the angles of the lateral ventricles. We did not find a large number of afferent vessels penetrating inward to the vicinity of the lateral ventricles and then turning back toward the brain surface (centrifugal), thereby creating a border zone 1 cm from the ventricular surface as described by van den Bergh [9] and de Reuck [10]. Nor did we find any major source of the centrifugal arteries seen by the same authors originating at the ventricular angles. Instead, arteries, branching and diminishing in size and number as they pass from the brain surface through the centrum semiovale, send terminal arterioles in different directions, forming numerous small sequential contact or border zones with adjacent afferent arteriolar systems throughout the whole depth of the white matter (Fig. 6A). This pattern is encountered throughout the centrum semiovale. Medullary veins likewise converge, but these enlarge as they proceed toward the lateral ventricular angles to join subependymal veins (Fig. 6B) and are clearly distinguished from the arteries by the technique used.

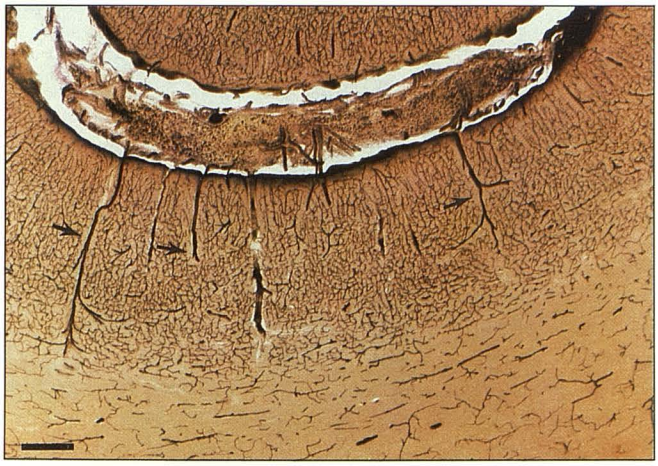

Fig. 2.—Arteriolar supply to cortex. Light photomicrograph of 100-μm celloidin section with alkaline phosphatase vascular stain, counterstained with cresyl violet acetate and light green. Medium-sized pial artery and vein are encased in common connective tissue sheath in space between two gyri. Cortical arterioles penetrate cerebral surface. It is possible to differentiate gray matter from white matter by density of capillary bed. This is an example of single supply with adjacent arterioles arising from a common source. Cortical arterioles share capillary network. Note capillary-free zone (*arrows*) surrounding alkaline phosphatase-stained arterioles, which is anatomic evidence that arterioles have a primary nutritive responsibility to their surrounding neural tissues. This was observed [4] prior to general recognition of this fact by physiologists [5]. This periarteriolar capillary-free zone will not be easily distinguished on thicker specimens imaged with microradiography because of superimposed capillaries above and below particular arteriole. (See Fig. 4.) Bar = 500 μm.

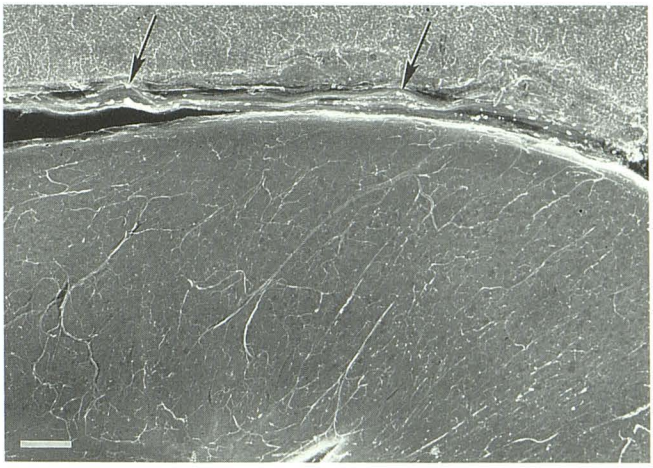

Fig. 3.—Corpus callosum, sagittal plane (anterior is to reader's right). Microradiograph of 500-μm-thick section with alkaline phosphatase vascular stain. Anterior cerebral artery (*arrows*) is seen between cingulate gyrus and corpus callosum below. This vessel is not stained but can be imaged because of some calcification in its wall and ability of muscular artery wall to attenuate extremely soft (low-kVp) X-rays. Arterioles supplying corpus callosum are short to intermediate in length, and adjacent ones tend to arise from a single source. Smallest vascular structures seen on this and subsequent microradiographs are capillaries. Bar = 1 mm.

The basal ganglia and thalamus are supplied by long arterioles and long muscular arteries, all from adjacent sources at the base of the brain. The terminal arterioles of one artery, often relatively narrow and short, have a tendency to enfold the parent artery; they do not interdigitate with the terminal arterioles of the next adjacent basal perforating artery (Fig. 7). Terminal branches of the most lateral thalamic arteries and the lateral striate arteries of the basal ganglia (i.e., area 6, Fig. 1) form a border zone with medullary vessels (area 5, Fig. 1) in the lowest portion of the centrum semiovale.

Discussion

We believe the alkaline phosphatase histochemical method of staining the vessel walls of the brain microvasculature is

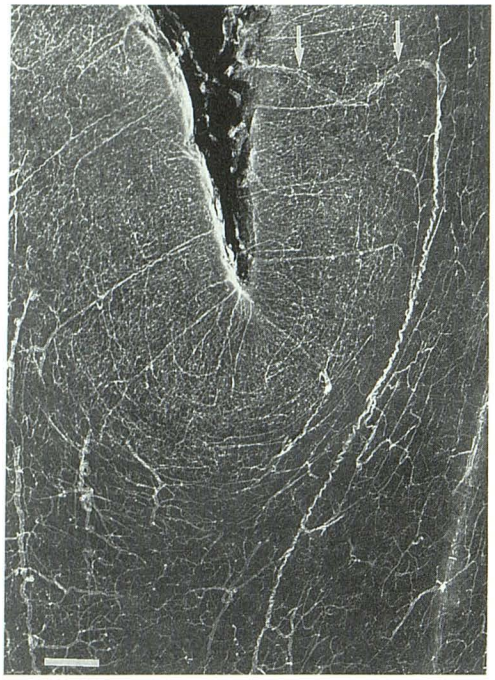

Fig. 4.—Dual blood supply in region of U fibers. Microradiograph of 500-μm-thick section, alkaline phosphatase stain. Large medullary arteriole (*arrows*) passes without branches through cortex, then turns to run with subcortical U fibers until it leaves this tract to reach its ultimate destination in centrum semiovale. This is a characteristic configuration (imposed by rapid cortical growth with infoldings of cerebral mantle in late fetal/perinatal development) of medullary arterioles entering cortex on down slope of sulcus rather than apex of gyrus or base of sulcus. Earliest branches of this arteriole interdigitate with terminal branches of longest cortical arterioles; the two often arise from different surface pial-arachnoidal vessels, giving this region a dual blood supply. This arteriole is near the surface of the cut section and is actually dislodged from its groove in the tissue for the segment between the *arrows*. In this segment the arteriole should have a straight course through the cortex. Bar = 500 μm.

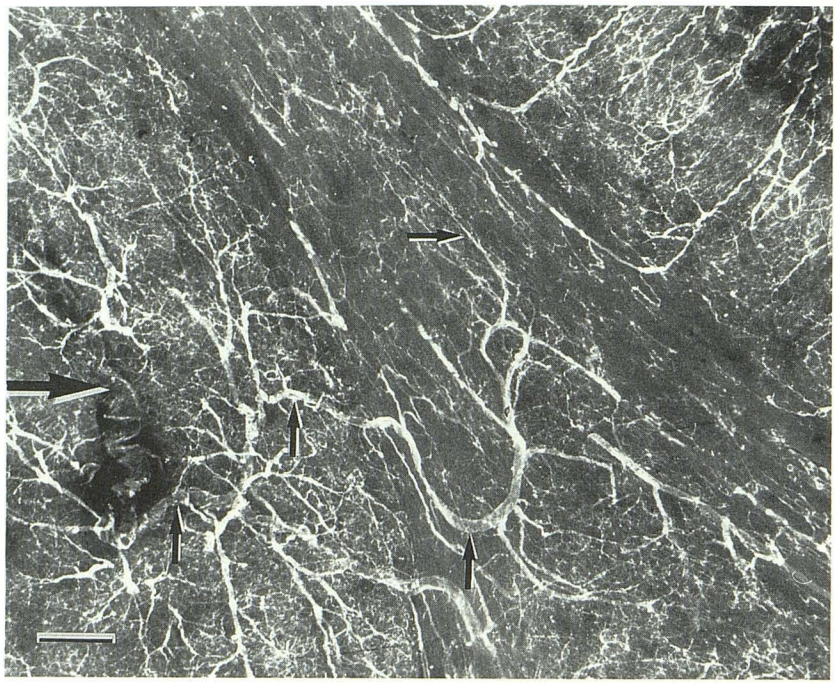

Fig. 5.—External capsule/claustrum/extreme capsule region, coronal plane. Microradiograph, 1000-μm-thick alkaline phosphatase vascular-stained section. Zone of dense capillaries on left is putamen, on far right is insular cortex. Extreme capsule is simply U-fiber area of insular cortex. Mid-zone of field pictured, which includes claustrum, has triple blood supply: terminal branches of insular cortical arterioles, medullary arterioles penetrating through insular cortex, and lateral-most branches (*small arrows*) of lateral striate artery (*large arrow*). Parent pial-arachnoidal arteries for these three vessel types are likely to be at widely separated points on surface of cerebrum. Bar = 500 μm.

superior to methods that require staining intravascular contents (i.e., blood) or postmortem injection of a contrast agent because (1) rupture, incomplete filling, and other artifacts of injection are avoided; (2) the arterial side of the microvasculature can be discriminated directly from the venous (the former stains, the latter does not); (3) the specimens can be examined by both light and X-ray microscopy; (4) the background neural tissue can be examined with standard or even special stains; and (5) the contents of the vessels can leak at the cut section surface without compromising the observations.

The strong feature of the microradiographic technique used in this study is the ability to survey the fine detail and differences in distribution patterns of the microvasculature in thick sections. We use film with silver halide crystals no larger than 0.0005 μm and tight-contact radiography, which provide better resolution and allow inspection of our microradiographs with a light microscope without the "snowstorm" of graininess that characterized this maneuver with most previously available films. Combined magnification of up to 250 times is possible before blurring (owing to X-ray focal spot unsharpness) degrades the image. When viewed with a microscope, the lead sulfide-stained capillary network is readily visible on the radiographs (Figs. 5, 6, 7B, 8, and 9).

Light microscopy is superior to radiography for sections 100 μm thick and less, since the vessel wall histology and the background neural tissue can be studied. Alkaline phosphatase stain (lead sulfide salt) is brown-black as seen by light microscopy and, in our preparations, is precipitated in both luminal and abluminal membranes of the endothelial cell [11].

Why not examine a 500 to 1000-μm piece of tissue with the light microscope? Even though the light source can be increased to penetrate a 1000-μm tissue section, the diffraction of light from structures over 100 μm deep renders the structures first indistinct, then at a deeper level invisible. Radiographs, however, faithfully record all the radiopaque features contained in the full section thickness. Those features farthest from the film emulsion may be slightly blurred, but this effect, rather than detracting from the value of the image, assists in three-dimensional interpretation.

What does the presence of alkaline phosphatase enzyme denote? As the arterial tree is traced distally, the enzyme is seldom seen in pial arteries or the anastomotic arteriolar plexus over the surface of the brain. In penetrating brain arteries, it is first seen in the smallest arteries (i.e., 200 μm or less in diameter) in a patchy or streaky pattern [6], suggesting that the enzyme is active only in alternate endothelial cells. As the artery reaches its termination, the enzyme activity gets

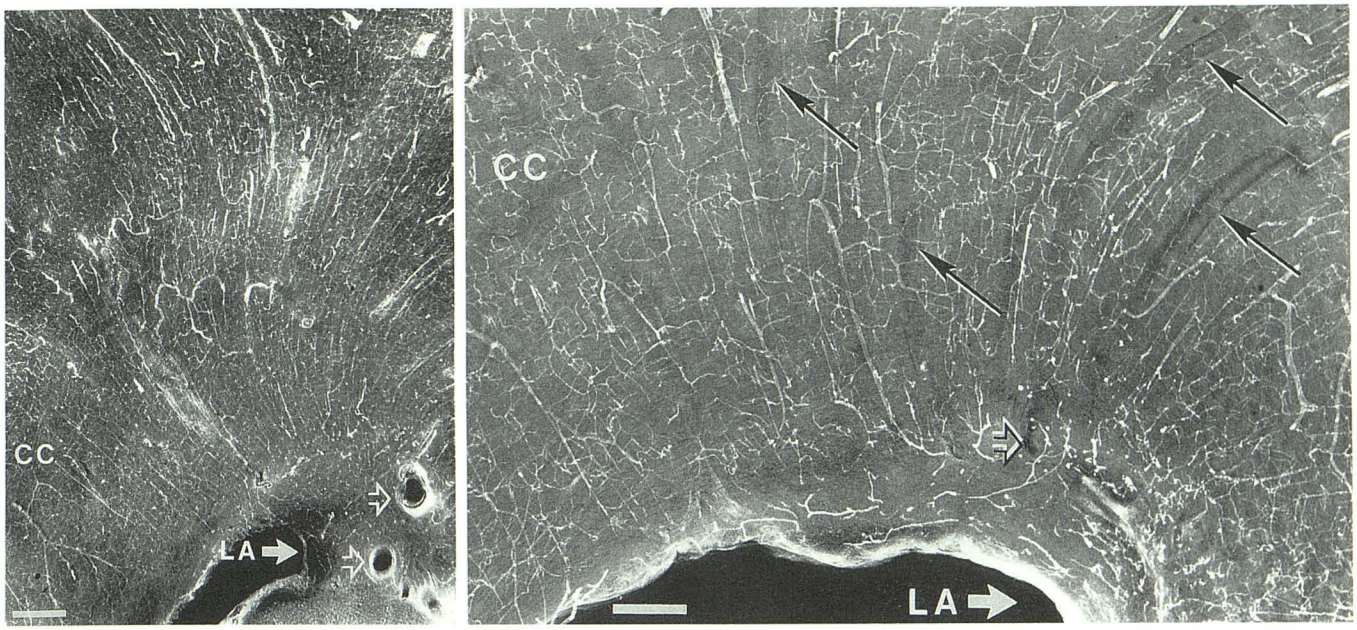

Fig. 6.—Microradiographs of 500-μm alkaline phosphatase–stained sections display microvascularity of centrum and lateral angle of lateral ventricle in coronal section. Lateral angle (LA) is at the bottom, corpus callosum (CC) to the left, and centrum to the right. *Open arrows* mark subependymal veins.

A, At level of frontal horn. Arterioles and capillaries have stain in their endothelia. Subependymal veins are seen end-on. They are surrounded by extravascular halo of stain as a result of alkaline phosphatase in neuropil of that particular area. A few arterioles recurve toward brain surface, but this phenomenon occurs throughout centrum and is not restricted to arteries that previously reached the ventricular wall. Bar = 1 mm.

B, At level of mid-thalamus. Medullary veins (*arrows*) can be seen as unstained, radiolucent, gently curving channels converging toward subependymal veins at lateral angle. We believe these veins will fill during techniques requiring injection of dye or contrast material into proximal arteries and have been mistakenly called centrifugal arteries [9, 10]. Bar = 500 μm.

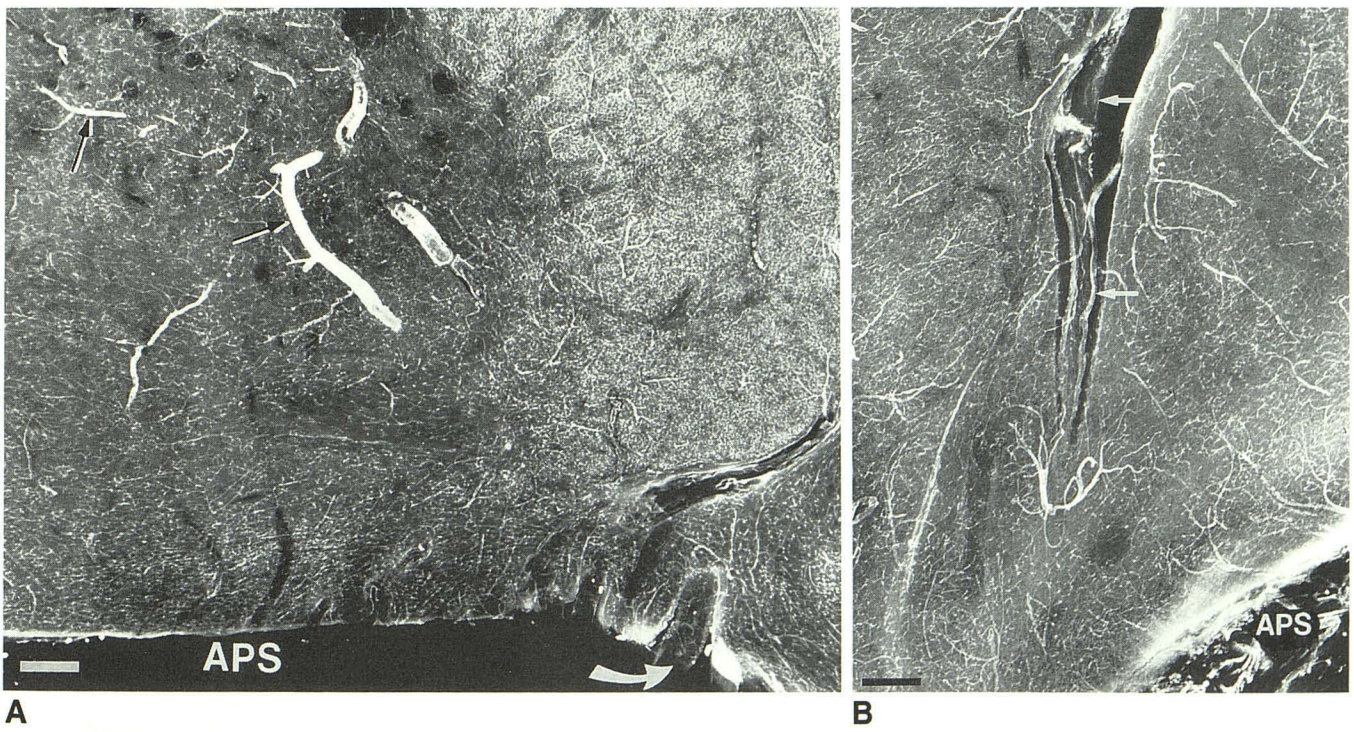

Fig. 7.—Vascular supply to basal ganglia; globus pallidus is to the left and putamen to the right. Coronal microradiographs, 500-μm-thick alkaline phosphatase-stained sections. Brain surface is called anterior perforated substance (APS) because of density of perforating vessels, many of which are too large to stain but can be visualized by their ability to attenuate soft X-rays (*curved arrow*).

A, Proclivity of globus pallidus arteries for calcification is apparent (*straight arrows* indicate one small and one large calcified artery; they are much "brighter" than vessels opacified only by lead sulfide salt as a result of action of alkaline phosphatase). Putamen has significantly denser capillary bed than globus pallidus, but large arteries in former area are not calcified. Bar = 1 mm.

B, Unstained large muscular striate artery (*arrows*) courses through section. Second-order vessels are stained and "arborize" parallel to and sometimes wrap around parent artery like branches of Lombardy poplar tree. Terminal arterioles tend not to interdigitate with arterioles of next adjacent lenticulostriate artery. Bar = 500 μm.

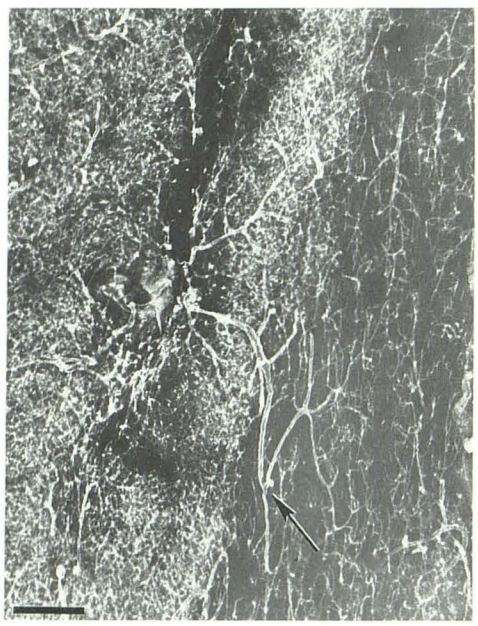

Fig. 8.—Anastomotic arteriolar system associated with lacuna. Microradiograph of 500-μm-thick section with alkaline phosphatase stain. Putamen is at left, showing long narrow dark (radiolucent) cavity of lacunar infarct; white matter of external capsule is at right. Vessels within lacuna are stained and viable, but pattern is distorted. Large arteriole apparently links lacunar system to another arteriole in white matter (*arrow*). Such connections may reflect a distortion of normal branching pattern (see Fig. 5) or a vascular reorganization after injury. We predict such a reorganization would be common in moyamoya disease. Bar = 500 μm.

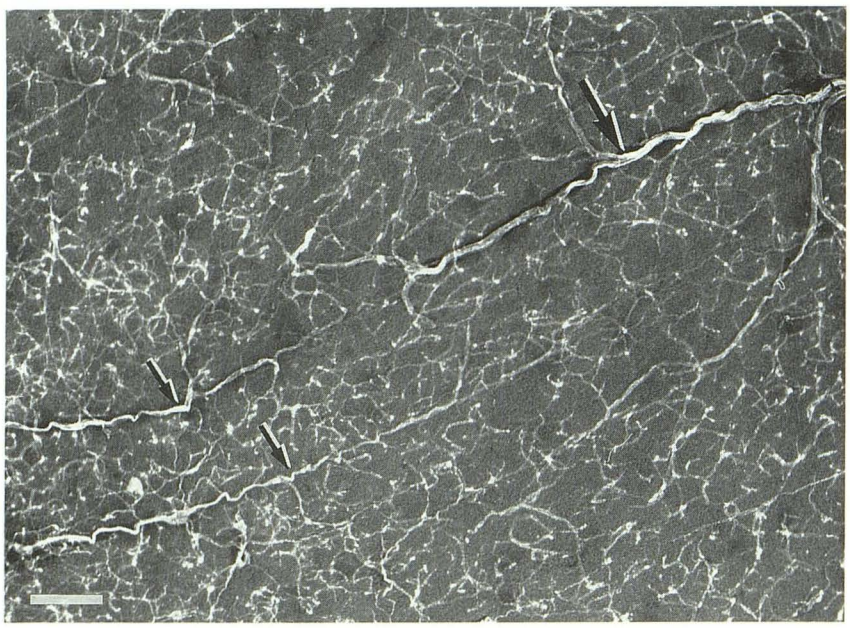

Fig. 9.—Zone of interdigitating triple blood supply in external capsule/claustrum/extreme capsule region. Microradiograph, alkaline phosphatase stain, 500-μm-thick tissue. Lateral branches of lateral striate artery (*small arrows*) run from left to right. Medullary arteriole (*large arrow*), having entered through insular cortex, runs from right to left. A zone of multiple blood supply exists in which parent cortical pial-arachnoidal arteries are at widely separated points on surface of brain. Smallest stained vessels are capillaries. Bar = 250 μm.

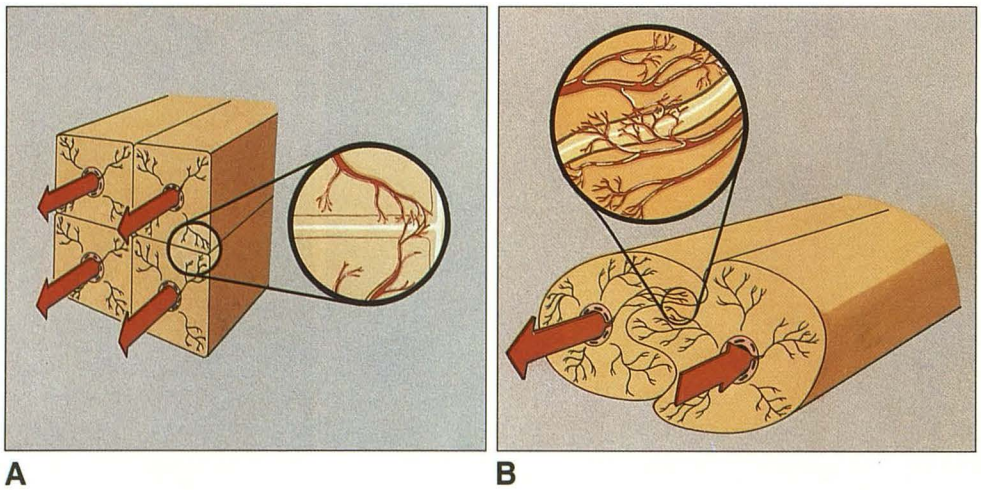

Fig. 10.—Scheme of single and dual blood supply to human brain.

A, Cortex (see also Fig. 2) is example of single supply. All these medium-sized arterioles took origin from the same surface pial-arachnoid artery, and blood flow is in the same direction (*red arrows*). Ubiquitous continuous capillary network is only represented in inset, where network is seen crossing imaginary boundary between zones of territorial responsibility for two adjacent arterioles.

B, Scheme for dual blood supply such as seen in subcortical U-fiber region (see also Figs. 4 and 9). Parent surface pial-arachnoidal arteries are different and blood flow comes from opposite (or at least different) directions (*red arrows*). Continuous capillary network is seen crossing imaginary territorial boundary between arterioles (inset). Although not proved conclusively, we believe that the arteriolar territories within these dual supply zones interdigitate like a jigsaw puzzle creating much more opportunity for collateral cooperation between major arterioles *via* the capillary network. This arrangement offers relative protection from hypotension.

TABLE 1: Pattern of Vascular Supply as a Factor in Predicting Vulnerability of Various Cerebral Regions to Anoxic or Hypoperfusion States

Area	Intraparenchymal Vessels	Capillary Bed	Risk
1. Cortex	Short arteriole, single supply	Dense	Anoxia (hypoperfusion at watershed)
2. Corpus callosum	Short/intermediate arteriole, single supply	Sparse	–
3. U association bundles	Intermediate-length arteriole and small artery, dual supply	Sparse	–
4. External capsule/claustrum/extreme capsule	Intermediate-length arteriole and small artery, triple supply	Intermediate	–
5. Centrum	Long arteriole and small artery, single supply	Sparse	Hypoperfusion
6. Basal ganglia/thalamus	Long muscular artery and arteriole, single supply	Dense	Hypoperfusion, anoxia

stronger so that arterioles and capillaries are densely stained. In general, postcapillary venules and veins do not stain. This pattern is consistent among most commonly used laboratory animals except the rabbit, whose brain vessels are alkaline phosphatase–negative [1, 12]. The presence or absence of a blood-brain barrier does not influence the alkaline phosphatase staining pattern of the microvessels [12]. The presence of the enzyme, believed to be active in some exchange or transport process across the vessel wall, does seem to correlate with a nutritive obligation of the vessel to its surrounding tissue. Alkaline phosphatase–stained capillaries will closely approach a large muscular artery without endothelial alkaline phosphatase, suggesting that diffusion across the arterial wall is inadequate to sustain surrounding tissue, but a periarteriolar capillary-free zone will coincide with the appearance of alkaline phosphatase enzyme in the endothelium of a small artery/arteriole (Fig. 2) [4, 5]. A discussion of the unusual vessels of the choroid plexus is beyond the scope of this report, but will be the subject of a later communication [6, 12].

Intraparenchymal Vascular Anastomoses

In their treatise on the vessels of the cortex, Duvernoy et al. [8] reviewed contradictory statements in the literature regarding intraparenchymal arteriolar-to-arteriolar anastomoses. Normally, we did not see them in the cortex or deeper structures, but we found one example at the margin of a lacunar infarct (Fig. 8), suggesting that ischemia might stimulate this unusual linkage. Although we have not had the opportunity to examine tissue from a patient with moyamoya disease, we believe this type of ischemia-induced anastomosis should be common there.

We did not find shunts between the precapillary arterioles and venules, but the interested reader should refer to the Duvernoy et al. [8] review of cortical vessels. The phenomenon of identifying large microspheres in the venous sinuses following carotid artery injection of these particles might be explained anatomically by the choroidal capillaries (whose staining characteristics we have been studying [12]) that can reach 50 μm in size.

We and others [3, 13–15] believe there is a continuous capillary network within the brain allowing weak collateral flow from one arteriolar territory to the next. In effect, adjacent arterioles share a capillary bed. The alternative to an anastomosing capillary bed is the capillary loop, in which a paired arteriole and venule supply and drain their unique capillary bed, and there is not a continuous capillary network. Marsupials have cerebral capillary loops that interdigitate but do not anastomose with each other; Placentalia generally do not have capillary loops [3]. If the concept of a continuous anastomosing capillary network in the human is accepted, the identification in certain brain areas of interdigitating arterioles with separated origins is not trivial: When the primary blood supply is compromised the tissue might be more efficiently rescued by perfusion from a remote source.

Zones of Blood Supply

We suggest that three features of cerebral microvascular beds enhance the opportunities for collateral flow, and that the presence or absence of these features helps to determine a region's vulnerability to vascular insult:

1. A *continuous capillary network* is found in the CNS of Placentalia; it provides weak collateral flow across borders of adjacent arteriolar territories.

2. A *multiple supply* is found in certain brain regions where adjacent arterioles arise from two or three widely separated surface (pial) arterial sources.

3. *Interdigitation* describes an overlapping and interpenetration of adjacent arteriolar territories; the imaginary boundaries of perfusion responsibility in the capillary bed between these arterioles fit together like a jigsaw puzzle rather than smoothly.

The first feature is ubiquitous in human white and gray matter; only in certain areas is it supplemented by the second and third features, which usually seem to occur together and confer added protection.

Figure 10 illustrates the advantages conferred by a dual supply, supplemented by interdigitation: first, the relatively straight margins between the obligatory perfusion territories of adjacent noninterdigitating arterioles in Figure 10A contrast with the curvilinear nature of the boundary between the interdigitating arteriolar zones in Figure 10B; second, the parallel course and closely related origins of the arterioles in Figure 10A contrast with the different flow directions and

sources in Figure 10B. It is readily observed that in species with a continuous capillary network there is much more opportunity for collateral flow between the interdigitating multiple source arterioles shown in Figure 10B. Figure 9 is a microradiograph that illustrates yet another advantage of interdigitating arterioles; that is, overlapping of long segments of these vessels that arise from widely separated surface pial sources, in this case anterior perforated substance and insular cortex. Figure 2 is an example of noninterdigitating arterioles from a single parent.

The regions in the human cerebrum with interdigitating arterioles arising from different parent arteries on the surface of the brain are the subcortical U fibers and the external capsule/claustrum/extreme capsule area. All other areas of the cerebrum have arterioles from adjacent sources with capillary beds that each nourish a cylinder of brain, and other arterioles usually do not penetrate that particular unique cylinder. In the hypothetical situation in which there is severe narrowing of a surface artery, the distal intraparenchymal ramifications of such a vessel in a zone of arteriolar interdigitation might receive more collateral blood supply from the capillaries of a separate undiseased surface source than if the arterioles are not interdigitated. Indeed, in an examination of our material for lacunar infarcts, none was found in the U-fiber region [16]. We postulate that this interdigitation of arterioles from separate sources offers favored regions of the brain unique protection from hypotensive events; this is most apparent when hypotension is superimposed on an already compromised vascular system.

In those selected regions of the cerebrum under investigation, areas with interdigitating distal arterioles also had dual or triple blood supply and vice versa. We are not prepared to state at this stage that one arrangement always coincides with the other.

There are no capillaries in the pia-arachnoid, and the arteries and arterioles over the surface of the brain are a connected plexus [2]. The cortex (apart from the border zones between major surface arterial systems) and corpus callosum, although supplied by closely adjacent sources whose arteriolar fields do not interdigitate, are offered some protection from hypotension by the short distance from the pial plexus, and by having an afferent supply solely from arterioles [7], which are not usually subject to atherosclerosis.

The centrum semiovale, basal ganglia, and thalamus are supplied by long arteries and arterioles and do not have interdigitating arteriolar fields. These regions are the most frequent sites for small ischemic (lacunar) infarcts [16]. Their arteries are subject to luminal narrowing from atherosclerosis (especially in hypertension and diabetes mellitus) and other degenerative vessel wall conditions. In some cases, hypertension also appears to exacerbate aging changes such as twists, spirals, and loops in the long arteries and arterioles. In such vascular deformations there is a theoretical pressure drop associated with the consequent increase in length, and a further pressure drop because of each alteration in flow direction [17]. These areas are particularly vulnerable to acute or chronic decreases in perfusion.

Table 1 lists different regions of the cerebrum and predicts which areas should be most vulnerable to circulatory alterations. Relative vulnerability may be influenced by other factors not listed in Table 1. We define anoxia as adequate perfusion of deoxygenated blood and hypoperfusion as inadequate perfusion of fully oxygenated blood. In clinical practice a combination of these conditions often exists. We make the assumption that gray matter is more vulnerable than white matter to pure anoxia because of its higher metabolic rate. That the gray matter (because of this higher metabolic rate) has a greater capillary density than white matter is a well-established principle; the further regional distinctions between brain areas with different patterns of blood supply are, however, original to this study.

Cortical Border Zones and Hippocampus

In this discussion we will not review the phenomenon of "border zone" or "watershed" cortical infarct. Suffice it to say the cortex is vulnerable to circulatory hypoperfusion in those areas in which distal middle and anterior (or posterior) cerebral artery distributions meet [18].

The hippocampus has an intimate admixture of gray and white matter requiring an intermediate capillary density; short penetrating arterioles arise from long winding surface arterioles, some of which may anastomose. As archicortex, the hippocampus represents one variation on the general cortical cytoarchitecture; its arteriolar pattern similarly appears to conform, in a general way, to the cortical single supply illustrated in area 1, Figure 1. The vascular supply to the hippocampus has been extensively studied by Spielmeyer [19] and by one of us [20, 21] in aging and demented people.

Centrifugal/Centripetal Arteries

Van den Bergh [9] and de Reuck [10] popularized the concept of centrifugal and centripetal orientation of the vascular supply to the centrum semiovale, with a border zone 1 cm from the ventricle. We think the concept of centrifugal arteries was overstated for two reasons: First, in any injection preparation such as those used in their studies, the opportunity for "flow-by" exists, wherein the injection medium flows through the capillaries and fills the veins. The medullary *veins* converge in radial fashion out of the centrum semiovale toward the ventricles in patterns identical to the vessels they termed centrifugal arteries. We think the published account of their injection preparations illustrates both arteries and veins, as discussed by Salamon and Raybaud [22]: "I ask myself whether these small vessels have been correctly interpreted [as arteries] in each case because very often small veins also fill up and we did not pay sufficient attention to such patterns."

Second, in our preparations there was random branching of the arterioles of the centrum semiovale all along their lengths; some of the small branches and terminal arterioles did turn back toward the brain surface, but this occurred throughout the entire depth of the centrum and not just at the ventricular surface (Fig. 6). Many of the smaller arteriolar penetrators stopped at various distances well before reaching the ventricular area. A substantial number continued, termi-

nating conventionally near the ventricular angle; these vessels did not recurve to form a border zone 1 cm from the ventricular surface, nor did lenticulostriate arteries originating below the centrum semiovale spray outward from the ventricular angles to contribute to such a border zone (Fig. 6), as illustrated by Van den Bergh [9].

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