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**Dyke Award. The search for human telencephalic ventriculofugal arteries.**

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## **Dyke Award**    **The Search for Human Telencephalic Ventriculofugal Arteries**

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Our study traced the vascular development of the fetal telencephalon in the last two trimesters of gestation and the first 15 years of life in 60 fetal and childhood brains. We filled the macro- and microvascular beds with Microfil and made stereoscopic observations of cleared 0.5- to 1.0-cm-thick sections. Separately, we identified developing vascular structures histologically. In our youngest specimen (16-weeks gestation), transcerebral channels with walls consisting of a single layer of endothelium and varying in diameter from 10 to 50  $\mu\text{m}$  originated from leptomeningeal arteries and veins at right angles to the surface and passed through the cortical plate (future cortex). They branched at varying depths within the mantle and germinal matrix surrounding the lateral ventricles. At deeper levels the channels freely anastomosed with each other. A cortical microvascular network did not appear until 22 to 24 weeks. The new endothelial channels were derived from leptomeningeal vessels and from larger transcerebral channels. Most regions of isocortex developed a microvascular plexus simultaneously, regardless of degree of maturation. Striatal channels matured earlier than extrastriatal channels, having developed a muscularis to within 100  $\mu\text{m}$  of the ganglionic eminence by 22- to 24-weeks gestation. Maturation of the vascular walls of extrastriatal channels into proper arteries and veins occurred during the first postnatal year. Anastomotic channels were present throughout the leptomeningeal, striatal, and extrastriatal regions in all of our specimens from 16 weeks gestation to 15 years old.

Our study does not support the existence of ventriculofugal arteries and deep white matter arterial border zones in the human fetus and neonate, which have been postulated to be the basis of "periventricular" leukomalacia.

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In 1969 van den Bergh [1] described a network of subependymal arteries in the adult human brain that turned away from the lateral ventricular surface to terminate in the deep cerebral white matter. He named these vessels ventriculofugal arteries. Independent studies of the fetal and term telencephalic microvasculature claimed confirmation of such vessels in the very young human [2-4]. A putative vascular border zone thus created between the long medullary arteries (ventriculopetal) and ventriculofugal arteries conveniently "explained" how hypoperfusion of the late gestational or neonatal brain could produce focal white matter lesions commonly called "periventricular" leukomalacia. Models of these relationships have been published numerous times (Figs. 1 and 2) [1, 2].

Unfortunately, none of these authors histologically confirmed that all injected vessels were arteries. Further, the two-dimensional radiographs of the injected specimens used by each of these investigators did not allow inspection of very small channels or separation of superimposed vessels.

With this in mind, we studied the telencephalic microvasculature of 60 human fetal and childhood brains to confirm or deny the existence of ventriculofugal arteries.

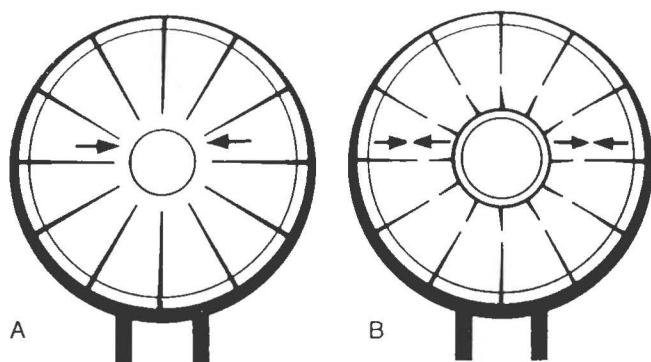


Fig. 1.—Proposed models of cerebral circulation. (Reprinted with permission from Yasargil [5].)

A, Model of Cohnheim [6]. Classical view is that brain is perfused by independent penetrating end arteries (ventriculopetal) from surrounding anastomotic leptomeningeal network.

B, Model of van den Bergh [1] and Vander Eecken. Ventriculofugal arteries meet ventriculopetal arteries to make a periventricular vascular border zone.

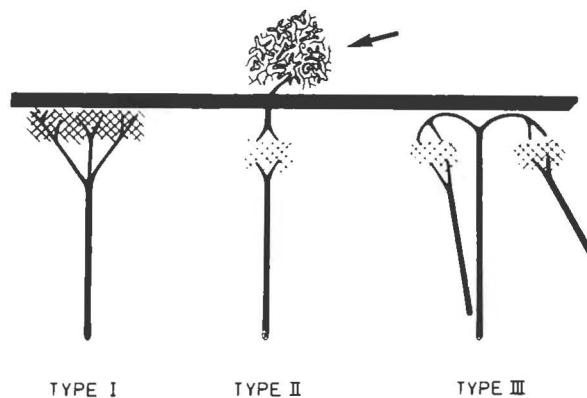


Fig. 2.—Model of deReuck [2] illustrates the three types of periventricular arterial border zones. (Reprinted with permission from deReuck [2].)

Type I, Terminal arterial bed formed by a ventriculopetal perforating or medullary branch ending adjacent to ventricular wall.

Type II, Border zone formed by ventriculopetal perforating or medullary branch and ventriculofugal branch from choroidal arteries of choroid plexus (arrow) traversing lateral ventricle and ependyma to reenter parenchyma.

Type III, Border zone formed by ventriculopetal perforating or medullary branches between one another.

Heavy black line represents ventricular wall.

## Materials and Methods

Sixty postmortem human brains, ranging in postconception age from 16 weeks to 15 years, were used in our studies (43 brains were from specimens 44 weeks old or less; 20 had been used in an earlier report [7]). Gestational age of the fetal specimens was determined by Dubowitz criteria when available and/or by congruency of body weight, crown-rump length, head circumference, and brain weight with the approximate postconception age of the fetus [8, 9]. One or both internal carotid arteries were cannulated prior to scalp incision and infused with Microfil (Canton Bio-Medical Products, Boulder, CO) by using either a hand-held syringe or a Harvard Pump. Microfil is a liquid silicone rubber compound designed to fill and opacify microvascular and other spaces of nonsurviving animals and postmortem tissues under physiologic injection pressure. Five to twenty-five milliliters was adequate for each perfusion. Polymerization of the Microfil

required 30–60 min. The brain was subsequently removed by using a modified Beneke procedure [10]. The brain was weighed (as part of the determination of gestational age), suspended in 10–20% formalin for 10–14 days, and then cut into coronal slabs 0.5–1.0 cm thick. The slabs were divided in the median plane. One half was used for histologic sections and the other half was carried through graded alcohols and cleared in methyl salicylate. The slabs were examined under a stereomicroscope (SMZ-10, Nikon, Tokyo, Japan) equipped with a drawing tube. The microvasculature was either drawn or photographed with a combination of direct and indirect lighting in single field or stereoscopic pairs while in methyl salicylate.

In four specimens, the entire parasylvian and lateral convexity leptomeninges (LM), including the border zone regions between the anterior, middle, and posterior cerebral arteries with their Microfil-filled vascular beds, were dissected free of the cerebral hemispheres and examined stereoscopically and photographed while floating in methyl salicylate. In the other specimens, portions of the LM were removed and examined similarly.

The lateral surface of one hemisphere from a 26-week specimen was removed in an oblique sagittal plane down to the lateral ventricle to expose the vascular supply of the germinal matrix.

Subsequently, blocks of the cleared specimens were processed, embedded in paraffin, sometimes serially cut in 5- to 15- $\mu$ m-thick sections, and stained with hematoxylin and eosin.

Measurements of least vessel lumen diameters were made by using a calibrated reticle and stage micrometer. They were subject to distortions caused by fixation, dehydration, or the Microfil injection itself.

Densities of microvessels were estimated by counting the number of vascular lumina of the desired diameters within a calibrated grid at a magnification of  $\times 200$ . Five counts were made in the region of interest in each specimen and averaged together to provide the tabulated means and standard errors. The cortex of the superior frontal gyrus and white matter of the corona radiata in the coronal slab taken just anterior to the foramen of Monro were the areas selected for sampling in all specimens.

We designated vessels of less than two red-cell diameters as "capillaries" and endothelial sinusoids of greater diameter as "channels" for operational purposes. Arteries and veins were distinguished by one or more of three criteria: (1) *connections*—vessels arising from identified surface arteries and veins were considered to be the same as the parent vessel to the point where the main trunk divided; (2) *location*—large arteries or veins in known locations were assumed to be the designated vessel, for example, a large single vessel in the midline anterior to the pons was the basilar artery; and (3) *histology*—channels with at least one layer of smooth muscle cells were designated "arteries" and channels with only a collagenous adventitial sheath were designated "veins."

We defined "striatal vessels" as those supplying the corpus striatum (caudate and putamen) and "extrastriatal vessels" as those supplying the remaining portions of the telencephalon (except for the amygdala), including both cortex and white matter.

Infant deaths were attributed to serious conditions including respiratory distress syndrome, congenital heart disease, asphyxia, white matter necrosis, sepsis, and germinal matrix and intraventricular hemorrhage. The older children had died as the result of trauma, sepsis, leukemia, or neoplasia not involving the brain.

## Results

### LM Plexus

All of our specimens, ranging from 16-weeks gestation to 15 years old, contained separate, well-organized LM arterial

and venous plexuses lying between the pia and arachnoid. Larger arteries divided into smaller branches that frequently were interconnected (Fig. 3). LM veins also were interconnected but less frequently than in the arterial plexus. In all specimens, both the arterial and venous networks were continuous over the border zones between anterior, middle, and posterior cerebral arteries. No capillary beds were found in the LM plexus. In all 60 specimens, smaller vessels branched off at right angles toward the cerebral surface from LM arteries, arterioles, veins, and venules. They immediately perforated the pia and penetrated the cerebral surface. LM veins larger than 1 mm tended to be superficial to the rest of the LM plexus, but the smaller branches of both arteries and veins interweaved so that no general statement of the relative positions of the arteries and veins could be made (e.g., the veins are superficial to the arteries).

LM arteries varied from 15 to 75  $\mu\text{m}$  in luminal diameter at 16-weeks gestation. The largest LM arterial diameters (excluding the first two segments of the anterior, middle, and posterior cerebral arteries) increased to 200  $\mu\text{m}$  at birth and to 260–280  $\mu\text{m}$  at 15 years. LM veins (excluding the vein of Galen and large superficial collecting veins draining into the dural sinuses) varied from 50 to 100  $\mu\text{m}$  in luminal diameter at 16-weeks gestation. The maximal LM venous luminal diameter increased to 225–250  $\mu\text{m}$  at birth and to 280–300  $\mu\text{m}$  at 15 years.

Histologically, all specimens had LM vessels with a well-defined muscularis or adventitia (Fig. 4). In younger specimens, 15–50  $\mu\text{m}$  in diameter, endothelial channels were present in both LM arterial and venous networks without a muscularis or adventitia. LM arteries at the base of the brain were larger in diameter and had more smooth muscle layers than LM arteries over the convexities at all ages. LM veins contained a single layer of endothelium with surrounding collagen layers constituting the adventitia. Larger-diameter LM veins had more collagenous layers than smaller veins.

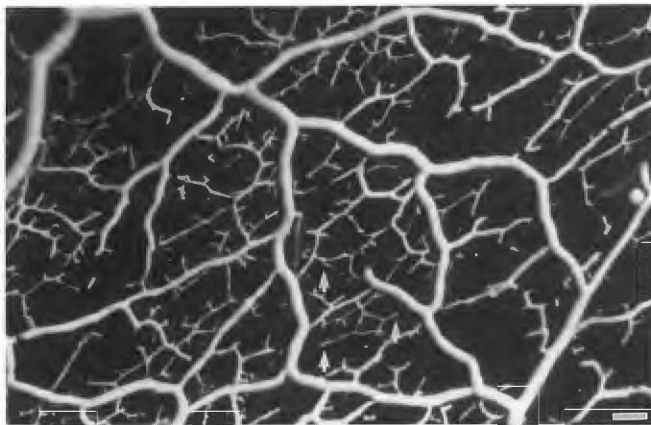


Fig. 3.—Photograph of cleared thick section shows microfil-injected leptomeningeal arterial plexus from parietal border zone in a 28-week fetus. Interconnecting vessels form a network of both large and small channels. From this network, penetrating channels (arrows) branch at regular intervals to pierce pia and enter cortex at right angles to surface. Scale bar = 1 mm.

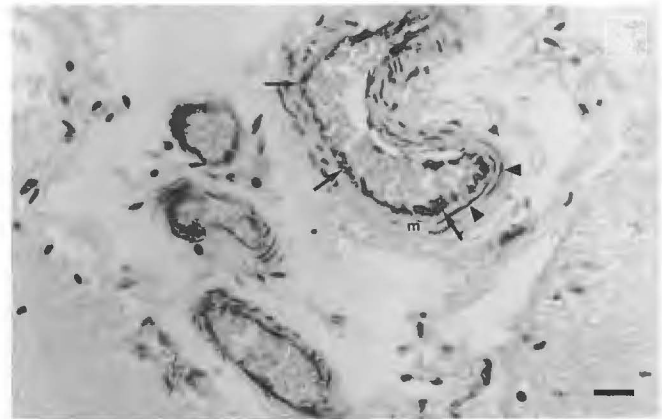


Fig. 4.—Photomicrograph of leptomeningeal plexus at 20 weeks; non-injected specimen. Arteries have a well-developed muscularis (m). Endothelial cells (arrows); smooth muscle cell nuclei (arrowheads). Scale bar = 50  $\mu\text{m}$ . (Factor VIII H and E counterstain,  $\times 100$ )

#### Striatal Circulation

In specimens of 16- to 20-weeks gestation, striatal vessels branched from the M1 segment of the middle cerebral artery and penetrated the pia at the base of the brain. These channels passed through the putamen and caudate and distally entered the ganglionic eminence of the germinal matrix (Fig. 5). The longest striatal channel measured 60  $\mu\text{m}$  in diameter at the base and 15 mm in length. Striatal vessels were larger at the base, then progressively tapered into smaller channels as they coursed toward the lateral ventricle. Side branches diverged at acute angles. Smaller channels, both in length and diameter, were present and branched in the middle and inferior aspects of the putamen. No striatal vessels in this age group had a muscularis or adventitia.

Specimens of 22–26 weeks had approximately the same number of long striatal channels reaching the germinal matrix of the ganglionic eminence when compared with the 16- to 20-week group. However, these channels were larger and longer (longest, 18 mm). Striatal vessels measured to 75  $\mu\text{m}$  in diameter at the base, tapering to 10–20  $\mu\text{m}$  distally before entering the ganglionic eminence of the germinal matrix (Fig. 6).

Striatal arteries had a muscularis to within 100  $\mu\text{m}$  of the ganglionic eminence in all specimens 24–26 weeks of gestation (Table 1). In specimens 28- to 30-weeks gestation, several large channels (50–100  $\mu\text{m}$  in diameter) situated between the germinal tissue and head of the caudate developed adventitial layers characteristic of veins. These channels could be followed in injected specimens as they anastomosed with collecting veins of the internal cerebral venous system.

The longest striatal arteries increased in length from 20 mm at birth to 45 mm at 15 years, and increased in maximal diameter from 250  $\mu\text{m}$  at birth to 500  $\mu\text{m}$  at 15 years of age. (These are not to be compared with the LM arterial branches distal to the M1 segment.)

The ventricular surface of the ganglionic eminence of the germinal matrix overlying the caudate was free of large chan-

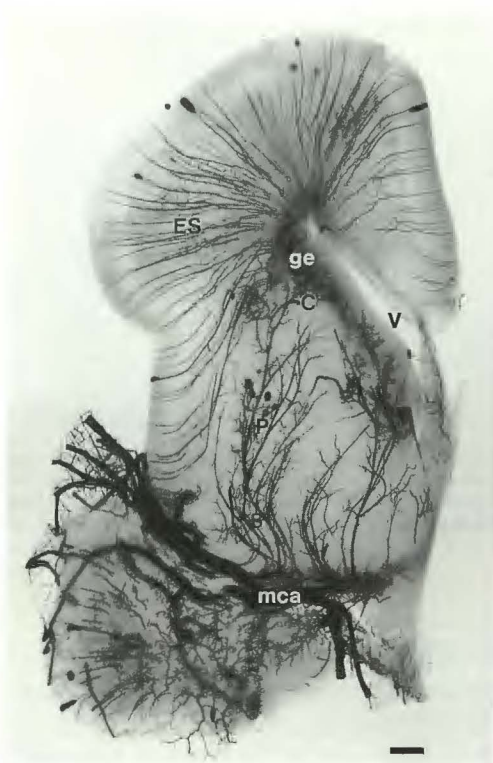


Fig. 5.—Photograph of cleared thick coronal section of left hemisphere immediately anterior to foramen of Monro at midgestation. Striatal channels (S) branch early and course lateral to globus pallidus through putamen (P) and caudate (C) to end in ganglionic eminence of germinal matrix (ge). Extrastratial transcerebral channels (ES) penetrate to various depths as they course toward lateral ventricle. These long extrastratial transcerebral channels do not branch within developing cortex. They frequently intercommunicate via anastomosing channels in white matter and germinal matrix. V = lateral ventricle, mca = middle cerebral artery. Scale bar = 2 mm.

nels or veins. Veins were located immediately subjacent to the ventricular surface in all other regions of the lateral ventricle. Similar veins lay between the caudate and the ganglionic eminence during the entire existence of the ganglionic eminence. Later in gestation, after the loss of the ganglionic eminence, these subependymal veins acquired their usual subventricular location over the caudate and reached a diameter of 200  $\mu\text{m}$  at birth and 300  $\mu\text{m}$  at 15 years of age.

The capillary bed was continuous between striatal and extrastratial circulations in all specimens of all ages, and precapillary anastomotic channels were located between extrastratial insular channels and the most lateral striatal channels.

Striatal vessels or their major branches never coursed superior and lateral to the outer corner of the lateral ventricle to end in the corona radiata in any of our 60 specimens.

#### Extrastratial Telencephalic Circulation

Penetrating channels 15–50  $\mu\text{m}$  in diameter branched off at right angles from LM arteries and veins at approximately 100- $\mu\text{m}$  intervals in all specimens of 16–20 weeks. These channels crossed the pia and cerebral surface to extend

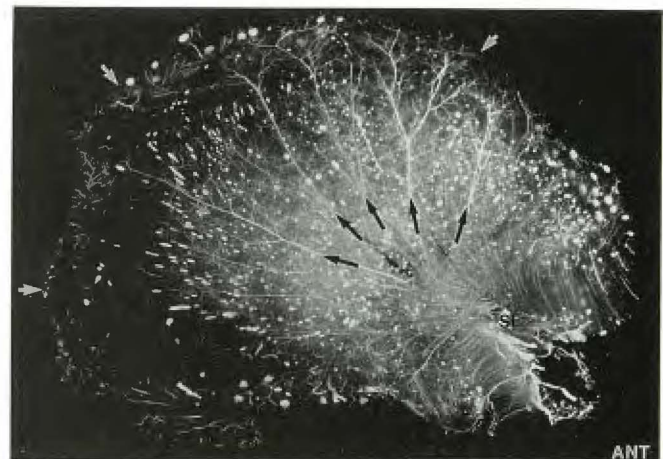


Fig. 6.—Photograph of cleared thick section shows blood supply of ganglionic eminence of germinal matrix of lateral ventricle. Lateral view of right cerebral hemisphere (26 weeks) with surface dissected to expose lateral striate branches (black arrows) that spread out radially and branch distally within germinal matrix. Edge of specimen (white arrows) is ventricular surface of ganglionic eminence. SF = sylvian fissure, ANT = anterior. Anteroposterior distance = 25 mm.

TABLE 1: Muscularization of Telencephalic Arteries as Identified on Photomicrographs

| Arterial Area  | First Identification of Smooth Muscle Layer |
|----------------|---|
| Leptomeningeal | Present at 16-weeks gestation               |
| Striatal       | 20- to 22-weeks gestation                   |
| Extrastratial  |   |
| Medullary      | Term to 1 month after birth                 |
| Cortical       | 6–9 months after birth                      |

variable lengths toward the nearest lateral ventricle before branching (Fig. 5). Larger channels, 50  $\mu\text{m}$  in diameter, nearly spanned the entire thickness of the cerebral wall, then branched into smaller vessels that anastomosed with branches from other vessels in the subependymal germinal matrix lateral to the ganglionic eminence. Some transcerebral channels were larger at their ventricular ends, some remained approximately the same diameter, and some narrowed at their ventricular ends. Smaller channels, 15–40  $\mu\text{m}$  in diameter, divided short of the germinal matrix in the marginal layer to branch out and anastomose with side branches from other larger channels and/or with branches of equal- or smaller-diameter vessels at various distances from the cortical surface. All channels passed through the cortex or cortical plate in younger specimens without branching, then provided right-angle or oblique branches to connect with other channels (Fig. 7). Histologically, all extrastratial endoparenchymal channels consisted of a single layer of endothelial cells (Fig. 8).

The surface area of the growing forebrain increased concomitantly with cerebral bulk. More penetrating channels formed from the LM plexus and loosely maintained 100- $\mu\text{m}$  intervals.

In specimens of 22- to 26-weeks gestation, transcerebral channels were longer (9–14 mm in length) and larger in



Fig. 7.—Photograph of cleared thick section of frontal-lobe white matter (23 weeks). Regularly spaced transcerebral channels branch at right angles and anastomose with nearby channels in deep white matter (arrows). Note difficulty in separating crossing and superimposed channels in this two-dimensional image. Crossing points (arrowheads) were easily separable stereoscopically. Scale bar = 100  $\mu$ m.

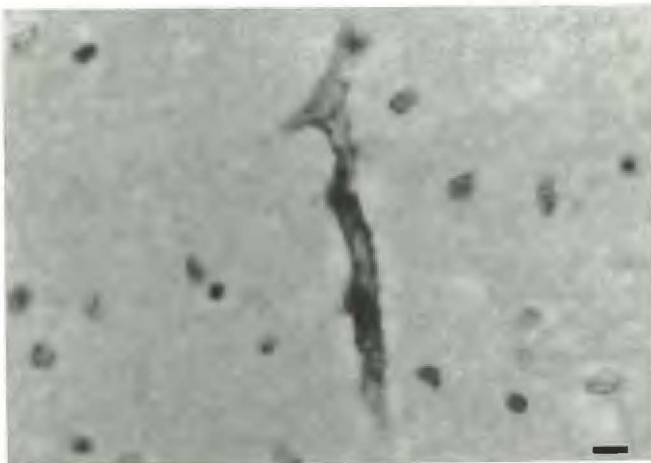


Fig. 8.—Photograph of parietal white matter (34 weeks); noninjected specimen. Simple endothelial transcerebral channel with side branch. Alkaline phosphatase lightly stains endothelial cells of channel. Scale bar = 10  $\mu$ m. (Alkaline phosphatase H and E counterstain,  $\times 200$ ).

diameter than the transcerebral channels of 16–20 weeks. The longest channels were the largest, measuring to 75  $\mu$ m in diameter. In specimens between 22 and 24 weeks of gestation, a new series of short penetrating channels branched from the LM plexus. These channels measured 10–30  $\mu$ m in diameter and to 1.5 mm in length and branched and

anastomosed solely within the cortex. Larger transcerebral channels occasionally provided a side branch to the new cortical network before entering the white matter. Isocortical regions that differentiate early in the third trimester, such as the calcarine and motor cortices, did not vascularize ahead of other regions of the cortex.

There was no histologic differentiation between channels connected to LM arteries and those connected to LM veins. Branches from arteries and veins arose at both acute and right angles. Separation of arterial from venous channels was possible only by identification of parent surface vessels.

Sulci and gyri develop with advancing age. Throughout sulcation, penetrating parenchymal channels remained perpendicular to the pia and the cortical plate as gyri developed. Long channels passing through the cortex into the deep white matter turned up to another 90° at the corticomедullary junction before proceeding toward the nearest corner or other surface of the lateral ventricle (Fig. 9).

Least and maximal distances from the cerebral surface to the lateral ventricle varied with age (Table 2). At 16-weeks gestation, only primary fissures were present and the maximal transcerebral width was 10 mm. The maximal cerebral surface to lateral ventricle distances increased to 21 mm at birth and 40 mm at 15 years of age. However, the distance from the bottom of a primary sulcus to the lateral ventricle was never more than 10–15 mm. No point within the extrastriatal telencephalic white matter was more than 10–15 mm from an LM surface. Large branches from LM arteries at the bottom of each sulcus passed through the cortex to branch out in the deep white matter near the lateral ventricular wall. No regions of consistently hypovascularized white matter were present either near the corner of the ventricle or in the subsulcine white matter.

Muscularized extraatrial, endoparenchymal vessels were first identified in specimens of 38- to 40-weeks gestation when the largest transcerebral channels were approximately 200  $\mu$ m in diameter (Table 1). They seemed to develop layers

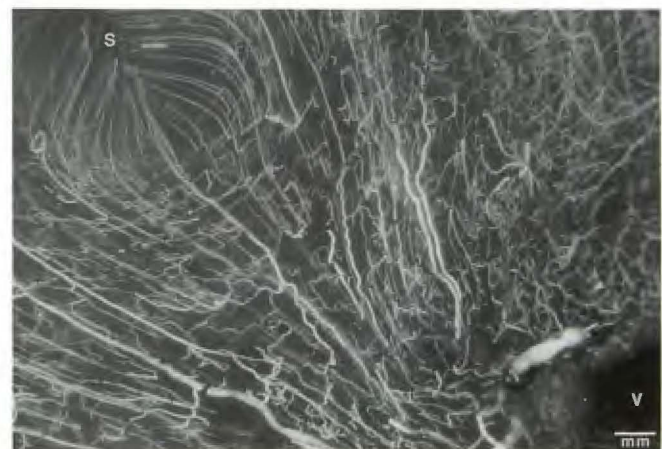


Fig. 9.—Photograph of cleared thick section of frontal lobe (31 weeks). Long channels maintain their 90° pial penetration angle, cross cortex, then turn to run within white matter toward nearest corner of lateral ventricle (V). Note rich vascularity in subsulcal and deep white matter. S = bottom of sulcus.

**TABLE 2: Critical Dimensions in the Vascular Development of the Fetal Telencephalon**

| Dimension                                | Measurement (mm) |          |          |
|--|------------------|----------|----------|
|  | 16 Weeks         | 40 Weeks | 15 Years |
| Cortical plate/cortex                    | 0.8              | 2        | 3.5      |
| Surface to lateral ventricle             | 10               | 21       | 40       |
| Bottom 1° of sulcus to lateral ventricle | — <sup>a</sup>   | 10       | 10–15    |
| Base of brain to top of caudate          | 15               | 20       | 42       |

Note.—Measurements were subject to distortions caused by fixation and dehydration of the specimen.

<sup>a</sup> No sulci were present at this age.

of smooth muscle from the LM end of the channel as the layers of smooth muscle were greatest at their LM ends. Long transcerebral channels connected to LM veins developed an adventitia between 40 and 48 weeks.

Cortical arterial channels that branched and anastomosed solely within the cortex measured up to 25  $\mu\text{m}$  in diameter at birth and to 40  $\mu\text{m}$  at 15 years of age. The longest of these channels increased in length from 3 mm at birth to 3.5 mm at 15 years of age. Cortical arterial channels developed a muscularis between 6 and 9 postnatal months (Table 1). Similarly, some cortical channels connected to LM veins developed an adventitia between 6 and 9 postnatal months, while others remained simple endothelial sinusoids.

Interconnecting precapillary anastomotic channels were present in the cortex and white matter of all of our specimens at all ages (Fig. 5). No vessels were found in any of our specimens that crossed the ependyma of the lateral ventricle from the choroid plexus to branch in the white matter.

The microvasculature of the germinal matrix remained a network of capillaries and sinusoids. No muscularis was present in any vessel, at any age, in the germinal matrix (Fig. 10). As the germinal matrix regressed early in the third trimester, the capillaries and sinusoids within the matrix regressed.

The density of microvessels 5–100  $\mu\text{m}$  in diameter was greater in the white matter than in the cortical gray matter throughout the last half of gestation (Table 3). Toward the end of the first postnatal year, in contrast, the opposite pattern developed, that is, the density of the cortical vessels became much greater than that of cerebral white matter (Table 3).

## Discussion

The development of the telencephalic vasculature begins around 24 days of gestation when primordial angioblastic islands coalesce to form the epiparenchymal LM plexus [11]. The channels spread from the base of the brain over the convexity with maturation of arteries and veins in the same sequence. According to Padget [12], the relative position of the major LM cerebral arteries is set by 40 days, predating the sprouting of endoparenchymal endothelial sinusoidal channels. This suggests that the relatively consistent positions of major LM arteries are not influenced by endoparenchymal flow dynamics.

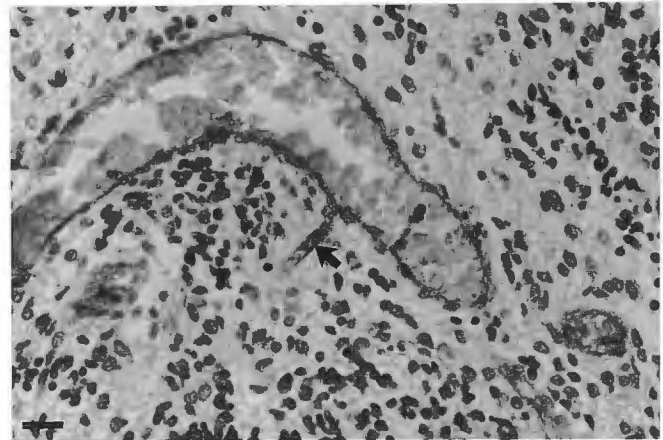


Fig. 10.—Photomicrograph shows ganglionic eminence of germinal matrix (28 weeks). Large endothelial sinusoidal channel has smaller branch (arrow) in matrix of germinal cells. No muscularized vessels are found at any age within germinal matrix. Scale bar = 50  $\mu\text{m}$ . (Factor VIII H and E counterstain,  $\times 100$ )

**TABLE 3: Density of Microvessels 5–100  $\mu\text{m}$  in Diameter per 500– $\mu\text{m}^2$  Area**

| Area         | No./500 $\mu\text{m}^2$ |                    |             |
|--------------|-------------------------|--------------------|-------------|
|              | 19 Weeks Gestation      | 40 Weeks Gestation | 2 Years Old |
| Cortex       | 6 $\pm$ 2               | 9 $\pm$ 2          | 29 $\pm$ 5  |
| White matter | 11 $\pm$ 3              | 13 $\pm$ 2         | 17 $\pm$ 3  |

We found no “terminal” arteries in the LM circulation in any of our specimens. We specifically looked at the major border zones between anterior, middle, and posterior cerebral arteries and found the same interconnecting vessels that are present throughout the rest of the LM plexus. We believe cortical vascular border zones are not related to LM end-arteries, but are functionally related to systemic pressure and to the perfusion pressure within each of the major cerebral vessels [13].

The LM plexus in turn gives origin to all endoparenchymal vessels [6, 11, 12, 14–16]. During the seventh gestational week, endothelial channels sprout from both LM arteries and veins, penetrate the pia, and enter the brain parenchyma at right angles to the surface [15, 16]. These penetrating channels give rise to the continuous capillary network that is established throughout the telencephalon [14–16].

The striatal channels support the growth of the caudate, putamen, and ganglionic eminence of the germinal matrix by branching, enlarging in diameter, and increasing in length.

The development of the extrastriatal channels is different and seems governed by the large increase in cortical surface area, with penetrating channels maintaining approximately 100– $\mu\text{m}$  intervals.

At 7–8 weeks of gestation, extrastriatal channels penetrate the surface of the brain and grow toward the nearest surface of the lateral ventricle, where the channels branch and anas-

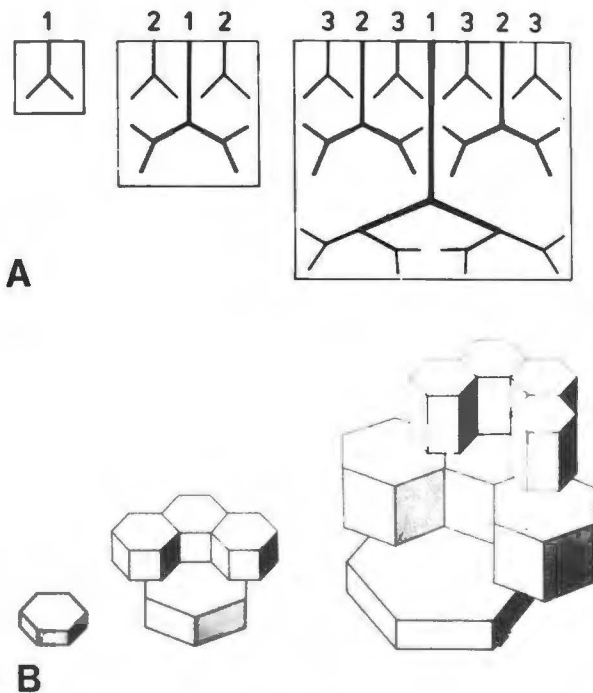


Fig. 11.—Model proposed by Bär [17] of telencephalic angiogenesis for the rat. (Reprinted with permission from Bär [17].)

A, On left, transcerebral channels (1) first ramify in subventricular zone. As fetal brain grows (middle), branching of transcerebral channels in subventricular zone continues (1) and additional large channels are added that branch deep in telencephalon (2). With continued growth in width and surface (right), subventricular branches of transcerebral channels become more extensive (1), deep telencephalic branches are added (2), and additional penetrating channels (3) branch more superficially.

B, Hexagonally packed regions of supply for each of these crops of branching vessels are indicated.

tomose to form a subependymal plexus [15]. This latter plexus supplies all of the germinal matrix lining the ventricles except for the ganglionic eminence over the caudate (supplied by striatal channels). Once beyond the developing cortex, these channels frequently anastomose with each other.

With further cerebral growth, more channels are added that penetrate a shorter distance (relative to the ventricular wall) than their predecessors. Between 22 and 24 weeks the cortex develops a vascular network to support the increasing metabolic demands. Numerous short, regularly spaced channels penetrate the cortex, branch, and anastomose without entering the white matter.

Bär [17] demonstrated a similar system of cerebral channels in the developing rat brain, and proposed that these channels supported a system of hexagonally packed vascular supply units that develop in response to local tissue demands during the growth of the brain (Fig. 11). Our human specimens are consistent with such a model.

By midgestation the walls of LM vessels have developed a muscularis or a collagenous adventitia to become proper arteries or veins. The extra-striatal endothelial channels develop a smooth muscle coat only as far as the pia, and do not begin to muscularize within the brain parenchyma until after 38–40 weeks, when muscular development proceeds in

a peripheral to central direction. Similarly, striatal veins develop collagenous layers beginning in the third trimester.

We believe the undifferentiated networks of anastomosing endothelial channels have the capacity to become arteries or veins, or to regress if hemodynamically superfluous. The extra-striatal transcerebral channels ultimately develop into medullary arteries and veins. Their transcerebral nature and multiple interconnections persist into adolescence, forming the basis for both arterial and venous collateral flow.

The existence of precapillary anastomoses in the human brain has been controversial [18–22]. We found anastomotic channels from 10 to 40  $\mu\text{m}$  in diameter throughout the telencephalon. We believe some investigators missed these connections for two reasons: (1) sections 1 mm thick or less would not allow adequate visualization of the complex interconnections of a single vessel and (2) two-dimensional imaging techniques do not allow separation of superimposed vessels. Microradiographs of well-injected thick sections produce an unintelligible maze of vessels, necessitating thinner sections that cut off branches and interconnections.

We were able to recreate patterns that simulated the ventriculofugal images of deReuck and van den Bergh by photographing our specimens nonstereoscopically at low magnification. We found no vessels that originated in the choroid plexus, crossed the ventricle, and penetrated the ependyma from the ventricular side (deReuck type II [see Fig. 2]). Their "recurrent arteries" appear to have resulted from the injected material filling a transcerebral endothelial channel into its distal anastomotic branches only to partially back fill an adjacent channel (deReuck type III [see Fig. 2]). What appeared to be a large striatal artery extending from the base of the brain to end in the corona radiata was in all cases superimposition of a striatal arterial branch in the putamen with medullary veins at the corner of the lateral ventricle. Similarly, Moody et al. [23] reported the absence of ventriculofugal arteries in the deep white matter, and no striatal arterial supply to the corona radiata in the adult human. Thus, a terminal arterial border zone between ventriculopetal and ventriculofugal arteries seems not to exist in the fetus, neonate, infant, child, adolescent, or adult.

This is a commonly held misconception that the arterial supply to the deep telencephalic white matter is from medullary arteries that span the distance from the external cerebral surface and pass down the core of a gyrus to finally branch in the deep white matter (20 mm in length in the neonate and 42 mm in the adult). While these long medullary arteries extend from the crests of gyri, shorter medullary arteries, 4–15 mm in length, branch from the LM arterial plexus at the bottom of deep primary sulci and pass through the cortex to supply the same periventricular white matter. Short medullary branches from the LM plexus in different sulci frequently supply the same deep white matter region. In our study, the deep telencephalic and subsulcal white matter had a rich vascular supply (Fig. 9).

Various aspects of telencephalic angiogenesis have been described [6, 7, 11–25]. We provide new observations on the sequence of endoparenchymal vessel wall maturation (Table 1). The potential for cerebral autoregulation in the fetal and



neonatal telencephalon seems limited by our observation of extraatrial channels lacking a muscular coat once within the pia. The only possible active control would exist in the LM arterial plexus, or possibly in the prepial muscularized segment of the artery still within the leptomeninges. Perhaps they act as valves or sphincters.

The finding of muscularized branches of lateral striate arteries within 100  $\mu\text{m}$  of the ganglionic eminence by 24 weeks supports the premise that systemic blood pressure instability transmitted through these vessels results in rupture of the endothelial sinusoids within the germinal tissue [26]. Similarly, an elevation of intracranial venous pressure could have the same result.

### Conclusions

The ventriculofugal/ventriculopetal model of periventricular arterial border zones is not supported by our study of the fetal and neonatal telencephalic microvasculature. Our new observations on the maturation of the parenchymal telencephalic microvasculature have direct implications regarding preterm and neonatal regulation of cerebral blood flow, and the genesis of germinal matrix hemorrhage.

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The reader's attention is directed to the commentary on this article, which appears on the following pages.