

Commentary

The Controversy of the Periventricular White Matter Circulation: A Review of the Anatomic Literature

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Over the past several decades, neuroscientists have become progressively aware of a group of cerebrovascular diseases in which the deep structures of the cerebrum are affected in preference to the cortex. Examples include subcortical dementia, subcortical infarction, intracerebral hemorrhage, and neonatal germinal matrix/intraventricular hemorrhage. To understand the pathogenesis of the diseases of the deep cerebral or periventricular white matter, many studies have focused on the microvascular anatomy of this region. The preceding article by Nelson et al. [1] is one of the most recent of this type. The authors primarily reemphasize the absence of ventriculofugal arteries in an important attempt to put an end to the popular and probably incorrect model of a "ventriculofugal/ventriculopetal" vascular border zone of the periventricular white matter. The background for this paper lies in earlier work done by van den Bergh [2] and deReuck [3].

The concept of human ventriculofugal cerebral arteries of the periventricular white matter was introduced by van den Bergh as early as 1961 [2, 4, 5]. The human cerebral angioarchitecture was, until then, thought to be centripetal or ventriculopetal (i.e., toward the center of the brain or toward the ventricle), in which arteries arising from the leptomeninges penetrate the cortex and the base of the brain at right angles to the surface of the brain, branching to supply the capillary beds of the cerebral parenchyma throughout the course of the arteries toward the ventricle [6–8]. However, van den Bergh described certain human cerebral arteries that origi-

nated from choroidal and striate arteries; traveled toward the frontal horn, body, and posterior horn of the lateral ventricle; and, on reaching a subependymal location, turned back into the white matter away from the ventricle. The terminal portions of these arteries thus delineated a centrifugal or ventriculofugal course (i.e., away from the center of the brain or away from the ventricle) to supply a white matter region between the cortical and ventricular surfaces. In this region, ventriculopetal and ventriculofugal arteries were said to form "a three-dimensional border area between a centripetal network surging from the periphery and a centrifugal network, dependent from well defined branches" [5]. Van den Bergh summarized this concept with a diagram (see Fig. 1 in Nelson et al.). In other words, the angioarchitecture included not only a classical "end zone" capillary bed abutting the ventricle formed by end arteries converging centripetally from the surface of the brain but also a "border zone" capillary bed situated between and supplied by ventriculopetal and ventriculofugal end arteries in an ill-defined region (up to 15 mm away from the ventricle, according to van den Bergh) of the deep cerebral white matter. Van den Bergh believed that neonatal periventricular leukomalacia and hemorrhage as well as other periventricular white matter vascular diseases could be understood as selectively involving either the ventriculopetal arteries, the ventriculofugal arteries, or both.

Shortly after van den Bergh's reports were published, de Reuck's research [3] popularized the border-zone model, illustrating different types of border zones, depending on the

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arterial systems involved, and adding another important diagram (see Fig. 2 in Nelson et al.). Moreover, deReuck described ventriculofugal/ventriculopetal border zones surrounding the entire ventricular system. The model appealed to other workers because, analogous to cortical "watershed" areas [9, 10], the white matter border zone between ventriculopetal and ventriculofugal arterioles was seen as having a special susceptibility to hypoperfusion. This allowed the causes of various periventricular white matter diseases to be explained by an attractive, unifying theory. For example, in the 1960s neonatal periventricular leukomalacia was shown to be associated with episodes of severe cardiopulmonary injury with systemic hypoperfusion [11–13]. The new model supported these observations, describing the lesions as watershed-like infarctions in the periventricular border zone [14–18]. Similarly, the periventricular border zone was accepted by other investigators as the region in which germinal matrix/intraventricular hemorrhage would originate in the premature neonate [16, 17]. Finally, adult periventricular white matter infarctions, once thought to be a rare phenomenon (e.g., Binswanger subcortical arteriosclerotic encephalopathy), were thought to be periventricular border-zone infarctions due to fibrohyaline sclerosis of cerebral ventriculopetal and ventriculofugal arteries [2, 3, 19–25]. To this day, reviews and textbooks use the ventriculofugal/ventriculopetal border-zone model to describe the pathogenesis of these diseases.

Kuban and Gilles [26], in their 1985 report, appear to have been the first to directly contradict the ventriculofugal/ventriculopetal periventricular white matter vascular border-zone model by denying the existence of the ventriculofugal arteries described by van den Bergh and deReuck. When Kuban and Gilles injected the cerebral arteries of human fetal cadavers with silicone and then made high-power stereomicroscopic observations of thick (up to 1.0 cm), cleared specimens, they were unable to visualize any ventriculofugal arteries despite a specific "search for a separate deep ventriculofugal arterial system" [26]. Furthermore, they stated that they were able to reproduce the earlier authors' results by observing their own preparations at low magnification and without stereomicroscopy. Kuban and Gilles think that both van den Bergh and deReuck mistook "transcerebral channels" (which Kuban and Gilles believe have the capacity to become arteries or veins) within the periventricular white matter, superimposed on the distal ends of striate arteries, for ventriculofugal arteries. Kuban and Gilles added that this error was due, at least partly, to a lack of histologic determinations of the vasculature studied by van den Bergh and deReuck, so that no one could be certain of the nature of the vessels studied.

Moody et al. [27], on the basis of previous research [28–31], used a different technique to study the microvascular anatomy of the periventricular white matter. The technique involves a series of histochemical reactions, taking advantage of an alkaline phosphatase that is present in the endothelial cells of cerebral capillaries, arterioles, and small arteries but not venules or veins. The final result is a precipitate of lead sulfide within endothelial cells. As Moody et al. [27] have indicated, the procedure eliminates the problem of discriminating between arteries/arterioles and veins/venules. Sections of the prepared tissue can be examined by light micros-

copy, with and without standard histopathologic stains, and by microradiography. Using adult human cadavers, Moody et al. [27] showed intricate patterns of intracerebral microvasculature. This powerful technique reveals the complex configuration of brain arterioles almost as clearly as scanning electron microscopy does, as in the excellent study by Duvernoy et al. [32] of the cortical vasculature. Moody et al. [27], like Kuban and Gilles, noted an inability to identify the ventriculofugal arteries of van den Bergh and deReuck. Furthermore, Moody et al. [27] stated that "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." Moody et al. [27], like Kuban and Gilles [26], also believe that the likely cause of the errors made by van den Bergh and deReuck was mistaking veins for arteries.

The current paper by Nelson et al. [1] is a continuation of the earlier work of Kuban and Gilles; it uses the same technique (and some of the same specimens). The new study adds an examination of the brains of children and adolescents to the previous study of only fetal brains in describing some characteristics of later cerebrovascular maturation. The authors restate the belief that the terminal ventriculofugal/ventriculopetal vascular border zone seems not to exist.

Historically, research into the angioarchitecture of the brain has been hampered by the distinction between arteries and veins. According to Scharrer [33], Pfeifer wrote extensively on the vascular anatomy of the cat and human brain, only to be shown later by Campbell [34], Scharrer [33], and Saunders [35] that he had mistaken the arteries for veins and veins for arteries. Solnitzky [36] appears also to have made this error with regard to the brain of the rhesus monkey. Finally, the probably incorrect model developed by van den Bergh and deReuck appears to have been the result of the same problem.

Interestingly, van den Bergh [2] himself pointed out that "the ventricle is surrounded by a fan-shaped array of radial ventriculopetal veins which present a nearly identical localization and orientation as the arterioles. . .so that the latter can easily be confounded with the more numerous venules," although he seemed certain in his identification of ventriculofugal arteries. He even described the difficulty encountered in injecting only the arteries and not the veins with his contrast material (which could pass through capillaries to fill the veins), though he did not indicate how he then was able to be certain of the results of his injections. Van den Bergh's technique consisted of obtaining radiographs of thick (5–10 mm) brain sections after intraarterial injection of a contrast medium, stereoscopically viewing thin (200–300 μm) sections after injection of Chinese ink and staining of the vascular walls, and histologically examining thin sections with stained vascular walls and contents. From his photographs, it can be seen how the preparations could have been misleading (Fig. 1A). DeReuck used brains injected with colloidal barium and based his observations on low-magnification microradiographs and translucidations of thick (1.5–2 cm) sections of the tissue. Unlike those of van den Bergh, deReuck's photographs and illustrations are not clear, because of the low-power magnification and our inability to appreciate the translucidity effect.

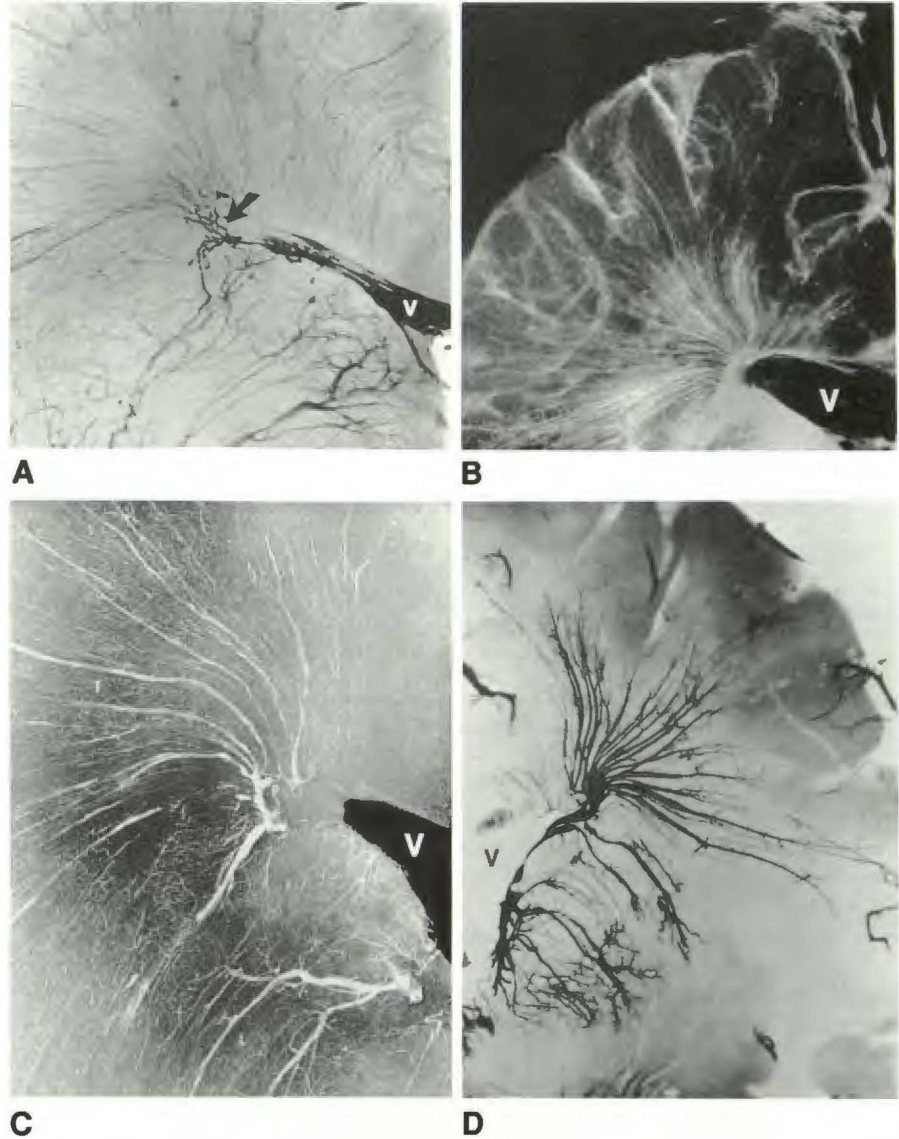
Fig. 1.—Probable venous basis for concept of ventriculofugal arteries. Note similarity of ventriculofugal arteries (A) to transcerebral, paraventricular veins (B–D). V, indicating lateral ventricle, was added by Mayer and Kier.

A, One of the original photographs of an ink-injected specimen on which concept of ventriculofugal arteries was based. Arrow points out origin of ventriculofugal arteries at lateral angle of lateral ventricle. (Reprinted with permission from van den Bergh [4].)

B, Cerebral venogram of a specimen injected with aqueous lead sulfamate shows radial convergence of transcerebral veins toward lateral edge of lateral ventricle. (Reprinted with permission from Kaplan [37].)

C, Microangiogram of a specimen injected with barium gelatine shows clearly the convergence of transcerebral and paraventricular veins at lateral angle of lateral ventricle. (Reprinted with permission from Saunders et al. [38].)

D, Postmortem cerebral venogram of a cerebral hemisphere with contrast material injected into internal cerebral vein. (Reprinted with permission from Burger and Vogel [39].)



Moody et al. [27] noted that in fact many branches of medullary arteries do curve back toward the cortical surface (although these are not what van den Bergh was referring to when he described ventriculofugal arteries). For this reason, Moody et al. believe that the ventriculofugal/ventriculopetal model of van den Bergh was "overstated." They have shown that these branches occur throughout the cerebrum, not just near the ventricle. Lewis [7], Rowbotham and Little [40], Saunders and Bell [29], Saunders et al. [38], and Duvernoy et al. [32] also noted this pattern of recurrent branching in the cortex, describing them as candelabra- or grapnel-shaped.

In retrospect it seems that the injected ventriculofugal arteries should have been interpreted as veins by van den Bergh and deReuck, considering the vessels' location, shape, and diameter greater than both the terminal portions of the striate arteries and the long cerebral medullary arteries. As noted by Moody et al. [27], Salamon and Raybaud [41] appear to be the first to have realized this. Perhaps the reason for van den Bergh's promulgation of the hypothesis of a ventriculofugal/ventriculopetal vascular supply is that it conformed to his beliefs about the evolution of the cerebral vasculature [4].

Van den Bergh noted that the mainly centripetal arrangement of the cerebral vasculature was contrary to that of most internal organs, in which the vasculature stems from a central hilus, with perfusion directed centrifugally. He stated that the cerebral vasculature evolved from a primarily centrifugal system in fish, amphibians, reptiles, and primitive mammals to a primarily centripetal one in primates and humans. Van den Bergh appears to have believed that human ventriculofugal arteries were both analogous to centrifugal arteries of other organs and homologous to centrifugal cerebral arteries of earlier species.

Although Kuban and Gilles (and Nelson et al.) have stated that it was primarily their use of stereoscopic vision that allowed them to discover the mistakes made by van den Bergh and deReuck, van den Bergh did claim to have used stereomicroscopy in his studies. Stereomicroscopy was used in cerebrovascular injection studies at least as early as 1925

TABLE 1: Partial List of Cerebrovascular Research Techniques

Technique	References	Technique	References
Vascular Injections		Histologic Preparations	
Air	See Cole [53]	Benzidine vascular stains	Pickworth [58], van den Bergh [2, 4, 5], Bannister [28], Takashima [15, 18], Duvernoy [32]
Barium sulfate, colloidal	Fay [42], Saunders [35, 38], van den Bergh [2, 4, 5], deReuck [3, 21], Salamon [41]	Golgi	Duckett [59], Marin-Padilla [50]
Barium sulfate, gelatine	Salamon [41, 54], Kier [55], Theron [43], Takashima [15, 18]	Metal impregnations "Standard"	Hasegawa [47], Duvernoy [32], Bannister [28], Banker [11], Abramowicz [12], Hasegawa [47], van den Bergh [2, 5], Gilles [13], Duckett [59], deReuck [14, 21], Ginsberg [20], Bell [30, 31], Moody [27]
Blue, Berlin	Cobb [51]	Microscopy	
Blue, Monastral fast	Lewis [7]	Electron microscopy, scanning	Anderson [49], Duvernoy [32]
Carmine, gelatin	Bannister [28], Solnitzky [36]	Electron microscopy, transmission	Marin-Padilla [50]
Ink	van den Bergh [2, 4, 5], Strong [8, 56]	Stereomicroscopy	Fay [42], Pickworth [58], Strong [56], Saunders [35], Strong [8], van den Bergh [2], Duvernoy [32], Kuban [26], Nelson [1]
Ink, gelatin	van den Bergh [4], Hasegawa [47], Duvernoy [32]	Miscellaneous	
Lead oxide, colloidal	Theron [43]	Corrosion casting	Anderson [49], Duvernoy [32]
Lead, painter's red, and Vinylite	Kaplan [37, 57]	Enzyme staining	Bannister [28], Bell [30, 31], Moody [27]
Red lead (minium), gelatine	Salamon [54]	Microradiography	Many authors, but see Kaplan [57], Saunders [35], Hall [60]
Lead sulfamate, solution	Kaplan [37]	Tissue clearing	Strong [8, 56], Duvernoy [32]
Lead phosphate, colloidal, with blue dye	van der Eecken [9, 10]	Translucidation	deReuck [3, 21]
Mercury	Fay [42]		
Plastics/latex	Kier [55], Theron [43], Anderson [49], Fujii [45], Duvernoy [32], Nagata [46]		
Silicone	Kuban [26], Nelson [1], Nagata [46]		
Starch	Fay [42], Scharrer [33]		

[42]. The main difference between van den Bergh's technique and that of Kuban and Gilles (and Nelson et al.) is the thickness of the specimens studied. Van den Bergh examined thin, uncleared sections injected with Chinese ink, whereas Kuban and Gilles used thick, cleared slabs injected with silicone. Presumably this made the difference.

Finally, the diagrams drawn by van den Bergh and de Reuck, which represent the basis of the ventriculofugal/ventriculopetal border zone model, do not appear to depict the correct anatomic relationship of the choroidal arteries to the ventricles. On de Reuck's diagram, for example (see Fig. 2 in Nelson et al. [1]), the choroidal arteries appear to reside in the intraventricular space, with some branches penetrating from their intraventricular (i.e., intraplexal) location, back through the ependyma, into the brain parenchyma to make up one class of ventriculofugal artery (deReuck's type II). The choroidal arteries lie outside the ependyma everywhere, except the branches that supply the choroid plexus itself, and these branches do not leave the choroid plexus to penetrate the brain (although some subependymal plexal branches may run parallel to the ventricle for a distance before supplying the brain) [43-46]. The precise anatomy of the relationships of the choroidal arteries, leptomeninges, choroidal fissure, tela choroidea, ependyma, and choroid plexus is complex and currently is being elaborated by us.

The problems discussed here illustrate the caution that must be exercised when arriving at a given anatomic conclusion. In anatomic communications, it is important to show exactly what material is being used to reach exactly which conclusions, providing, for example, complete data tables and adequate numbers of well-labeled photographs. This has been a weakness with much of the anatomic literature. Considering the importance of making the new results persuasive,

Nelson et al. could have fortified their paper with many more pictorial examples and with a more complete, systematic tabulation of their findings. For example, although the most important point in their paper is that they were able to reproduce the (overlapping) vascular patterns of van den Bergh and then stereoscopically resolve the patterns into spatially separated vessels, no photographs of this observation are given. Kuban and Gilles [26] and Moody et al. [27] do show photographs of the crucial area adjacent to the frontal horn of the lateral ventricle. Because the conclusions of Kuban and Gilles have been reproduced independently by Moody et al. by using a different technique, the refutation by Kuban and Gilles (and Nelson et al.) of the ventriculofugal/ventriculopetal periventricular white matter vascular border-zone model is strengthened.

Other fundamental questions have arisen throughout the study of cerebrovascular anatomy, and their elucidation will likely also require the development of better anatomic and neuroradiologic techniques. For example, the existence of precapillary anastomoses and their significance remain controversial [1, 26, 32, 47-50]. Also, the observation that the capillaries of the mammalian brain exist as a continuous network [7, 27, 32, 50, 51], as opposed to capillary "loops" of the brains of certain fish, amphibians, reptiles, and marsupials, requires further explanation [33, 52].

The techniques used to study cerebral vasculature are protean (Table 1). Some publications have been devoted to the detailed description [28, 35, 37, 56, 57, 59, 60] or history [53] of technique.

The vascular physiology of the brain as it relates to selective abnormalities of the periventricular white matter is not yet fully understood. The development of MR imaging has revealed a striking number of abnormalities of this region, with

probably several different causes [61–63]. With the recent apparent refutations of the ventriculofugal/ventriculopetal model, the periventricular vascular supply is again an open issue. We believe that the answer will lie in a better understanding of the comparative anatomy of the periventricular region, as suggested by Abramowicz [12] and think that this would be a fruitful avenue of research. Neuroradiologists have an opportunity to continue as major contributors to new concepts in cerebrovascular anatomy and physiology.

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