Review Article

Etiology of intracranial berry aneurysms

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The congenital theory of the etiology of intracranial berry aneurysms has been widely accepted for many years. Review of the supporting evidence indicates that it is not based on sound scientific data but on unscientific and unsubstantiated allegations. There is no evidence of a congenital, developmental, or inherited weakness of the vessel wall. The most plausible explanation is that the aneurysms are acquired degenerative lesions — the effect of hemodynamic stress. The mural atrophy leading to aneurysmal dilatation is an acquired lesion which can be produced experimentally by hemodynamics alone. Hypertension and connective tissue disorders associated with acquired loss of tensile strength of the connective tissues are not essential: they appear to be aggravating rather than causal factors. Occlusion of one or more feeding vessels may enhance the possibility of aneurysm formation at large arterial forks subjected to the augmented hemodynamic stress associated with collateral flow.

KEY WORDS • berry aneurysm • atherosclerosis • hemodynamic stress • connective tissue disorders • cerebral aneurysm

In 1859, Gull contended that a berry aneurysm was a simple pouch with the sac wall being as transparent and normal in appearance as the parent vessel, giving the impression of a preexisting deformity. At a loss to explain the morphology in the absence of overt atherosclerosis or other disease, he regarded these aneurysms as congenital developmental errors or due to an inborn mural defect. This congenital theory has been widely promulgated. The alternative view is that they are degenerative in nature due to hemodynamic stress. A review of the etiological evidence is presented.

Clinical Features and Etiology

Patients' Age

Examination of infants' cerebral arteries has failed to reveal berry aneurysms in neonates. Proponents of the congenital theory now accept that these aneurysms are absent at birth and rarely occur during childhood. A review of reported cases in infancy provides good reason for doubting their validity in support of this theory, as most of the aneurysms were inflammatory or traumatic. Some were associated with an arteriovenous shunt and were most likely secondary to degenerative changes prone to occur in the afferent artery. This is not to deny the possibility of aneurysms occurring in infants severely affected by a metabolic connective tissue defect. The occasional report of an aneurysm in a young person is no basis for a "congenital etiology" theory. Some have suggested that the cause of saccular aneurysms in infancy differs from that of berry aneurysms in adults. However, it is now conceded that berry aneurysms are acquired; most specimens encountered clinically or at autopsy are in individuals between 40 and 70 years of age, with the mean age being approximately 50 years only 6 years younger than the subjects in an autopsy study of primary intracerebral hemorrhage. The possibility of a congenital mural weakness exists, but the age distribution is more consistent with a degenerative etiology than a developmental defect.

Familial Incidence

Sporadic instances of a familial incidence of berry aneurysms have been reported and a dominant inheritance has been suggested. Generally, only two relatives are affected, but in a few instances several individuals have been afflicted in one family, and at a younger age than is usual for patients with this entity. Occa-
sionally, hypertension may account for a familial occurrence but it is more likely that some hereditary connective tissue disorder is responsible. Bannerman, et al., could not demonstrate any hereditary tendency in their genealogical study. Pakarinen reported that 11 patients and 15 of their relatives suffered from ruptured cerebral aneurysms but the familial relationship was considered too infrequent to be significant.

**Propensity for the Cerebral Circulation and for Man**

Berry aneurysms characteristically arise from the crotch and adjacent walls of bifurcations of large cerebral arteries which have high flow rates and, less frequently, from the bifurcations of splanchnic arteries. They also occur on enlarged collateral spinal arteries in aortic coarctation or associated with spinal arteriovenous aneurysms, suggesting that the high blood velocity is a factor in their development. This cerebral preponderance is also believed to be due to architectural peculiarities of cerebral and spinal arteries (namely, the thin media and adventitia). Most of the elastin is in the internal elastic lamina with only a few fibrils in the adventitia and less in the media. The propensity for berry aneurysms to arise in man has been attributed to the greater longevity, larger cerebral arteries, greater severity of atherosclerosis, and higher incidence of hypertension in humans than in lower animals.

An association was found with three of 18 different antigens in a study of genetic markers in 45 patients with cerebral aneurysms; however, in such a small number some associations are likely to be found, although not necessarily of biological significance. Moreover, it is not certain that all aneurysms in that report were of the berry type. Ter Berg, et al., reported seven members of a large family with cerebral aneurysms. This high incidence, together with the knowledge that two unaffected family members had Marfan's syndrome, led the authors to conclude that the aneurysms may have been the consequence of a hereditary connective tissue disorder.

Lozano, et al., concluded from the literature that aneurysms rupture earlier in familial than in nonfamilial cases and the sacs are somewhat smaller. They alleged that familial aneurysms were more likely to occur at identical or mirror sites than in nonfamilial cases. This view may be biased due to the enhanced tendency for such aneurysms to be reported, and more detailed analysis of the circles of Willis would be required for a proper comparison than is usually recorded. While overt cases of inherited connective tissue disorders may have been excluded, the possibility of some hereditary connective tissue disorder must be entertained. Currently, reports of familial occurrence even in twins do not indicate genetic inheritance of aneurysms per se and cannot be used as evidence to support the congenital theory of berry aneurysms.

**Multiplicity of Aneurysms**

No particular significance can be attributed to the frequent multiplicity of berry aneurysms as it is also a common feature of extracranial arterial aneurysms. Multiplicity can just as readily be attributed to widespread degenerative disease, such as atherosclerosis, as to hypothetical congenital factors. Moreover, Housepian and Pool found arteriosclerosis more frequently in patients with multiple aneurysms than in those with single aneurysms, and it is thought that hypertension enhances the incidence of multiplicity. The anatomical variation of the circle of Willis is often regarded as congenital abnormalities and, when associated with aneurysms, have been used to support the congenital theory of aneurysm etiology in the belief that congenital abnormalities tend to coexist. There is no agreement on the criteria used for classifying deviation from the hypothetical normal circle, and little has been shown to substantiate the hypothesis that anatomical variations are congenital abnormalities. Variability is the rule and each circle is no doubt unique. Identical twins do not have identical vasculature of forearm veins, retinas, or circles of Willis. Anatomical variation is seen in the cerebral vessels of lower animals and in the human coronary arterial tree, yet berry aneurysms of these vessels are rare. Padget alleged that variation of the circle of Willis was more frequent in association with cerebral aneurysms than in the general population, but Stehbens drew attention to methodological flaws in her figures which, when corrected, refuted her thesis. There is no evidence of any structural mural weakness associated with anatomical variation from the hypothetical textbook circle of Willis, which is an illusory norm. Moreover, topographical modification of the circle occurs during postnatal development of the brain and with arteriectasis, atherosclerosis, and secondary modification of collateral vessels in pathological occlusive disease.

Although variation of the circle of Willis may not be associated frequently with congenital aneurysms, some configurations may be correlated with aneurysms for other reasons. Several authors drew attention to inequality in size of the proximal segments of the anterior cerebral arteries in the presence of an aneurysm of the anterior communicating artery. In cases where there is a sizeable shunt from one anterior cerebral artery to the contralateral vessel, the aneurysm arising in the crotch of the fork thus formed has been attributed to augmented hemodynamic stress. Lagarde, et al., reported a small or "hypoplastic" internal carotid
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Aneurysms have been alleged to arise from persistent vestigial vessels at the apex or crotch of arterial forks. This is just speculation and has never been demonstrated. Small knob-like or club-shaped dilatations of small vessels in the vicinity of the anterior communicating artery have been reported but not confirmed by other authors and, in the absence of histological studies to exclude polyarteritis, no credence can be given to the assertions. Stehbens reported such lesions in one human and one sheep, and histological studies revealed polyarteritis in both. No substantiation exists for Drennan’s hypothesis that some residual vestigial vessels from the primordial capillary plexus may persist without acquisition of their connective tissue sheaths. Berry aneurysms are of such prevalence that vestigial capillary anlagen would have been recognized during routine histological analysis of arterial forks by the serial section technique. Such vessels would acquire musculoelastic coats and would have developed into large vessels since hemodynamics is important in determining major or lesser trunks. If aneurysms arise from such defective tissue, it is possible that the sac walls might not be able to differentiate into the connective tissues of the arterial wall; however, histologically, aneurysmal sac walls retain the reactions of the arterial wall, including proliferation of endothelium, smooth-muscle cells, collagen, proteoglycans, and vasa vasorum, which are similar to changes occurring in experimental aneurysms. Elastic tissue tends to be sparse, but this is true for aneurysms in general (as in experimental venous graft aneurysms), the hemodynamic stress presumably being responsible for its degeneration and loss.

Medial Defects

In 1930, Forbus drew attention to interruptions of the media in the crotch of cerebral and extracranial arterial forks of infants. At such sites an adventitial wedge extends to the internal elastic lamina, interrupting the media. Calling them “congenital medial defects,” he inferred without evidence that they were loci minoris resistentiae where aneurysms would develop. No distinct media was discernible histologically in most of these aneurysms, so he assumed that they developed from “medial defects.” It was suggested that medial defects should be called “medial gaps” because no functional deficiency is suggested by the name; however, “medial raphe” would be more appropriate because it also indicates their functional role. In acute angles the medial muscle in the adjoining walls would tend to pull virtually in opposite directions during vasoconstriction, and in biology where this occurs there is usually a bone, ligament, or raphe for muscle fiber attachment. This concept is consistent with their propensity for acute angles at the apex or lateral angle of the fork. The raphe acts in the capacity of a sheet anchor for the muscle. It could act as a reinforcement like the prow of a boat but if this is so, the absence of raphe at obtuse-angled forks requires explanation.

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It has been demonstrated that Forbus’ raphes increase in frequency with age, proving that some at least are acquired. In older individuals they are wider and denser than in the fetus or infant. Their biological distribution in intracranial and extracranial arteries of man and lower animals is in variance with the frequency and distribution of berry aneurysms. Moreover, their prevalence in acute angles, whether at the apex or the lateral angle of a fork or union, suggests that mechanical factors are important in their localization. Study of early aneurysm formation indicated that preaneurysmal mural thinning or microevagination often occurred to the side of the apical raphe which, if involved in the pathogenesis of aneurysm formation, was involved fortuitously and “taken up” into the expanding aneurysm wall rather than always being the sac initiation site. There was no evidence that Forbus’ raphes enlarged to become preaneurysmal lesions such as mural thinning or infundibular dilatations. Moreover, the entrance to most cerebral aneurysms is considerably wider than are medial defects, so the relatively abrupt media termination at the sac entrance must be acquired.

Associated Congenital Abnormalities

Despite allegations to the contrary, the coexistence of congenital abnormalities and cerebral aneurysms had no statistical significance in the only retrospective comparative study so far conducted which, while not disproving the allegation, precludes assumptions in the absence of more reliable evidence. Moreover, the incidence of several lesions together was actually lower in the aneurysm series than would be expected in the general population. The appearance of aneurysms in subjects with aortic coarctation (adult type only) and polycystic disease of the kidneys is sufficiently high as to render the association a clinical entity or syndrome although definitive statistical proof is lacking. These two disorders are the only two congenital abnormalities usually associated with severe secondary hypertension, and the association is more plausibly attributed to the presence of hypertension and severe degenerative vascular disease so common in these patients. In the absence of further evidence, it is untenable to assume that cerebral aneurysms are attributable to some hypothetical vascular weakness affecting only cerebral vessels when associated with either of these two developmental disorders. Furthermore, poststenotic aneurysm beyond an aortic coarctation is a nonspecific reaction or fatigue phenomenon secondary to vibrational stress and there is no reason to preclude the possibility of other aneurysms associated with coarctation being of similar nature.

Cerebral Arteriovenous Aneurysms

The coexistence of arteriovenous and berry aneurysms has been regarded as an association of congenital abnormalities. Currently, there is no evidence that cerebral arteriovenous aneurysms are malformations. More plausibly they are traumatic in etiology, as are most extracranial arteriovenous aneurysms. There is strong evidence that the aneurysms occur on cerebral arteries feeding the arteriovenous aneurysms. It has been suggested that augmented flow in the afferent artery is the major factor causing the aneurysm, but other hemodynamic factors may also participate. The afferent arteries to extracranial and experimental arteriovenous fistulae are prone to secondary degeneration with ectasia, tortuosity, mural atrophy, and eventually aneurysm formation and tears in the internal elastic lamina which appear within 2 to 5 days after experimental production of arteriovenous fistulae. It is pertinent that the afferent artery of arteriovenous shunts and the apical region of arterial forks are both prone to atrophic lesions (including elastic tears) and at times recoil of the margins of the interrupted internal elastic lamina. Study of experimental cerebral arteriovenous fistulae in lower animals (ideally the chimpanzee) could provide final proof of this concept, but evidence is strong that aneurysms on the afferent arteries are secondary to the hemodynamic stresses associated with the shunt. Cerebral aneurysms in subjects with meningiomas, which are known to have a significant arteriovenous shunt, could be due to the hemodynamic stress on the afferent arteries. There is such a high incidence of aneurysms in man that the occurrence of berry aneurysms in isolated cases of rare disorders could be fortuitous.

Hereditary Connective Tissue Disorders

Since collagen and elastin are the fibrous proteins primarily responsible for the strength of the vessel wall, it is natural that cerebral aneurysms have been found in association with hereditary connective tissue disorders which manifest loss of tensile strength of the vessel wall (Ehlers-Danlos syndrome, pseudoxanthoma elasticum, arachnodactyly). However, not all of these aneurysms are of berry formation. The Ehlers-Danlos syndrome is a heterogeneous group of inherited connective tissue disorders, type IV of which manifests loss of tensile strength of the vessel wall (Ehlers-Danlos syndrome, pseudoxanthoma elasticum, arachnodactyly). However, not all of these aneurysms are of berry formation. The Ehlers-Danlos syndrome is a heterogeneous group of inherited connective tissue disorders, type IV of which manifests a deficiency of type III collagen and a propensity for arterial fragility and coexistent aneurysms quite apart from other phenotypic features of this disease. Cerebral berry aneurysms may occur in this disease and so do carotid-cavernous fistulae and unexplained subarachnoid hemorrhage; however, not all of these aneurysms are of the berry type. Pope, et al. reported type III collagen deficiency in seven of 12 patients with berry aneurysms, suggesting that some cerebral aneurysms are associated with connective tissue disorders like Ehlers-Danlos syndrome (type IV). Although other features of the Ehlers-Danlos syndrome were apparently absent, type III collagen appears to be prominent in early intimal proliferation or repair. Its deficiency may therefore predispose to aneurysm formation.

Cerebral aneurysms may occur occasionally in cases of pseudoxanthoma elasticum and Marfan’s syndrome, but not of cutis laxa. Not all are berry
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aneurysms and their association with these inherited disorders is too low for statistical analysis. They may be considered to lend support to the congenital theory but the arterial fragility, varicose veins, or skeletal disorders in these diseases are late manifestations resulting from accelerated “wear and tear.” The aneurysms must be regarded as a complication or secondary manifestation of a primary connective tissue defect which aids naturally occurring degenerative changes in the vessel wall. It is misleading to contend that all aneurysms are inherited defects because some are the outward manifestations of an inherited metabolic disorder.

The observations of Pope, et al., and the extreme variability of joint hypermobility in children support the possibility of the existence of formes frustes of hereditary connective tissue disorders and perhaps of as yet undetected metabolic disorders of connective tissue proteins. It is likely that the biochemistry of human connective tissues is as individualistic as human scent, fingerprints, and topography of the superficial veins of the upper limb, and the possible correlation of type III collagen deficiency with severe atherosclerosis warrants investigation.

Cerebral aneurysms have also been observed in association with fibromuscular hyperplasia. The role of hypertension must be taken into account along with the possibility that this is a connective tissue disorder associated with vascular fragility, since the tears in the renal arteries bear a remarkable resemblance to the lesions induced by Methocel (methyl cellulose) in rabbits. The etiology of fibromuscular hyperplasia being uncertain, coexistence with cerebral aneurysms is of unknown significance.

Histopathology of Early Berry Aneurysms

The side of the entrance to these aneurysms often exhibits relatively abrupt termination of the media, so as to suggest the side of a preexisting medial raphe, but the disparity in width of medial raphes and aneurysms indicates that the abrupt termination of the media is acquired. The postnatal and also the experimental development of medial raphes supports this possibility. At the entrance to some aneurysms, the media may be reflected into the base of the aneurysm for a distance. However, the study of early aneurysmal changes reveals that mural thinning may occur to the side of the apical raphe, suggesting that medial raphes may at times be involved secondarily and therefore fortuitously. Microevagination can involve only part of the medial raphe and the remainder of the raphe does not bulge, despite elastic degeneration. Herniation therefore appears to be into rather than of the medial raphe. These microevaginations correspond to the trough to the side of the apex observed in some experimental aneurysms produced in rats and primates by Hashimoto and colleagues. Some microevaginations occurring to the side of the medial raphe in man again suggest that the latter is not of prime importance in berry aneurysm etiology.

Hypertension

Theoretically, hypertension can be expected to enhance aneurysmal development and rupture, and its association with both polycystic and aortic coarctation supports this concept. Hypertension is more usual with primary intracerebral hemorrhage than with berry aneurysms, but several authors have indicated an association between hypertension and either the aneurysm or subarachnoid hemorrhage. Aneurysms have occurred in association with pheochromocytoma. In general, cerebral aneurysms have been regarded as part of the hypertensive complex, with a reported association with atherosclerosis and medial fibrosis of the cerebral arteries.

Theories of Berry Aneurysm Etiology

The Congenital Theory

The congenital theory evolved from assumptions and circumstantial evidence which do not withstand scientific analysis for three reasons. 1) Lack of gross atherosclerosis in many cases led to the assumption that the sac wall macroscopically was as “normal” in appearance as the parent vessel and hence the sac was claimed to be a naturally occurring diverticulum. This was not so microscopically. 2) It was assumed that the medial raphe was a physical defect of the wall and it was then correlated with a relatively abrupt termination of the media at the entrance to the sac. 3) The association of cerebral aneurysms with congenital abnormalities and variations of the circle of Willis was not analyzed statistically. Aneurysms were assumed to be associated with hypothetical defects in the cerebral arteries. The association between aortic coarctation, polycystic renal disease, and cerebral arteriovenous aneurysms was assumed to be due to congenital or developmental factors rather than the degenerative arterial changes so profound in these diseases. Patients’ age, distribution and multiplicity of aneurysms, medial raphes, and the early development of aneurysms, and the association with other lesions, anatomical variations, and hypertension fail to substantiate the congenital theory. The congenital defect argument remains hypothetical, with no persistent vestigial vessels leading to aneurysmal dilatation demonstrated.

The Degeneration Theory

Proponents of the degeneration theory assert that aneurysms occur at cerebral arterial forks, are due to degenerative changes in the arterial wall, and are acquired lesions. Stehbens attributed berry aneurysms to hemodynamically induced degenerative changes related to atherosclerosis associated with loss of the tensile strength and/or cohesive properties of the vessel wall, as in the poststenotic dilatation. Circumstantial evidence, rather than favoring the congenital theory, supported the degeneration theory. Early or preaneurysmal changes can be regarded as degenerative in nature and part of the atherosclerotic process. More recently,
these changes have been classified as atrophic lesions similar to those arising in the afferent artery of arteriovenous fistulae and those seen at the greater curvature of bends (WE Stehbens, unpublished data) where the flux of blood flow impinges on the vessel wall.

Some authors have attributed aneurysms to some inborn defect in the vessel wall in association with a degenerative process that occurs naturally at arterial forks,\cite{12,13,16,17,98} without doubting the validity of the hypothetical congenital factors. Carmichael\cite{12,15} mistook areas of mural thinning for the medial defects or raphes described by Forbus,\cite{28} and Crawford\cite{46} attributed the etiological importance of developmental faults, atherosclerosis, and hypertension to the age at which the aneurysms developed despite their histological similarity at all ages. The latter views ignore the young age at which degenerative intimal changes occur microscopically and ultrastructurally,\cite{78,85,92} and the fact that they can be induced very rapidly by hemodynamic means.\cite{78,92} It is basically unscientific to invoke participation of hypothetical factors without substantial evidence.\cite{92}

**Experimental Evidence**

No evidence, experimental or otherwise, exists to demonstrate that medial defects or raphes are loci minoris resistentiae. Their location, ubiquity, and morphology are all inconsistent with this assertion or that they play a causative role in aneurysm formation. Stehbens\cite{52} reported the development of a medial raphe in an acute flexure induced experimentally in the common carotid artery of a sheep. This should be confirmed in more animals but its occurrence is consistent with the known appearance and enlargement of these raphes postnatally in man.\cite{70}

Hassler\cite{41} ligated the common and internal carotid arteries on one side of the neck in a series of rabbits and reported that the altered hemodynamics led to enlargement and bulging of the medial raphes. Enlargement was reported at the basilar bifurcation and bilaterally at the origin of the posterior communicating arteries, with the illustrations resembling microevagination rather than bulging medial raphes as was alleged.

Stehbens\cite{92} contended that the three most likely methods of producing cerebral aneurysms were by experimental hypertension, coarctation of the aorta, and cerebral arteriovenous fistula. He also reported aneurysm formation and atrophy of the common carotid artery feeding experimental carotid-jugular fistulae in sheep,\cite{83,84} and found this atrophic change at the greater curvature of experimental U-shaped bends in rabbits.\cite{82}

The wall was attenuated with complete loss of medial and elastic tissue similar to the mural thinning in the cerebral arteries of man that precedes aneurysm formation.\cite{45} By scanning electron microscopy of the atrophic lesions, tears in the internal elastic lamina were found as early as 2 and 5 days postoperatively\cite{33,34} depending on whether the artery was of the muscular or elastic type. The experiments demonstrated that mural thinning can be produced experimentally by hemodynamic means in the absence of specific connective tissue disease, thus substantiating a degenerative etiology. Aneurysms can also develop from the greater curvature of flexures in the internal carotid artery in man.\cite{60}

Hashimoto and colleagues\cite{39,40,42,43} successfully produced aneurysms of the cerebral arteries. Experimental lathyrism and hypertension with unilateral ligation of the common carotid artery induced aneurysms, particularly on large cerebral arteries participating in the collateral circulation in rats. In many of these saccs resembled the miliary aneurysms of Charcot and Bouchard\cite{42} or the polarteritis seen in mesenteric arteries of severely hypertensive rats with the wall consisting of fibrin or thrombus surrounded by adventitia, but in some the sac was thrombosed.\cite{39} Several aneurysms were fusiform and others were not associated with arterial forks. Early changes were observed in rats without lathyrism.\cite{43} The mural thinning occurred adjacent to the apex, appearing as a juxta-apical evagination in three dimensions. Similar aneurysms were produced in hypertensive lathyrismic monkeys with the preaneurysmal thinning or bulge occurring in the branch with augmented collateral flow. Aneurysms ultimately formed. These experiments and those of Hassler\cite{41} confirm the role of hemodynamic stress in the etiology of aneurysms. Lathyrism and hypertension act merely as aggravating factors.

**Implications for Man**

Ligation of the common or internal carotid artery is often performed in man for therapeutic reasons. The immediate hemodynamic changes distally depend on the topography of the arterial tree and thus vary with the individual. Some long-term pressure changes may ensue but no concerted effort has been made to follow such patients to autopsy. From the investigations of Hashimoto and his colleagues,\cite{39,42,49} it is conceivable that such patients might develop aneurysms secondary to the ligation, the sac forming at forks with hemodynamic imbalance due to the need for collateral flow. Jaffe and McHenry\cite{48} have reported such a case and similar examples occur in association with alleged agenesis of a constituent of the circle of Willis.\cite{52,54} It is also possible that aneurysms could occur on the internal carotid artery contralateral to stenosis or occlusion of a carotid sinus. Aneurysms have been found at sites of augmented hemodynamic stress in patients with Takayasu's disease and occlusion or stenosis of cervical arteries.\cite{50} Stern, et al.,\cite{96} reviewed 20 subjects with extracranial carotid stenosis and intracranial aneurysm. In only four instances were the aneurysms on the contralateral side, in seven patients either the aneurysms or the carotid sinus disease were bilateral, and in nine the aneurysms were on the homolateral side. While these figures do not support the effect of ligation, they warrant study of a larger number of patients. Aneurysm of the basilar artery could occur secondary to bilateral stenosis or occlusion of the internal carotid arteries, as
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in the case of Yamanaka, et al.,101 and such an occurrence in moyamoya disease50 is consistent with this concept. It is also possible that a change in the distal run-off from a branch might lead to some imbalance of flow at the fork sufficient to induce atrophic changes. Hypertension or a connective tissue disorder would augment this tendency.

The conclusion is that berry aneurysms are not congenital and are not due to hypothetical developmental errors. Available evidence overwhelmingly favors their causation by hemodynamically induced degenerative vascular disease. There is probably a predisposition to aneurysm formation in cases of hypertension and connective tissue disorders in which mural fragility develops. Furthermore, arterial occlusive lesions may also predispose to aneurysm formation postnatally at specific arterial forks affected by secondary imbalance of blood flow. There is an obvious need to determine the hemodynamic parameters most likely to induce the precursor atrophic lesions.

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