Bruch's membrane and vascular growth

The importance of an intact barrier between retina and choroid is underscored by the diversity of disabling diseases in which abnormal blood vessels transgress Bruch's membrane and reside in the potential space under the retinal pigment epithelium (RPE). Through processes of transudation, hemorrhage, local growth, and fibrous metaplasia, these vascular growths may exert deleterious effects on retinal (especially macular) function. Moreover, vascular violation of Bruch's membrane may be iatrogenic, the result of excessively intense photocoagulation. Not only may choroidal blood vessels grow through these induced defects in Bruch's membrane, they may also invade the sensory retina and vitreous. Despite the significance of these events, the physical and biologic properties of Bruch's membrane are only partially understood.

At the present time, one can only speculate about the precise roles performed by Bruch's membrane. Ultrastructural and other evidence suggests that this multilaminar structure acts as a loosely knit molecular sieve, possibly allowing passage of molecules up to a molecular weight of 70,000. Collagenous and elastic tissue provide some structural and elastic strength to Bruch's membrane, despite its thickness of only 0.7 to 3.3 microns. In view of the havoc threatened by blood vessels transversing Bruch's membrane, separation of retinal and choroidal vasculatures must be considered one of its most important normal functions.

Aging induces a series of important events. Bruch's membrane becomes denser and thicker and accumulates fragments of other materials, including calcium and possibly RPE phagosomes. Ring and Fujino, utilizing flat preparations of choroid and Bruch's membrane from apparently healthy adult eyes, found that round holes (15 to 30 microns in diameter) were "constantly present" in Bruch's membrane at the posterior pole, especially in the macular region. These defects were associated with sclerotic changes in the choriocapillaris and were less frequently observed in younger individuals. Although these holes might represent artifactual disinsertions of posterior ciliary arteries or veins, they may well be naturally occurring apertures that allow entry of plasma, erythrocytes, and/or vessels from the choroid into the sub-RPE space. Ring and Fujino, for example, found neovascular channels between Bruch's membrane and the RPE in 90 per cent of eyes over age 60. Sarks, also employing histologic techniques, studied 150 senile maculas and found a lower (20 per cent) but still impressive inci-
idence of sub-RPE neovascularization as a consequence of the normal aging process. Importantly, a majority of the involved eyes were not clinically suspected to have sub-RPE neovascularization on the basis of ophthalmoscopic examination, but fluorescein angiography was not performed. In the peripheral fundus, Sarks was able to confirm growth of new vessels from the choroid through definite breaks in Bruch's membrane in 4 per cent of eyes that appeared relatively normal, except for advanced age.

Pathologic breaks in Bruch's membrane are now presumed to be pivotal events in the pathogenesis of a large number of disabling macular disorders, including a variety of senile and presenile disciform macular degenerations, the presumed ocular histoplasmosis syndrome, high myopia, angiod streaks, and traumatic rupture of the choroid. Photocoagulation, often used in the treatment of these disorders, can actually induce or exacerbate sub-RPE neovascularization. Once present, sub-RPE vascular sheets can respond by excessive growth following photocoagulation burns that were too mild to obliterate them completely. In this regard, the neovascular sheets act like proliferative granulation tissue in response to local and surrounding injury. At the opposite end of the spectrum, overly intense photocoagulation burns can rupture Bruch's membrane and cause choroidal hemorrhage. Subsequently, growth of choroidal vessels can occur through the induced defect in Bruch's membrane into the sub-RPE space and sometimes into the sensory retina and even into the vitreous. The mechanism of vascular overgrowth is not clear, but may involve reparative processes, a vasotactic response to adjacent hypoxic tissue, or simply an opportunistic growth of vessels through a hole.

The ironclad separation of the retinal and choroidal vasculatures is breached in at least four types of circumstances: as variants of normal; when increased pressure in the central retinal vein induces development of retinociliary vessels; at the site of granulomatous or cicatrizizing processes involving both retina and choroid; and, importantly, following fundus photocoagulation.

In normal eyes, connections exist between retinal and posterior ciliary or uveal blood vessels at the optic nervehead. Their size and number vary from person to person. A large percentage of the normal population has cilioretinal arterioles supplying the macular and other regions. In occasional individuals, vascular connections between retina and uvea also occur at the ora serrata. For the broad expanse of fundus between disk and ora serrata, however, the two circulations are normally quite separate.

If mechanical resistance to outflow in the central retinal vein becomes significant, blood is shunted to the uveal circulation through pre-existing retinociliary (optociliary) anastomotic channels. These vessels become ophthalmoscopically prominent in such conditions as thrombosis of the central retinal vein, hyaline bodies of the nervehead, arachnoid cysts involving the intraorbital optic nerve, and sphenoid orbital meningioma. By themselves, these blood vessels do not cause clinical disease, and may, in fact, function as escape valves for blood that might otherwise be trapped in the retina and cause abnormal function. These vessels generally do not grow through Bruch's membrane, but pass around the border of Bruch's membrane at the optic nerve.

Granulomatous and cicatrizizing processes in the macular region can simultaneously involve adjacent retina and choroid. Reparative processes may induce granulation tissue to invade the inflamed or hemorrhagic retina and choroid. Under these circumstances, the structural integrity of Bruch's membrane is apparently made vulnerable by local inflammatory and hemorrhagic processes, and neovascular channels within organizing scar tissue are able to connect retinal and choroidal vasculatures. Anastomoses of this kind are most dramati-
ally observed (and have been histologically confirmed) in macular toxoplasmosis, toxocariasis, syphilis, and in disciform degeneration. A patient with sickle cell anemia showed a similar response. In this case, the course of events leading to chorioretinal anastomosis was unclear, but may have been the result of resolution and organization of a localized hematoma and hemorrhagic infarction. In the presence of retinal detachment, the peripheral fundus may demonstrate ringschwielle formation with uveoretinal vascular anastomosis.

Trauma to the eye can similarly induce localized fundus areas of hemorrhage and infarction with subsequent scar tissue formation. Choroidal ruptures, traumatized angioid streaks, and chorioretinitis sclopetaria are examples of blunt, nonpenetrating ocular trauma that may be followed in months or years by neovascular connections between retina and choroid.

Recent evidence suggests that trauma from photocoagulation may cause similar unwanted effects. Photocoagulation can cause proliferation of vascular tissue without rupturing or burning Bruch's membrane, as in the case of pre-existing sub-RPE or preretinal neovascular nets. When photocoagulation energy is sufficient to rupture Bruch's membrane, either by heat transmitted from surrounding melanin pigment or, more likely, by mechanical effects from an adjacent choroidal hematoma or vapor bubble, the subsequent clinical course of events may be extremely deleterious. Proliferating tissue may rather quickly (weeks to months) invade the sensory retina. Even the vitreous may then become involved. In some cases, the intravitreal neovascular channels appear to have parasitized old vessels of pre-existing retinitis proliferans. In other cases, the intravitreal vessels appear to carry blood with a high head of pressure, directly from major choroidal arteries, including the long posterior ciliary artery. In still other cases, the intravitreal fibrovascular stalks are enmeshed and surrounded by dense white connective tissue and by extravasated blood. For all these reasons, their therapeutic obliteration with additional photocoagulation, cryocoagulation, or diathermy can be exceedingly difficult and sometimes impossible.

In an attempt to understand, prevent, and treat the natural and iatrogenic disease processes described above, a comprehensive, concerted investigative attack on Bruch's membrane is warranted. What are the physical and biologic properties of this fascinating and important structure, and how can they be quantitated? How often, for example, do holes naturally occur in Bruch's membrane and what is their nature? What are the differences between these and other defects occurring in the macular region as opposed to those occurring in the fundus periphery? What are the electrical, flow, and permeability characteristics of Bruch's membrane? How do solutes interact with it? How are these characteristics affected by aging and by disease states? How do the adjacent RPE and choriocapillaris influence Bruch's membrane? Are the different layers of Bruch's membrane affected differentially? What are the vesicular and mineral deposits that occur in Bruch's membrane as a consequence of aging? What are the origin and biologic effects of the colloid material that collects under the RPE with aging? What is the relationship between this material and drusen? Does this material induce or permit growth of abnormal blood vessels? What are the elastic properties of Bruch's membrane, and how do they respond to normal and abnormal stress? Why does a youthful and intact Bruch's membrane generally resist the growth of blood vessels? What are the stimuli for choroidal capillaries to grow through Bruch's membrane? Are pre-existing holes necessary? Finally, what are the photocoagulation parameters (wavelength; burn duration, size, and intensity) that will destroy unwanted preretinal, retinal, sub-RPE, or choroidal tissue, but will leave Bruch's membrane unaltered? During the developmental years of laser photocoagu-
lation, short burn times with small diameter beams have been emphasized. Theoretical consideration suggests, however, that larger burns of wider diameter may more successfully protect the integrity of Bruch’s membrane. Each of these questions—and many more—deserve thoughtful inquiry. The tools are at the hand to test varying hypotheses and should be employed forthwith.

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REFERENCES