

## MINI REVIEW

## Bruch's membrane change with age

Age related macular disease is now the commonest cause of registered blindness in western communities,<sup>1,4</sup> and it is evident that the prevalence is rising with the increasing age of the population.<sup>5,6</sup> Both the realisation of the high prevalence of disease, and the prospects of therapy,<sup>7-9</sup> have stimulated recent interest in the disorder. Unfortunately it has now become evident that laser treatment will not have a major impact on blindness from age related macular disease.<sup>10-12</sup>

Since the historic monograph of Gass<sup>13</sup> there has been increasing clinical and laboratory research which has highlighted the role of neovascularisation and retinal pigment epithelial dysfunction in the pathogenesis of the disorder. However, there is still incomplete information on the natural history and the basic pathogenesis of age related macular disease, and the factors which determine the risk of visual loss are ill understood. There is now increasing circumstantial evidence that the chemical composition of deposits in Bruch's membrane may be an important determinant of the outcome of disease. It is hoped that current pathogenetic concepts will form a rational basis for future studies.

**Nature of Bruch's membrane change**

There is some evidence from microscopic studies that the chemical composition of Bruch's membrane deposits may differ from one subject to another. Conventional microscopy does not show large quantities of lipid in Bruch's membrane, since dehydration techniques tend to remove much of the lipid. Gaps in Bruch's membrane deposits have been thought to imply the presence of such lipid. Recently, by means of freeze drying techniques and histochemical staining, increasing quantities of lipid have been shown in Bruch's membrane with age. It was also demonstrated that the nature of the lipid differed from one patient to another.<sup>14</sup> Clinical studies imply that this may be relevant to disease.

The accumulation of debris in Bruch's membrane is a progressive phenomenon with age which may be detected by microscopy as early as 10 years, and is seen consistently by the age of 60 years.<sup>15-18</sup> This abnormal material is derived from the pigment epithelium,<sup>18-22</sup> and its accumulation is thought to result from failure to clear the debris discharged into this region.

The abnormal material may collect as discrete deposits in the inner portion of Bruch's membrane between the basement membrane of the retinal pigment epithelium (RPE) and the inner collagenous layer, which are recognised clinically as drusen. In addition diffuse accumulation occurs throughout Bruch's membrane. Thickening of the inner part of Bruch's membrane is compounded by excessive production of material resembling basement membrane by the pigment epithelium.<sup>16,23</sup>

**Discrete Bruch's membrane deposits**

Clinical studies have shown wide variation in the size and distribution of drusen from patient to patient, although there is remarkable symmetry between the two eyes of a single patient.<sup>4,24,25</sup> For example, in some patients the drusen may be confined to the central 5° in each eye, while in others the

drusen occur in a circle 12-16° from the fovea, the fovea itself being free of visible deposits.

Drusen may be brightly fluorescent during angiography in some patients, while in others this is not the case; this characteristic is also symmetrical between two eyes.<sup>25</sup> There is doubt as to the determinants of fluorescence, and therefore the significance of this finding to disease. Fluorescence may be dependent on the quantity of pigment in the overlying pigment epithelium, or more importantly on the presence or absence of fluorescein within the drusen material. It has been hypothesised that hyperfluorescent drusen must have a high water content, allowing free diffusion of water soluble sodium fluorescein into the abnormal deposit; there may also be binding of sodium fluorescein to polar molecules.<sup>26</sup> By contrast the hypofluorescence of other drusen would imply that they are hydrophobic. It has been suggested that the former are rich in protein and phospholipids, while the latter are rich in neutral fats.

**Diffuse Bruch's membrane deposits**

To date there are no established clinical correlates of diffuse changes. A clue as to a possible sign of such deposits was derived from Sorsby's fundus dystrophy in which thickening of the inner portion of Bruch's membrane occurs.<sup>27</sup> A slow filling phase on fluorescein angiography is often the first sign of the abnormal phenotype,<sup>28-30</sup> though the nature of the association is unclear. There are two alternative sequences of events: either the vascular changes initiate the disorder, or the deposits influence the choroidal vasculature. Change of the choriocapillaris causing reduced clearance of waste material from the extravascular space, predictably would cause accumulation in the outer portion of Bruch's membrane. However, at least in Sorsby's fundus dystrophy this cannot be the case since the deposits are internal to the inner collagenous layer.<sup>27</sup> The alternative explanation is based on evidence that implies that the retinal pigment epithelium regulates the choroidal capillaries,<sup>31,32</sup> and the mechanisms by which this regulation may take place have been identified.<sup>33</sup> If the two cell systems are separated by a diffusion barrier, changes in the choriocapillaris might be expected as a consequence. Although few systematic analyses of the human choroidal vasculature exist, histopathological studies imply that reduction in its cross-sectional area is common in the elderly.<sup>18,34,35</sup>

This led to the concept that a prolonged filling phase of the choroid during fluorescein angiography may indicate the presence of diffuse Bruch's membrane thickening. Recently this angiographic sign has been demonstrated in a proportion of patients (26%) with age related Bruch's membrane change.<sup>36</sup> Thus, there is evidence that a slow filling phase may signal the presence of diffuse thickening of Bruch's membrane acting as a diffusion barrier between the retinal pigment epithelium and choroid in age related change.

**Consequences of Bruch's membrane change**

Clinical studies have been directed towards the analysis of discrete deposits on the inner surface of Bruch's membrane, and have largely ignored the potential importance of diffuse

Bruch's membrane thickening. Logically, the diffuse deposits would be expected to play a major role in determining the outcome of disease. However, it is fortunate that the chemical composition of two forms of deposit appear to be similar,<sup>14</sup> such that studies based on drusen characteristics may indicate also the influence of diffuse change.

The mechanisms by which the deposits cause the sight threatening complications have not been clearly identified. The major lesions causing visual loss are the growth of new blood vessels from the choroid through Bruch's membrane towards the retina, detachment of the retinal pigment epithelium, and atrophy of the outer retina and choriocapillaris.<sup>10 37</sup> Some correlation exists between the type of drusen and the form of lesion causing visual loss.

Drusen which are hyperfluorescent, and therefore presumed to be hydrophilic, appear to predispose to sub-retinal neovascularisation.<sup>38 39</sup> Over the last decade some determinants of blood vessel growth have been identified, though the circumstances leading to neovascularisation have not been defined. The chemical nature of the interfibre matrix of Bruch's membrane, change in the pigment epithelial influence upon blood vessel growth, and the presence of macrophages<sup>40</sup> which stimulate neovascularisation may all be relevant. In particular, polar molecules may stimulate invasion of Bruch's membrane by macrophages or neutral fats may suppress blood vessel growth.

Patients with large confluent drusen in the central area which are hypofluorescent have a predisposition towards pigment epithelial detachments rather than neovascularisation.<sup>38 39</sup> It has been proposed that these presumed lipid rich deposits reduce hydraulic conductivity of Bruch's membrane,<sup>26 38 39</sup> so that water which is pumped from the retina towards the choroid by the retinal pigment epithelium accumulates in the sub-pigment epithelial space. In its extreme form the pigment epithelial detachment becomes progressively larger, generating sufficient tangential stress in the detached tissues to cause a tear.<sup>26 38</sup>

Loss of photoreceptors in the outer neuroretina is a constant association with age.<sup>22 41</sup> Areas of well defined geographic atrophy supervene, a process which has been well documented histologically.<sup>35</sup> Atrophy may follow spontaneous resolution of retinal pigment detachments,<sup>41</sup> though this probably accounts for a small proportion of such lesions. To what extent a diffusion barrier is responsible for geographic atrophy is unknown. It is easy to conceive that movement of molecules between the choroidal capillaries and the pigment epithelium would be impeded by the interposition of a layer of debris particularly if it was composed largely of neutral fats rather than polar molecules. Just as the diffusion across Bruch's membrane of water and growth factors produced by the retinal pigment epithelium would be hampered, complexes containing molecules essential for photoreceptor function would not pass freely from the choroid to the retinal pigment epithelium. Consequent functional deficit might be expected. A search for sensitivity loss has been relatively unrewarding over discrete deposits,<sup>42 43</sup> but major and consistent deficit has been identified in those with the angiographic sign of slow choroidal perfusion, and therefore presumed diffuse disease.<sup>44</sup> There is good evidence that the circulatory disturbance alone would not cause ischaemic dysfunction.<sup>17 45</sup> The relevance to age related macular disease of the proposed barrier to diffusion at the level of Bruch's membrane could be tested by longitudinal study of patients who manifest the sign of a slow choroidal filling phase on angiography.

The symmetry of drusen in terms of quantity, distribution, and chemical composition, and the concept that the form of Bruch's membrane deposits determine the nature and magnitude of risk to vision, together suggest that the two eyes of a patient should behave in a similar manner, and that there

would be differential risk from one patient to another. Several observations are compatible with this concept. In patients with unilateral visual loss there is the good correlation between the form of drusen in one eye and the type of lesion in the other.<sup>38 39</sup> It has also been shown in patients with a retinal pigment epithelial tear in one eye that there is a very high risk of a similar event occurring in the other.<sup>46</sup> With one exception,<sup>47</sup> all studies are compatible with an overall incidence of 10–15% per year of second eye involvement in patients with unilateral visual loss,<sup>14 48–50</sup> but, if the first eye had a tear of the pigment epithelium, the annual risk is much higher.<sup>51</sup>

## Conclusions

From these data it appears that age related macular disease represents a continuous or discontinuous spectrum of disease in which patients behave differently one from another. There is circumstantial evidence that the chemical composition as well as the quantity of accumulated material in Bruch's membrane may determine the magnitude and nature of the risk to vision. Many clinically accessible clues exist which allow the variants of disease to be identified. Longitudinal studies are required to define better the natural history of the disorder, and these should take into account the proposed determinants of risk. The information derived from such research is essential to advance the pathogenetic concepts concerning age related macular disease further and to identify new therapeutic strategies. It is particularly encouraging that many of the recent concepts can be tested in the laboratory.

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