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Doyne Lecture

Pathogenesis of Retinal Pigment Epithelial Detachment in the Elderly; the Relevance of Bruch's Membrane Change

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I am very conscious of the honour accorded to me by being asked to give the 1990 Doyne lecture. I have chosen the subject of Bruch's membrane disease and its relevance to age related macular degeneration, one of many aspects of ophthalmology to which Doyne made considerable contributions. He was not the first to describe these changes but introduced the concept that drusen may differ from one patient to another, and that there may be genetic influences in the pathogenesis of drusen.[1,2] These are considerations to which I will return repeatedly during this lecture. I hope to illustrate that there is both quantitative and qualitative variation of Bruch's membrane changes from one patient to another, and that these are relevant to the clinical outcome and to our understanding of the pathogenesis of disease.

Age related macular disease is now recognised as the commonest cause of registered blindness in Western Society,[3–6] and it is evident that the prevalence is rising.[7,8] Both the realisation of the high prevalence of disease, and the prospects of therapy,[9–11] have stimulated recent interest in the disorder. Since the historic monograph of Gass[12] 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.

Unfortunately, it has become evident that laser treatment will not have a major impact on blindness from age related macular disease.[13–15] This requires that our knowledge of the behaviour and aetiology of age related macular disease be re-examined, and alternative approaches to therapy sought. There is still incomplete information on the natural history and the determinants of risk, but hopefully the current pathogenetic concepts will form a rational basis for future studies and provide novel therapeutic approaches to this disorder.

The lesions identified as causing loss of central vision are subretinal neovascularisation and detachment of the retinal pigment epithelium. These are widely believed to occur in response to deposition of abnormal material within Bruch's membrane[12,16] which is a progressive phenomenon with age. Accumulation of debris may be detected by microscopy as early as 10 years, and is seen consistently by the age of 60 years.[17–20] There is now increasing circumstantial evidence that the chemical composition of the deposits in Bruch's membrane and the reactions they provoke are important determinants of the outcome of disease.

It is likely that blood vessel growth is suppressed by the metabolic environment of Bruch's membrane. This may be due to its intrinsic composition or to diffusible agents produced by the retinal pigment epithelium.

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Changes induced by the accumulation of abnormal material, and the presence of macrophages appear to be important in the induction of new vessel growth.[21]

In the early discussion of the potential pathogenesis of pigment epithelial detachments it was believed that the detachment was induced by passage of fluid through Bruch's membrane from the choriocapillaris, the physical attachment of pigment epithelium to Bruch's membrane having been disturbed by progressive accumulation of debris on the inner surface of Bruch's membrane.[12] The assumption that fluid was derived from the choroid is understandable since the fluorescein which fills the subpigment epithelial space during fluorescein angiography is derived from the choroid rather than the retina. This concept presumes high hydrostatic pressure in choroid, although experimental evidence implies that it is unlikely that the hydrostatic pressure in the choroid is greater than the pressure within the retina.[22] Indeed the little evidence that exists suggests that it may be somewhat lower. As an alternative mechanism fluid might be drawn into the subpigment epithelial space from the choroid by high osmotic pressure within this cavity, although the little that is known concerning the constituents of the subpigment epithelial space do not imply that this is the case. The acceptance that choroidal blood vessels may grow through Bruch's membrane and proliferate on the outer surface of flat pigment epithelium as a primary response to age-related Bruch's membrane disease, has led to the proposal that exudation from such a new vessel complex may be an altenative source of fluid causing pigment epithelium to detach.[23] However, neovascularisation is not universal in pigment epithelial detachments. It is undeniable that such blood vessels may modify the outcome of pigment epithelial detachments, but it is unlikely that this represents the initiating event in the pathogenesis of retinal pigment epithelial detachments.

One major weakness of these concepts is that none explains certain clinical behaviour characteristics of pigment epithelial detachments. It is hard to conceive how scattered photocoagulation over the surface of the pigment epithelial detachment would induce the pigment epithelium to flatten.[13] In addition it is difficult to explain the drop in vision which appears to be a common, if not invariable, with spontaneous flattening of the pigment epithelium at least in the elderly.[24] Finally, any hypothesis concerning the pathogenesis of these lesions would need to account for the phenomenon of tearing of the pigment epithelium.[25]

In 1986 a new concept was proposed in which it was suggested that the subpigment epithelial fluid is derived from the retinal pigment epithelial rather than from the choroid.[26] It is widely accepted that fluid is pumped from the retina to Bruch's membrane due to active movement of ions by the pigment epithelial cells. If Bruch's membrane became hydrophobic a significant resistance to water flow may be generated at this level causing fluid to collect between the pigment epithelium and Bruch's membrane. Such a mechanism demands that there be progressive accumulation of lipid or lipoprotein in Bruch's membrane and that this would vary from one patient to another. The observed entry of fluorescein from the choroid into the subpigment epithelial space would be explained by movement down a concentration gradient rather than the movement following fluid flow. This alternative explanation for the pathogenesis of retinal pigment epithelial detachments had the attraction over previous concepts in that it was compatible with the three observed behavioural characteristics of pigment epithelial detachments which were unexplained at that time:

(1) The destruction of pigment epithelial cells, and therefore some of the pump, by photocoagulation would cause reduction in the volume of fluid being moved into the subpigment epithelial space, and predictably would be followed by flattening of the pigment epithelium.

(2) This concept explains the observation that flattening of pigment eithelial detachments is accompanied by loss of vision. Tissue failure as manifest by visual loss might be associated with reduction of fluid pumped into the subpigment epithelial space which would itself be accompanied by flattening of the pigment epithelium onto Bruch's membrane.

(3) The pigment epithelial pump might be powerful enough to produce tangential stress in the detached tissues sufficient to cause tearing of the pigment epithelium since it resists the influence of trans-cellular hydraulic pressure differences.[27]

The observed slow flow of fluorescein into the subpigment epithelial space in patients at risk of suffering a pigment epithelial tear would be in accord with the proposal that in these patients the hydrophobicity in Bruch's membrane would be high.

Therefore, this alternative hypothesis concerning the pathogenesis of retinal pigment epithelial detachments had many attractions for the clinician. It does not exclude new vessels growing within the inner portion of Bruch's membrane as a combination to the detachment. It is evident that decreased hydraulic conductivity of Bruch's membrane would be an essential pre-requisite for these vessels to cause accumulation of fluid in the sub-pigment epithelial space.

Some support for this concept is derived from both histopathological and biophysical observations. It has been reported that the hydraulic conductivity of Bruch's membrane becomes progessively less with age.[28] Clefts seen by histopathology in Bruch's membrane with linear deposits have been interpreted as water clefts consequent upon hydrophobicity of Bruch's membrane.[29]

During the last four years a series of laboratory and clinical studies have been undertaken to test this concept. In this paper an account of these is given, and an attempt is made to assess the significance of the accumulated evidence.

Laboratory studies:

In order to test the concept evidence was sought to support the proposal that there is progressive accumulation of lipids in Bruch's membrane with age. Increase of basophilia and PAS staining of Bruch's membrane has been long recognised by pathologists[30–33] and was thought to reflect progressive lipid deposition. However, because routine histological procedures removes lipids from the specimen, no systematic analysis of lipid content of the debris had been reported. A study of frozen tissue was undertaken using histochemical staining techniques on 30 human eyes with an age range between one and 95 years.[34] The composition and ultrastructure of Bruch's Membrane were recorded by electron microscopy on the same specimens. The results analysed in three age groups, 0–30 years, 31–60 years and older than 60 years showed progressive accumulation of lipids in Bruch's Membrane with age. Differences were found in the specific types of lipids present. Some eyes stained for neutral lipids alone, some stained predominantly for phospholipids and others stained equally for both neutral lipids and phospholipids. The deposits were associated with the progressive destruction of the native architecture of Bruch's Membrane but no correlation was identified between specific inclusions in Bruch's Membrane with a particular lipid.

To confirm these conclusions, material extracted by lipid solvents from tissue of fresh eyes from the Moorfields Eye Bank was analysed by think layer and subsequently gas chromatography.[35] After separation, the chemical species were identified by mass spectroscopy. This study confirmed the conclusion that the quantity of lipid in Bruch's membrane increased with age, and that the ratios of phospholipids to neutral fats varies from one subject to another. Other substances were also detected in each lipid fraction but not in the lipid standards which had been treated in an identical manner. Mass spectrography showed these to be plasticisers. The most prominent plasticisers were phthalates, adipates and tributyl acetylcitrate; the relative amounts of each varied markedly between specimens. The amount of plasticiser as a percentage of the total quantity of material extracted rose as the quantity of lipid increased. In the specimen with most lipid, 80% of the extracted material was plasticiser.

Every effort was made to avoid contamination of samples during processing, a problem that is well recognised in studies of this type.[36] A measure of the exclusion of contamination is the absence of detectable plasticisers in the lipid standards, and in those specimens containing no lipid. These findings plus the very large quantities found in those specimens with high lipid content implied that the plasticisers were derived from the specimen.

These findings pose several questions concerning the origin of the plasticisers and their relevance to disease. Plasticisers are used to impart flexibility to synthetic polymers, particularly PVC, and may constitute up to 40% of the weight of the finished product.[37] As a result of their widespread use, plasticisers have now become ubiquitous in the environment.[38] Human consumption of plasticisers results largely from the use of PVC as food packaging material.[39] The level of intake depends upon several factors relating both to the food product and the packaging. Since plasticisers are fat soluble, food with higher lipid content will dissolve more plasticiser from its wrapping. As early as 1964 it was estimated that the average individual daily intake in Western Society is about 1mg/1Kg body weight.[40]

Soon after the introduction of phthalates in 1935 the toxic potential was judged to be low.[41,42] Realisation that there was regular intake by man stimulated many animal studies. Little evidence exists of long term sequestration of phthalate following intravenous or oral administration with near complete excretion occurring with 48 hours.[43–45] However, there is increasing awareness of the potential influence of phthalate upon metabolic systems. In rodents on long term high dose administration many aspects of liver metabolism are altered,[46–50] and testicular atrophy occurs due to a toxic effect on Sertoli cells.[51]

In man the limited data reinforce the view that the half life of phthalates in the body is short,[44] and the toxic effects recorded in rodents have not been found. However, accumulation of plasticisers may occur in abnormal tissues. In kidney phthalates have been found in the presence of nephrosclerosis but not otherwise;[52] it was postulated that the plasticiser may be sequestered in extracellular lipid. Phthalates may also influence renal function, occasional reports ascribing cystic glomerular change to plasticisers in patients on repeated dialysis.[53,54]

As in the kidney,[52] the good correlation between the quantities of lipid and plasticiser in Bruch's membrane indicates that they may become sequestered in tissue rich in extracellular lipid. It is possible only to speculate upon the metabolic effects of plasticisers in Bruch's membrane. There may be an influence upon metabolic systems as occurs in liver since large quantities of lipid and protein are handled by the retinal pigment epithelium, and the high level of degradative activity in pigment epithelium is comparable to that in the Sertoli cell. Furthermore, the incorporation of plasticisers into lipids in Bruch's membrane would increase the total mass of hydrophobic material, and may also serve to stabilise the deposits.

Conclusions: Evidence from laboratory studies gives support to the proposal in that lipids accumulate in Bruch's membrane with age, and that the nature and quantity of the lipids varies widely between patients of a similar age. This is compatible with the proposal that the hydrophobicity of Bruch's membrane increases with age, and that there is considerable variation from one subject to another. The relevance of plasticisers to disease is uncertain. If the plasticisers expand the mass of hydrophobic material, and stabilise the deposits, their presence would have a marked influence upon the conductivity of Bruch's membrane impeding movement of water and other metabolites passing between the choroidal capillaries and the pigment epithelium. Thus, even if the plasticisers do not initiate age related macular degeneration, they would undoubtedly hasten visual loss. This represents a potential environmental influence upon the pathogenesis of age related macular disease which has not been considered to date.

Clinical studies

Drusen

The hypothesis concerning the pathogenesis of pigment epithelial detachments can be tested further by studying the behaviour of disease, and seeking correlation of outcome with the clinical characteristics of Bruch's membrane change. It would be predicted that the highest resistance to water flow in Bruch's membrane would be found in eyes destined to suffer tears of the detached retinal pigment epithelium in which the concept implies that sufficient tangential stress is induced in the detached tissues to cause them to rupture. The determination that a tear in one eye implied high risk of a similar event occurring

in the fellow eye[55] allowed the opportunity to test the concept. A comparison was made of the drusen in the fellow eye of a tear with those of a fellow eye of one with visual loss due to subretinal neovascularisation. It was shown in two studies that the drusen was larger, more confluent, and less fluorescent in the former group than in the latter.[56,57]

There is doubt as to the determinants of fluorescence of drusen, and therefore the significance of this finding to disease. Fluorescence may be dependent upon the quantity of pigment in the overlying pigment epithelium, but perhaps a more important determinant is the presence or absence of fluorescein within the drusen material itself. It has been hypothesised that drusen that are hyperfluorescent must be hydrophylic allowing free diffusion of water soluble sodium fluorescein into the abnormal deposit; there may also be binding of sodium fluorescein to polar molecules.[26] By contrast the hypofluorescence of other drusen would imply that they are hydrophobic and lack polar compounds. It was suggested that the former are rich in protein and phospholipids, while the latter are rich in nutral fats. If these conclusions are correct, they would indicate high hydrophobicity of Bruch's membrane in an eye at risk of having a tear of the retinal pigment epithelium.

The observations that the form of drusen correlate with the type lesion consequent upon Bruch's membrane change, and that there is some symmetry of behaviour of the two eyes in an individual imply that drusen are symmetrical in their characteristics. This is a concept which dates from the last century,[58] and several newer observations support the proposal.[6,59] Nevertheless, symmetry had not been tested in a formal way until recently. A study of the drusen characteristics in 81 patients with bilateral age related changes at the level of Bruch's membrane and good vision has shown that very close symmetry exists between the two eyes.[60] The greatest symmetry was of fluorescence, both early and late in the fluorescein angiogram, indicating that the biophysical properties, and therefore the chemical composition, of drusen are peculiar to the patient.

Another possible implication of these observations is that the form of drusen may determine not only the type of lesions which may cause visual loss but also the magnitude of risk. This was tested in patients with unilateral visual loss due to tears of the retinal pigment epithelium.[61] This study showed that the annual risk of fellow eye visual loss was between 35% and 50%, 80% losing second eye vision within the first three years of review. This is considerably higher than the accepted figure of about 12% per year in all age related macular disease.[16,62,63] This study also confirmed the symmetry of sight threatening lesion in that 31 of the 36 losing vision in the second eye did so as a consequence of a retinal pigment epithelial detachment.

Diffuse Bruch's membrane change:

Microscopic studies show that thickening of Bruch's membrane may be in the form of discrete deposits on its inner surface, or diffuse (linear) accumulation which is seen as a continuous layer in the inner or outer portion of Bruch's membrane. This thickening may be compounded by secretion of material by pigment epithelium between its basal plasma membrane and basement membrane.[29,64] There is associated reduction of the cross-sectional area of choriocapillaries,[65,66] and the normal pattern of sinusoidal capillaries may be replaced by a tubular system.[67,68]

Clinical studies have been directed towards the analysis of discrete deposits on the inner surface of Bruch's membrane which can be recognised clinically as drusen. However they have largely ignored the potential importance of diffuse Bruch's membrane thickening, due to the lack of any recognised clinical manifestations of linear change. Logically, the diffuse deposits would be expected to play a major role in determining the outcome of disease. It is fortunate that the chemical composition of two forms of deposit appear to be similar,[34] such that studies based upon drusen characteristics may indicate also the influence of diffuse change.

As a result of studies on Sorsby's fundus dystrophy,[69–71] it was suggested that a prolonged choroidal filling phase on fluorescein angiography may be a clinical sign of diffuse thickening of Bruch's membrane. In this autosomal dominant condition a continuous layer

of abnormal material of up to 30 microns in thickness is deposited between the inner collagenous layer of Bruch's membrane and the basement membrane of the retinal pigment epithelium.[72] In contrast with the normal rapid filling, a contiguous area of prolonged, patchy choroidal fluorescence is seen during the transit phase of the angiogram.[69–71] Major choroidal blood vessels are seen prior to filling of the choriocapillaris. The dye appears initially in the inner choroid as small points of fluorescence which gradually enlarge and coalesce with one another over several frames of the angiogram. Continuous fluorescence indistinguishable from the surrounding normal fundus is not apparent until the venous phase of the retinal circulation. This pattern of choroidal filling is characteristically seen in patients with known choroidal hypoperfusion as part of general vascular disease.[73–75]

Fluorescein angiography transit photographs were analysed in 100 eyes of consecutive patients with age related changes at the level of Bruch's membrane.[76] Of these, 26 had evidence of a prolonged choroidal filling phase during the initial dye transit. This angiographic sign could represent the clinical correlate of changes in the choriocapillaris as identified by microscopy.[65–68]

In order to establish the potential significance of this clinical sign, visual sensitivity was measured in eight eyes with this angiographic finding, and in six eyes with similar amount of drusen but normal choroidal filling.[77] Scotopic threshold was measured using the Humphrey automated perimeter and fine matrix mapping. In eyes without delayed choroidal perfusion, no discrete area of increased threshold was found when compared with the background sensitivity. By contrast, in seven of the eight eyes with fluorescein angiographic evidence of prolonged choroidal filling, discrete areas of scotopic threshold elevation of up to 3.4 log units were recorded which corresponded closely to regions of choroidal perfusion abnormality.

The visual acuity and the fundus appearance were identical in patients with and without abnormal choroidal perfusion such that neither clinical attribute segregates these two populations. Although no simple clinical clues exist to identify those patients with loss of scotopic sensitivity and abnormal choroidal perfusion, functional correlates were evident to the patients. They report the need for increased light intensity for reading, fading vision after a few minutes in bright light, and easy fatiguability when doing close work.

Dark adapted threshold elevation in the macular area in eyes with age related macular disease had been documented by others.[78,79] However, no correlation between the sensitivity and the number of drusen was found, and the threshold elevation over drusen and non-drusen areas was similar. On the basis of these findings, it was concluded that more diffuse pigment epithelial or retinal dysfunction must be present other than that caused by drusen.

No established pathogenetic concepts are readily available to explain either the changes in choroidal fluorescence or the functional loss. Diminution of the choroidal capillary bed with age has been shown by structural studies, but the absence of change in the arteries make it unlikely that it is due to arterial obstruction or systemic hypertension.[80–82] It is doubtful that capillary changes are due to physical displacement by the debris since the same angiographic phenomenon occurs in Sorsby's Fundus Dystrophy[69–71] in which the deposits are internal to the inner collagenous layer of Bruch's membrane.[72] Furthermore, observations on acute and chronic choroidal ischaemia make it unlikely that there would be significant retinal dysfunction as a consequence of the observed perfusion abnormality.[65–67,83]

It has been suggested that a continuous layer of debris in Bruch's membrane may act as a barrier to metabolic exchange between the retinal pigment epithelium and the choroidal capillaries. If this is the case it would explain both the psychophysical and angiographic findings observed in this and other studies. Normal photoreceptor function is dependent on the free diffusion through Bruch's membrane of large molecule complexes as they pass from the choriocapillaris to the pigment epithelium.[84] Predictably such molecules would not pass freely through a continuous layer of debris. This has been suggested with respect to alteration of proteogly-

cans in the inter-fibre matrix of Bruch's membrane.[85] However the debris deposited into Bruch's membrane by the retinal pigment epithelium is likely to be a more important determinant of conductivity. The magnitude of change would depend upon the thickness and chemical composition of the Bruch's membrane; the disturbance would be particularly marked in the presence of a large quantity of neutral fats.[34,35]

There is circumstantial evidence that the behaviour characteristics of the choriocapillaris are determined by the retinal pigment epithelium,[86] and it has been proposed that the diffusible agents from the pigment epithelium modulate the choroidal vasculature.[87] Based on these hypotheses, it was proposed that a barrier to diffusion at the level of Bruch's membrane would result in changes in choroidal capillaries.[71,72] If the normal characteristics of the choroidal capillaries are dependent upon the diffusible agent, failure of this agent to reach the choroid would result in the vessels reverting to the more common tubular arrangement of capillary beds.

However, it cannot be assumed that angiographic appearance implies perfusion deficit alone, since it may also be modified by the accumulated material in Bruch's membrane. Although the initial choroidal fluorescence is likely to be derived from the dye in the choroidal blood vessels and extracellular space of the choroid, the subsequent distribution of fluorescein has not been well defined particularly in disease. Fluorescence microscopy shows the dye to be in Bruch's membrane and some drusen rather than in the extracellular space of the choroid soon after injection.[26] It is likely that the dye is bound to extracellular polar molecules. If this is the case, choroidal fluorescence would be modified by changes in the speed of effusion of dye from the choroidal capillaries, the diffusion characteristics of the tissues, and the binding properties of Bruch's membrane as well as by the speed of blood flow. The influence of neutral fats upon fluorescence characteristics may be complex, and by modifying several of these functions would serve to slow down the appearance of dye during angiography.

Conclusions: It is evident that there is correlation between the number, density, confluence and fluorescence angiographic characteristics of drusen on the one hand, and the subsequent outcome of disease on the other. These clinical observations give further circumstantial support to the original concept of change in hydraulic conductivity of Bruch's membrane with age and that the effect differs from one subject to another. The functional deficits imply that it is not just water movement that is affected but that there may be global reduction of metabolic exchange between the retinal pigment epithelium and choriocapillaris.

The variability of drusen in their putative chemical composition and combined with the symmetry of disease in the individual, imply that age related macular disease cannot be considered a single disorder but as a spectrum of disease.

Pathogenesis of Bruch's membrane change

The question arises as to whether or not these conclusions of selective deposition of material into Bruch's membrane are compatible with the current concepts of the pathogenesis of Bruch's membrane disease with age. The material within the abnormal deposits is derived from the pigment epithelium.[20,33,88–90] Shedding of the photoreceptor cell outer segment tip occurs daily; the cell fragments are phagocytosed by the retinal pigment epithelium, and degraded by various lysosomal enzymes which are specific to their substrate.[91–99] There is good evidence that the retinal pigment epithelium discharges cytoplasmic material throughout life into the inner portion of Bruch's membrane[100,101] which subsequently diffuses through Bruch's membrane to be cleared by the choroidal capillaries. By this mechanism it is conceived that the pigment epithelium voids the products of phagosomal degradation. Thus it was believed that the material discharged into Bruch's membrane consisted of degradation products photoreceptor outer segment material.

A major alternative source of material results from retinal pigment epithelial autophagy, a phenomenon common to all long lived cells with high metabolic activity by which cytoplasmic renewal takes place.[102,103] However, it has not been proven that the

photoreceptors represent the original source of abnormal material or that it derived from phagosomes. Neither rhodopsin sequences nor phagosomal enzyme activity have been shown in Bruch's membrane deposits using monoclonal antibodies.[104] It is now believed by many that the debris discharged by Bruch's membrane is a product of retinal pigment epithelial metabolic activity in general rather than being directly derived from outer segment material. This is not to deny that a relationship may exist between the state of the photoreceptors and the volume of material produced, since retinal pigment eithelial activity is likely to reflect the quantity of outer segment membrane renewal.

Accumulation in Bruch's membrane is thought to result from failure to clear the debris deposited into this region. It is possible that the material discharged into Bruch's membrane is abnormal as a consequence of incomplete phagolysosomal degradation, and in particular may contain large molecules and membrane complexes, such that free outward diffusion does not occur. Both lipids and proteins are contained within the phagosomes. Failure of those enzymes responsible for degrading or modifying the lipids, might result in the accumulation of fats within Bruch's membrane, and conversely defective protease activity might cause protein accumulation. In addition to the contents of phagosomes and cytoplasmic material discharged into Bruch's membrane, the membranes surrounding the vesicles and any plasma membrane shed would add to the load.

Finally, there is formation of an additional layer of material internal to the retinal pigment epithelial basement membrane which had been called basal linear deposit.[32] This is believed to be a product of retinal pigment epithelium. It is not known if this process is central to age related macular disease or simply a reaction of an abnormal cell. Once thickening of Bruch's membrane is established, the deposits would be expected to aggravate the situation by changing the diffusion characteristics of Bruch's membrane, and further hamper outward diffusion.

Conclusion: It is evident that the current theories as to the cause of accumulatin of debris in Bruch's membrane are compatible with the proposal that there may be selective deposition of protein or lipid, and that the form of lipid may be different from one subject to another.

Comments

There is increasing circumstantial evidence that age related macular disease represents a continuous or discontinuous spectrum of disease in which patients behave differently one from another. Many clinically identifiable clues exist which allow the variants of disease to be defined and which provide a basis upon which the determinants of disease may be defined. Both laboratory and clinical observations lend circumstantial support to the concept that reduced hydraulic conductivity of Bruch's membrane gives rise to retinal pigment epithelial detachments. In addition, the functional deficits so common in the elderly can be explained by alteration of the diffusion characteristics of Bruch's membrane. The corollary is that sub-retinal neovascularisation as the initiating event in age related macular degeneration occurs as a result of changes that are different from those which give rise to pigment epithelial detachments.

The factors which determine the nature of Bruch's membrane change have yet to be identified. Longitudinal studies are required to define the natural history and epidemiology of the disorder better, and these should take into account the proposed determinants of risk. The relative importance of genetic and environmental influences are unknown, and yet are accessible to investigation by epidemiological studies.

Ocular tissue is available to laboratory scientists from eye banks so that it is possible to obtain a great deal more information concerning the chemical composition and biophysical properties of Bruch's membrane. Techniques exist to seek correlation of these attributes with the degradative enzyme activity in the retinal pigment epithelium. If selective loss of degradative function is identified it may be possible to reactivate enzyme function. This therapeutic approach was highlighted by the suggestion that zinc may be important to pigment epithelial function and its administration may influence age related change.[105,106] It has been shown that lysosomal

material accumulating in the cytoplasm of the pigment epithelium may displace vital organelles and interfere with intrinsic cellular function. Zinc is found in high concentration in the choroid/pigment epithelium complex, and is also known to be a coenzyme of carbonic anhydrase and alcohol dehydrogenase. It may also serve as cofactor for a number of the lysomal enzymes within the pigment epithelium. By increasing the activity of certain enzyme systems, zinc may be effective in patients with certain specific metabolic defects but not others.

Retinal pigment epithelium is readily cultured allowing investigation of its physiological properties with respect to water movement and identification of possible agents by which it can be manipulated. This may allow therapeutic flattening of retinal pigment epithelial detachments.

These studies lie within the province of the clinician and laboratory scientist, and will only succeed if the efforts of workers in different disciplines are coordinated. Despite the activity of the last two decades there is little to offer patients at present beyond low vision aids. It is to be hoped that during the next decade research will provide hope for alternative and rational therapeutic approaches to this intractable problem.

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