NEW CONCEPTS IN THE PATHOPHYSIOLOGY OF MACULAR DISEASE: MORPHOLOGICAL RESPONSES IN THE CHORIOCAPILLARIS AND BRUCH'S MEMBRANE.

Volume III

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Chapter IV

Clinical Studies

In this section, some clinical studies and observations which help to support the histopathological and experimental sections of this thesis will be described.

Firstly in relation to case I, a group of patients with different manifestations of age-related macular degeneration were examined, in an attempt to further subdivide and classify degenerative lesion, with the ultimate aim of offering more accurate prognostic information. The evolution of individual lesions was also studied in an attempt to relate the natural history to the findings in the laser experiments in monkeys. A few patients with macular drusen who required laser treatment for vision-threatening lesions and who consented to laser to drusen are also included.

Secondly, a group of patients with different types of glomerulonephritis were studied and were found to have an asymptomatic ocular lesion, very similar to that demonstrated by case III. This study was done in collaboration with Dr. C. Short, Department of Medicine, University of Manchester.
I. Age-related macular degeneration

A. Classification of macular lesions

As discussed in chapter II 1, the terminology of age-related macular degeneration is imprecise. Numerous clinicopathologically correlated studies of individual cases have been published, but they lack an overall classification in relation to terminology, clinical findings, and prognosis.

I have collected a group of patients with various patterns of age-related macular degeneration and have studied them over periods of up to two years, in an attempt to classify the various abnormalities and to relate them to prognosis for vision. Such a study, to be conclusive, would require many years to complete, with longterm followup of numbers of patients, and histopathological examination of donor eyes. However, I have attempted to find some clinical examples to illustrate the types of deposit described in chapter II 1.

"Typical Drusen"

Histopathologically, this was a smooth dome-shaped deposit on the inner aspect of Bruch's membrane, lifting the basement membrane of the retinal pigment epithelium away from the rest of Bruch's membrane. The retinal pigment epithelium is intact over these deposits but is often thinned.
Clinically, these lesions have sharp margins and appear yellow and slightly raised. They are of uniform size, bilaterally symmetrical and discretely hyperfluorescent. They cause no significant visual disturbance and do not progress to vision threatening macular degeneration (Fig. IV 1,2).

In some cases, the deposits, while still being uniform in size, are larger (Fig. IV 3). This is also a feature of so-called dominant drusen (Fig. IV 4).

Excessive basement membrane deposition represents a reactive response of degenerating RPE. This deposit is not discrete, but is patchily spread along the inner aspect of Bruch’s membrane. It is intensely hyperfluorescent early (Fig. IV 5,6) and is associated with some generalized deterioration of vision, and may progress to disciform macular degeneration as occurred in the fellow eye of case 6 and in case 7 (Fig. IV 7).

Avascular RPE detachment or retinal pigment epithelial detachment is a well-recognized sinister precursor of central visual loss. Histopathologically, it is associated with excessive basement membrane deposit, but this is not a prominent clinical association (Fig. IV 8). While there may be clinical evidence of excessive basement membrane, it is less well-marked than in Fig. IV 5 and Fig. IV 6, possibly indicating a generalized alteration which only focally gives rise to retinal pigment epithelial detachment, seen in Fig. IV 9 in the
Fig. Ivi. Case I. Red-free and fluorescein angiographic fundus photographs showing multiple discrete white perifoveal deposits which are bilaterally symmetrical and hyperfluorescent. This patient aged 50 years was asymptomatic with normal vision.
Fig. IV>. Case 2. Red free and fluorescein angiographic fundus photographs showing multiple discrete white perifovial deposits which are bilaterally symmetrical and hyperfluorescent. This 42 year old patient was asymptomatic with normal vision.
Fig. IV3. Case 3. Red free and fluorescein angiographic fundus photographs showing multiple discrete deposits, bilaterally symmetrically disturbed in the perifoveal region but larger than shown in the cases 1 and 2. The deposits are hyperfluorescent. This patient was aged 68 years, had no visual symptoms and normal visual acuity.
Fig. IV. Case 4. Red free and fluorescein angiographic fundus photographs showing discrete round deposits, bilaterally symmetrically distributed in the perifovial region in a case of dominant drusen. The patient was aged 25 years and was visually asymptomatic. Family members had similar fundus changes.
Fig. IVs. Case 5. Red free and fluorescein angiographic fundus photographs showing multiple deposits of various sizes in the macular area. They are intensely hyperfluorescent early in the angiogram. This patient was aged 75, with a corrected visual acuity of 6/18 N6 in each eye.
Fig. IVa. Case 5. Red free and fluorescein angiographic fundus photographs showing irregular distribution of white deposits which are intensely hyperfluorescent. This patient was aged 80, and had a corrected visual acuity in this eye of 6/13 N6. The central vision in the fellow eye was lost as a result of disciform scarring.
Fig. IV-1. Case 7. Red free and fluorescein angiographic fundus photographs showing multiple irregular shaped white deposits which are intensely hyperfluorescent, and associated with neovascularisation (arrowhead). This patient aged 55 years complained of metamorphopsia.
Fig. IVa. Case 3. Red free and fluorescein angiographic fundus photographs showing irregularly distributed white deposits which are not intensely hyperfluorescent, but associated with RPE detachment (arrowheads). This patient aged 31 years had 6/12 N5 vision in the eye but had lost central vision in the fellow eye which had a disciform scar at the macula.
Fig. IVa. Case 9. Red free and fluorescein angiographic fundus photographs of a patient with an early sub RPE neovascular lesion. Scattered white punctate deposits are present but they are not hyperfluorescent. This patient aged 32 had a visual acuity of 6/24 N8.
right eye of a patient who had a disciform scar in the left eye.

Sub RPE neovascularisation leads to the classical disciform response (Fig. IV 9,10,11) while at the early stage may only be represented by serous RPE detachment as is seen in Fig. IV 12, the right eye of a patient with a disciform scar in the left.

In addition, other changes may occur in the retinal pigment epithelium-Bruch's membrane. In one patient, a deposit similar to excessive basement membrane was present, but instead of leading to retinal pigment epithelial detachment, it led to a confluent atrophy of the retinal pigment epithelium without central visual disturbance (Fig. IV 13). In another patient (Fig. IV 14) a discrete but angular deposit was seen temporal to the macula, with minimal hyperfluorescence, and no visual disturbance. The nature of this material is obscure.

This sort of classification omits the most frequently encountered form of age-related macular degeneration, the atrophic form of retinal pigment epithelial detachment (Fig. IV 15).

Discussion

Age-related macular degeneration is the major cause of blindness in the developed world (55,93,152,312,416,417,543,583,584,610,628,694,1244). The Framingham Eye Study (583,584,610) and the Health and
Fig. IV:6. Case 10. Red free and fluorescein angiographic fundus photographs of a more advanced disciform lesion with accumulation of subretinal fluid and intraretinal haemorrhage. This patient aged 78 had a visual acuity of 6/24 N8.
Fig. IV11: Case II. Red free and fluorescein angiographic fundus photographs of an advanced disciform lesion. There is extensive chorioretinal scarring exposing the choroidal vessels to view (arrowhead) and a large intraretinal and preretinal haemorrhage. This patient aged 75 had only 6/60 N3b vision.
Fig. IV12. Case 12. Red free and fluorescein angiographic fundus photographs of a patient who had advanced disciform scarring in the left eye and an appearance reminiscent of the petalloid pattern of macular oedema in the right, which on red free shows multiple irregular deposits. The petalloid pattern is attributed to fluid accumulation in the retina, and was also present subretinally by biomicroscopic examination. This patient aged 76, had 6/6 NS vision in the right eye.
Fig. IV.3. Case 15. Red free and fluorescein angiographic fundus photographs showing multiple irregular discrete white deposits associated with geographic atrophy of the RPE. The patient aged 68 was visually asymptomatic.
Fig. IV. Case 14. Red free and fluorescein angiographic fundus photographs showing angular large deposits symmetrically distributed temporal to the macula with weak fluorescence. The patient, age 62, was visually asymptomatic.
Fig. IViI5. Red free and fluorescein angiographic fundus photographs showing the commonly encountered appearance of atrophic macular degeneration. The macular area is mottled, with areas of hyperpigmentation and large areas of RPE atrophy in the left. This patient aged 77 had a visual acuity in the right eye of 6/9 N5 and in the left counting fingers only.
Nutrition Examination Survey (HANES) (312,615) were large epidemiological studies, the findings of which in relation to macular degeneration have largely been verified by three more recent case control studies (223,544,736). The disease affects men and women equally (615,1059) although it is widely considered to affect women more frequently (583,584,610). The incidence is 20-25% of individuals over 75 years (203,312,635,694), about a third having clinically detectable subretinal neovascularization (203).

The disease is commoner in Caucasians (454,736,1183). It is interesting that while the incidence of drusen in whites is twice that of black Africans, the incidence of macular degeneration is 35 times that of black Africans (B53). In a study of an Indian population (561) the prevalence of macular degeneration was only a quarter that of the black African population. Histopathologically it has been shown that the degenerative changes described by Sarks in white patients (995) are much less advanced in a comparable group of Japanese (530).

Unfortunately, these extensive epidemiological surveys did not subdivide the lesions seen into different types of drusen. The information on the natural history of the different classes of deposit is therefore not available.

Visual acuity alone is not a good marker for macular disease since it falls with age (569) without there being clinically detectable macular changes (465,560).
correlating with photoreceptor dropout observed in aging individuals (389,667) and possibly also with loss of cortical neurones (569,1177).

The risk at which the fellow eye of an eye with visual loss due to age-related macular degeneration is subjected is high (116,440,453,563,1087) and worse if drusen are present (440,1193)).

The risk of developing exudative maculopathy over five years for patient with bilateral degenerative deposits is 14.5% (1041).

Having previously criticised the terminology of deposits of material in the region of the choriocapillaris/Bruch's membrane/retinal pigment epithelial complex, I will now avoid the use of the general term drusen, using it only for specifically defined types. There is some merit in using an earlier purely descriptive term for such lesions, the flecked retina (650) although this term is also used for a specific type of congenital nonprogressive night blindness (587) which is probably the same disease as congenital grouped albinotic retinal pigment epithelial spots (408). The diseases which give the flecked retina appearance, apart from age-related macular degeneration are fundus flavimaculatus, pattern dystrophies, fundus albipunctatus and Gaucher's disease. The differential diagnosis is discussed by Newell and colleagues (846). Some cases of fundus flavimaculatus are indistinguishable from cases described as "drusen" or age-related macular degenerative focal deposits (276).
Gass, in the latest edition of his textbook on the macula (408) no longer discusses "drusen" as an entity, but only includes familial drusen and basal laminar drusen. Basal laminar drusen are histopathologically inseparable from the retinal pigment epithelial basement membrane which is irregularly thickened, with associated retinal pigment epithelial degeneration. This type of lesion progresses, so that the spots coalesce in time and ultimately lead to retinal pigment epithelial detachment and subretinal pigmented epithelial neovascularization. They characteristically fluoresce early in an angiogram, giving the "stars in the sky" pattern. The deposits, which histopathologically are nodular excrescences on the inner aspect of Bruch's membrane under the retinal pigment epithelial basement membrane, he terms variable exudative drusen or typical drusen. RPE detachment with or without sub RPE neovascularisation occurs. If the sub RPE fluid resorbs, geographic atrophy of the retinal pigment epithelium is often the end result, or it may progress to neovascularisation with the development of a disciform scar. However, Gass says that basal laminar drusen are associated with a better prognosis for vision than patients with exudative or typical drusen, that is, with nodular excrescences under the retinal pigment epithelial basement membrane.

Familial drusen, Gass believes, include all the other cases formerly termed drusen, other than those of the basal laminar drusen already referred to. These lesions, which lie under the retinal pigment epithelial basement
membrane, become yellow as the overlying retinal pigment epithelium atrophies. It is this type which Gass interprets to undergo an alteration in consistency with "softening" resulting in retinal pigment epithelial detachment. With the evidence presented in chapter II 1, and on review of histopathological reports, it appears that he misinterprets the findings.

Kenyon and Maumenee (604) redefine drusen as "deposits between the basement membrane of the retinal pigment epithelium and the remainder of Bruch's membrane." They recognize four types: (i) hard or nodular formed either by apoptosis or lipoidal degeneration of the retinal pigment epithelium (ii), diffuse thickening of the inner collagenous zone of Bruch's membrane associated with pigment epithelial atrophy and progressive softening, retinal pigment epithelial detachment and neovascularization, (iii) soft drusen which are actually small retinal pigment epithelial detachments and (iv) calcified drusen. My findings do not fit with this classification either. However, in their paper, the figures show a deposit which is inseparable from the basement membrane of the retinal pigment epithelium, while describing the lesion as being in the inner collagenous zone of Bruch's membrane.

Familial drusen (17,229) are indistinguishable from age-related macular degenerative nodular deposits in Bruch's membrane histologically, but clinically, have a different appearance. They are usually diagnosed in young patients without any visual symptoms. The natural history of
familial drusen (288, 647, 846) can be divided into 3 stages. Stage 1 is seen in the first and second decade, in which small round pink lesions with uniform appearance and bilateral symmetry centred on the posterior pole, are seen (229). In stage II (4th decade) the drusen increase in number and become whitish and larger, with a tendency to calcify and associated RPE disturbance with pigment clumping. In stage III the drusen become confluent with pigment disturbance and reduction in visual acuity. Progression towards sub RPE neovascularisation frequently occurs (647). A foveomacular dystrophy with a different clinical appearance but similar histopathological findings to familial drusen has been described (403) suggesting a spectrum of changes. This is not unexpected, since the end result of many disease processes may be the same histopathologically. This condition is often diagnosed as presenile macular degeneration (972).

While deposits predisposing to age-related macular degeneration are usually centered on the fovea in their distribution, aging affects the entire retina (539, 707, 1082) and extramacular deposits are found in the majority of patients with symptomatic macular drusen (290).

The major diagnostic subgroups for age-related macular degeneration are the atrophic form and the exudative form associated with neovascularization (765, 766, 769, 1001), the former accounting for 20% of the visual loss in the population, and the latter 80% (831).
Atrophic macular degeneration is a slowly progressive form which ultimately leads to poor central visual function (535). The patchy atrophy may eventually progress to cover a confluent area (731,1186). At this stage, preexisting "drusen" may no longer be visible (451,996,1186). In the confluent stage, termed geographic atrophy, the condition is only distinguished from central areaolar choroidal sclerosis by the late age of onset (86). Histopathologically, choriocapillary atrophy is seen (450) and is considered to be pathogenetically related to atrophy of the RPE (451,996). Sarks (996) associated geographic atrophy with "hard" drusen, but it is likely that the association is with the absence of "soft" drusen.

Exudative maculopathy tends to present acutely and run a much shorter course to the end stage of disciform macular scar and poor central vision (653). The patient presents with blurred vision and metamorphopsia and clinically, a serous retinal pigment epithelial detachment with or without hemorrhage is seen. Rarely there is massive subretinal exudate (87). Fluorescein angiography reveals the neovascular frond if present (203,1103A). This comprises a number of large non-leaking vessels, and a network of leaking capillary loops (1103A).

In 10% of cases, no neovascular frond is present, the subretinal pigment epithelial fluid being from the choroid. These cases have a high risk of subsequently developing neovascularization (1104). Another way of
interpreting these findings is, however, to say that the sub RPE fluid is secondary to occult sub RPE neovascularisation which later becomes manifest. The detached retinal pigment epithelium may tear, giving a typical fluorescein angiographic appearance (155,406,445,531). RPE detachment in the elderly carries a poor prognosis for vision. Two-thirds of cases progress to sub RPE neovascularisation within 10 months (80). If a subfoveal neovascular membrane was diagnosed, 77% of patients in one series had lost four or more lines of vision within two years (463).

The same process is seen in young adults (325,352,983), and rarely may be attributed to intravascular coagulation in the choriocapillaris, associated with uveitis (984). The relative contributions of the retinal circulation, primary abnormality of the RPE and choroidal circulations to macular dysfunction is unknown.

Some years ago, the clinical observation that there is a dropout of precapillary vessels in the retinal circulation at the macula of the fellow eye of disciform cases was made (1249). This has been confirmed histopathologically (638) but has not been pursued and is not currently given any clinical significance. However, it may be worth investigating as a marker for small vessel disease, if that makes any contribution to the development of disciform macular degeneration.

Serous detachment of the retinal pigment epithelium is arbitrarily classified by age. If it occurs in patients
under 55 years, it is considered either to be due to vascular, neoplastic or inflammatory disease of the choroid (410, 412), or be idiopathic in which case the diagnosis is central serous choroidoretinopathy and has a good prognosis (985). In patients over 55 years, the diagnosis is exudative age-related macular degeneration (113, 1228).

Central serous chorioretinopathy is an idiopathic detachment of the neurosensory retina at the macula, with or without retinal pigment epithelial detachment in patients under the age of 55, without evidence of subretinal neovascularization (1229). Retinal pigment epithelial detachment may be present without retinal detachment (708). The pathogenesis is unknown, but a defect in the retinal pigment epithelium is shown to exist by fluorescein angiography and the favored terminology is now central serous pigment epitheliopathy (1230). Formerly a localized defect in the retinal pigment epithelium was thought to be the cause, but now a more widespread dysfunction is recognized (191, 402, 832, 858, 1081, 1165, 1230). At one time, altered permeability of the choriocapillaris was thought to be the underlying defect (392). Klien described one case histopathologically (619) but no abnormality of the retinal pigment epithelium or choriocapillaris was observed.

In some cases, a retinal pigment epitheliitis is recognized as a precursor of central serous pigment epitheliopathy (915, 916), or a diffuse form of exudative
pigment epitheliopathy may coexist with central serous pigment epitheliopathy (1257). A variety of underlying disease processes may produce the clinical appearance, including choriocapillary disease, and retinal pigment epitheliitis.

The natural history of central serous pigment epitheliopathy is variable. In the majority of young patients, recovery appears to be complete but in up to 10% of cases, it becomes chronic (632) and has been termed retinal pigment epithelial decompensation at this stage (564). In the chronic stage, the visual disturbance is marked despite flattening of the retina, possibly indicating persistent retinal pigment epithelial dysfunction (169). In elderly patients, an occult neovascularization membrane may be present (407,1004) and may later manifest its presence (295,789,924).

The contribution of choriocapillary pathology to age-related macular degeneration is probably minor, but it cannot be discounted totally. Hayreh has classified the lesions of the choriocapillaris which give rise to clinical disorders (487,488). He is of the opinion that chronic underperfusion at the macular choriocapillaris does exist and contributes to the development of age-related macular degeneration.

It is of interest that it has been reported that stellate ganglion block may improve the visual acuity of patients with age-related macular degeneration(838) suggesting that a reversible vascular component to the visual
disturbance is present. The clinical details reported, however, gave inadequate data on which to judge the results.

A variety of retinal pigment epithelial lesions are described clinically, and may shed light on the nature of the degenerative lesions considered central to the pathophysiology of age-related macular degeneration. Inflammation of the retinal pigment epithelium gives rise to the clinical syndromes of the presumed ocular histoplasmosis syndrome and presumptively, acute multifocal posterior placoid pigment epitheliopathy and geographic heliocoid peripapillary choroidopathy (820, 1002).

Acute retinal pigment epitheliitis (226, 266, 649) primarily affects the macular area and recovers to normal function. In acute multifocal posterior placoid pigment epitheliopathy, the lesions are larger and the prognosis poorer (275, 397).

Retinal pigment epithelial dystrophies have been described (316, 857), many of which are now classified as pattern dystrophies, because the shape the pigment epithelial lesion presents a recognizable pattern (201, 232, 536, 748). Despite very marked abnormalities of the macular retinal pigment epithelium in clinical examination, normal or near normal visual acuity is usually maintained.
Clearly the RPE and choriocapillaris are intimately related to each other and disease of either contributes to the clinical syndromes of macular disease.

B. Effect of laser on "drusen"

Three patients considered to have treatable subretinal neovascular membrane and "drusen" were recruited for study. Mild green argon laser burns were applied to individual discrete round hyperfluorescent deposits or "typical" drusen in the extrafoveal macula. The intensity of the lesion was such as to cause a minimal blanching of the retina, a few seconds after application. At spot size 100 μ for 0.1 sec. The dose ranged from 0.1 to 0.16 w. They were then examined over the ensuing weeks.

Results

The fundus photographs and fluorescein angiograms of two of the patients are shown (Fig. IV 16-20). The photographs of the third patient were of inadequate quality. Ten days following the treatment, there was an area of pallor in the very mild burns, and in the more intense burns, an area of pallor with central pigmentation was seen. Fluorescein angiogram at that time showed an area of hypofluorescence with no residual hyperfluorescence of drusen. At five to six weeks, no residual lesion was visible. As in the monkey experiment, the hypofluorescence might be attributed to macrophagic infiltration, blocking any underlying
Fig. IV. Red free (A) and fluorescein angiographic (B) fundus photograph showing discrete white deposits (arrows) which are hyperfluorescent. Note also the sub RPE membrane (arrowheads).
Fig. IV17. Red free (A) and fluorescein angiographic (B) fundus photographs of the same eye as in Fig IV14, ten days after laser treatment directly to "typical" drusen deposits. On the fundus photograph, an area of pallor was noted (arrows) which on fluorescein angiography was hypofluorescent (arrows) with a small halo of staining in the more intense burns, but no apparent drusen. Other lesions are test burns.
Fig. IV18. Red free and fluorescein angiography fundus photographs showing a few extrafoveal "typical" drusen (arrowhead). A small neovascular membrane is also present.
Fig IV19. Red free and fluorescein angiographic fundus photographs of the same eye as in Fig. IV18, 2 weeks after argon laser treatment directly to the drusen deposits. On the fundus photograph the deposit is less distinct, and on fluorescein angiography the hyperfluorescence is replaced by a central hypofluorescent spot with a halo of fluorescence (arrowhead). Note that the neovascular membrane has bled.
Fig IV20. Red free and fluorescein angiographic fundus photographs of the same eye as in Fig. IV18.19, 5 weeks after laser treatment. The lesion has disappeared on the fundus photograph and is barely discernable on the angiogram (arrowhead).
deposit. However, the appearances were sufficiently like those seen in the monkey to conclude that the tissue reaction to the retinal lesion was similar.

Discussion

Gass (400) treated drusen with laser, but did not detail the results. Cleasby et al (177) prophylactically treated drusen in the fellow eye of patients with disciform macular degeneration and reported a reduced incidence of disciform degeneration compared with a control population, but only in a short follow up of a small group of patients. They also treated drusen in patients with bilateral disciform degeneration and recorded regression of drusen.

The intention in this experiment, however, was not to develop a therapeutic modality, since drusen represent a widespread degeneration of the chorioretinal juncture, and focal treatment would not be rational and might even be dangerous. Rather the aim was to show that resolution which has been said to occur (104,400) is a real phenomenon and having shown that, to stimulate further study of the pathophysiology of mechanisms for removing material from Bruch’s membrane.
2. Glomerulonephritis

Morphology of glomerulus

The structure of the glomerulus parallels that of the chorioretinal junction in many ways. The glomerular basement membrane is a selectively permeable membrane with functional characteristics similar to those of Bruch's membrane (292). It is positively charged, limiting its permeability to anionic molecules, in a similar way to Bruch's membrane (168,952,1061). The glycosaminoglycan component is largely heparan sulphate (588,5891104, 1103). Its structure is not uniform, but has a directional component (157). The information available on the structure and turnover of the glomerular basement membrane is much greater than for Bruch's membrane.

Some pathological changes in the kidney are reminiscent of those in the eye. These are summarised in table IV 1. In aging, the glomerular filtration membrane thickens focally and vesicles are seen within it similar to those seen in ageing Bruch's membrane (477). Deposits form on it in aminoglycoside nephrosis on the epithelial side and have some similarity with drusen (658). Deposits also form in experimental immune complex glomerulonephritis (57). The membrane is ruptured in some types of glomerulonephritis (1105) with some similar to the breaks in Bruch's membrane termed angioid streaks.

The structure of the capillaries is very similar to that in the choroid with diaphragmed fenestration polarized
Table IV.

Similarities between Bruch's membrane and glomerular basement membrane.

Anatomy/Physiology
- Selectively permeable
- Positively charged
- High heparan sulphate content
- Directional permeability

Pathology
- Aging - vesicles
- Nodular deposits - aminoglycosides
- Ruptures
- immune complexes

Epithelium
- Functional barrier
- Aging - loss of basal infoldings/pedicels
towards the filtration membrane (365,953,1089). The haemodynamics in the glomerulus are similar, but the density of the fenestrations is less, and the diameter of the fenestrations larger in the choriocapillaris (1089). The fenestration themselves act as a sieve for macromolecules (680).

The epithelium of the glomerulus offers some barrier to the passage of filtrate (681) and degenerates with age (24) showing some parallel with aging retinal pigment epithelium (599) in that the basal infolding (retinal pigment epithelium) and pedicels (glomerular epithelium) are reduced in size and number. The nature of the filtration membrane is altered by enzyme digestion of glycosaminoglycans (590,735) possibly offering a new avenue for ophthalmic experimental research. The exchange of information between the two areas of research offers considerable potential, a concept which is reciprocated by renal experimental pathologists (156).
In type II mesangiocapillary glomerulonephritis (MCGN), deposits of electron dense material, often with a ribbon-like appearance, are found within the glomerular basement membrane. This is in contrast to the discrete deposits found in membranous nephropathy, where the material lies initially between the basement membrane and the epithelium, in type I MCGN where the deposit is predominantly subendothelial, between the basement membrane and the endothelium and in mesangial proliferative glomerulonephritis where the majority of the deposits are in the mesangium (Fig. IV21).

Type II MCGN is closely associated with partial lipodystrophy.

**Methods**

Seventeen patients with biopsy-proven glomerulonephritis and two further patients with partial lipodystrophy, one of whom had renal failure but never had a renal biopsy, were selected from the diagnostic index at the Manchester Royal Infirmary Renal Unit for an ophthalmologist (JDY), who examined the patients by routine clinical methods, fundus photography, and fluorescein angiography. All the patients were normotensive and had been for some months although many had had a period of hypertension during the course of
Fig IV.21. Predominant sites of deposition of immunoreactive and electron dense material in various glomerulopathies.
Figure IV 21
their illness. Patients 4, 7, and 13 had reached end-stage renal failure and been successfully transplanted at the time of the study. No patient was receiving dialysis.

Details of the patients are given in tables IV₂ and IV₃.

Results

None of the patients had ocular symptoms. All the anterior segments appeared normal and no hypertensive retinopathy was detected.

There were twelve patients without partial lipodystrophy, of which there were six with type I MCGN, one with minimal change disease, and five with membranous nephropathy. Ophthalmoscopic examination revealed a few drusen in some eyes (Fig. IV₂₂) but with no difference in frequency from that expected in a normal age matched population, and the angiograms showed only a few hyperfluorescent spots, corresponding to scattered drusen.

The other seven patients all had partial lipodystrophy: four had type II MCGN, one had MCGN (type unknown), where no tissue was available for electron microscopy, one who had reached end stage renal failure without being biopsied and one who had been followed regularly
Table IV 2
Clinical details at time of ophthalmic examination.

<table>
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<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Glomerular Disease</th>
<th>PLD</th>
<th>Time since BP diagnosis</th>
<th>Current Medication</th>
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<td>1</td>
<td>51</td>
<td>M</td>
<td>Membranous</td>
<td>No</td>
<td>2 years</td>
<td>180/100 Prednisolone Atenolol Nifedipine Rantidine</td>
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<td>2</td>
<td>43</td>
<td>M</td>
<td>Type II MCGN</td>
<td>Yes</td>
<td>7 months</td>
<td>140/90 Tenoretic Nifedipine Hydralazine</td>
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<td>3</td>
<td>45</td>
<td>F</td>
<td>MCGN (Type Unknown)</td>
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<td>27 years</td>
<td>135/90 Atenolol Metyldopa Aprinox</td>
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<tr>
<td>4</td>
<td>28</td>
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<td>Type II MCGN</td>
<td>Yes</td>
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<tr>
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<td>31</td>
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<td>Type I MCGN</td>
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<td>6 years</td>
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<td>F</td>
<td>Type I MCGN</td>
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<td>9 years</td>
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<td>F</td>
<td>Type I MCGN</td>
<td>No</td>
<td>6 years</td>
<td>160/90 Azathioprine Prednisolone Atenolol</td>
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<td>8</td>
<td>73</td>
<td>M</td>
<td>Membranous</td>
<td>No</td>
<td>5 years</td>
<td>140/70 Nil</td>
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<td>49</td>
<td>F</td>
<td>Type I MCGN</td>
<td>No</td>
<td>1 year</td>
<td>180/95 Prednisolone Rantidine Azathioprine Atenolol Nifedipine</td>
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<td>Type II MCGN</td>
<td>Yes</td>
<td>2.2 years</td>
<td>150/85 Allopurinol Captopril Frusemide</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>Membranous</td>
<td>No</td>
<td>6 years</td>
<td>125/90 Bendroflua-zide</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>M</td>
<td>Membranous</td>
<td>No</td>
<td>2 years</td>
<td>140/90 Prednisolone Tacamet Frusemide Spirono-lactone</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Sex</td>
<td>Clinical Presentation</td>
<td>Treatment Duration</td>
<td>Blood Pressure</td>
<td>Medication</td>
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</tr>
<tr>
<td>13</td>
<td>30 F</td>
<td>No biopsy but had a nephrotic syndrome</td>
<td>Yes</td>
<td>14 years</td>
<td>150/80</td>
<td>Cyclosporin, Prednisolone, Atenolol</td>
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<tr>
<td>14</td>
<td>25 F</td>
<td>Type I MCGN</td>
<td>No</td>
<td>1.5 years</td>
<td>150/90</td>
<td>Nil</td>
</tr>
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<td>15</td>
<td>50 M</td>
<td>Type I MCGN</td>
<td>No</td>
<td>13 years</td>
<td>160/90</td>
<td>Methyldopa, Frusemide, Slow K, Propranolol</td>
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<tr>
<td>16</td>
<td>29 F</td>
<td>Minimal change</td>
<td>No</td>
<td>3 years</td>
<td>90/60</td>
<td>Anxiolytics</td>
</tr>
<tr>
<td>17</td>
<td>43 F</td>
<td>No biopsy and no evidence of renal disease</td>
<td>Yes</td>
<td></td>
<td>110/70</td>
<td>Anxiolytics</td>
</tr>
<tr>
<td>18</td>
<td>50 F</td>
<td>Membranous</td>
<td>No</td>
<td>7 years</td>
<td>130/80</td>
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<tr>
<td>19</td>
<td>43 M</td>
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<td>Yes</td>
<td>31 years</td>
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<td>Case</td>
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<td>1</td>
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<td>CF 6/6 (amblyopic)</td>
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<td>Normal</td>
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<td>2</td>
<td>Type II MCGN</td>
<td>6/6 6/9</td>
<td>Massive drusen-like deposits with mottled pigmentation</td>
<td>Extensive hyperfluorescence in Bruch’s Membrane</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>MCGN (Type Unknown)</td>
<td>6/6 6/5</td>
<td>Drusen like deposits with mottled pigmentation</td>
<td>Few Hyperfluorescent spots corresponding with drusen</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Type II MCGN</td>
<td>6/6 6/6</td>
<td>Massive drusen-like deposits with mottled pigmentation - some large</td>
<td>Extensive hypofluorescence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Type I MCGN</td>
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<td>Normal</td>
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<tr>
<td>6</td>
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<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Type I MCGN</td>
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<td></td>
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<td>Scattered drusen</td>
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<td></td>
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<td>Massive drusen-like deposits with mottled pigmentation</td>
<td>Extensive hyperfluorescence in Bruch’s membrane</td>
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<td>Normal</td>
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<td>Normal</td>
<td></td>
<td></td>
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<td>6/36 6/24</td>
<td>Massive drusen-like deposits with mottled pigmentation</td>
<td>Extensive hyperfluorescence in Bruch’s membrane</td>
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<td></td>
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<tr>
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<td>6/6</td>
<td>Normal</td>
<td>Optic Nerve head drusen</td>
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</tr>
<tr>
<td>15</td>
<td>Type I MCGN</td>
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<td>6/5</td>
<td>Drusen</td>
<td>Drusen</td>
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</tr>
<tr>
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<td>6/9</td>
<td>Normal</td>
<td>Myopic crescent</td>
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<td>No biopsy, no evidence of renal disease but has PLD</td>
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<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
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<td>Membranous</td>
<td>6/6</td>
<td>6/6</td>
<td>Drusen</td>
<td>Drusen</td>
<td></td>
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<td>19</td>
<td>Type II MCGN</td>
<td>6/5</td>
<td>6/5</td>
<td>Massive drusen like deposits with mottled pigmentation</td>
<td>Extensive hyperfluorescence in Bruch's membrane</td>
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Fig IV22. Fundus photograph and fluorescein angiogram of case 18 showing scattered drusen at the posterior pole.
for many years with clinical or biochemical evidence of renal involvement.

All patients were normotensive at the time of the examination, although many were on antihypertensive therapy.

Two patients with partial lipodystrophy had normal ophthalmoscopic and angiographic appearances. One had unclassified MCGN and one had no evidence of glomerular disease.

A striking abnormality was seen in the fundi of the other five (Fig. IV 23-27): a regular, bilaterally symmetrical distribution of discrete yellow spots, similar to drusen, more densely present posteriorly, but spreading up to, and beyond the equator. The lesions were not elevated, but were associated with some irregularity of pigmentation. In the same five patients, fluorescein angiography showed gross abnormalities correlating to the drusen-like appearance and similar to that seen in the case described in Chapter II 3, with hyperfluorescence corresponding to the yellow lesions, but with no leakage of fluorescein. The visual acuity was unaffected.
Fig IV.23. Fundus photographs and fluorescein angiogram of case 2 showing scattered drusen-like lesion with intense hyperfluorescence.
Fig IV24. Fundus photograph and fluorescein angiogram of case 4 showing large pale deposits with pigmented halo temporal to the macula, associated with intense focal hyperfluorescence which extends towards the equator.
Fig IV25. Fundus photograph and fluorescein angiogram of case 10 showing scattered drusen-like deposits with intense hyperfluorescence.
Fig IV26. Fluorescein angiograms of case 13 showing patching distribution of punctate hyperfluorescence with additionally unusual peripapillary deposit.
Fig. IV27. Fundus photograph and fluorescein angiogram of case 19 showing extensive drusen-like deposits with hyperfluorescence.
Having identified this lesion, I recollected a patient seen in 1980, prior to beginning these studies. He was mildly diabetic but presented a paradox to the diabetic physician because he had end-stage renal failure which was too advanced to allow histopathological classification, yet had no evidence of diabetic retinopathy. Fundus examination revealed only a mild pigmentary disturbance but fluorescein angiography (Fig. IV 28) revealed numerous punctate hyperfluorescent lesions similar to those seen in MCGN type II, which is associated with glucose intolerance. This patient may have been my first case showing this lesion.

Discussion

These cases support my findings in Chapter II 3 that an abnormal deposit in the eye at the level of Bruch's membrane and the choriocapillaris occurs in type II mesangiocapillary glomerulonephritis. This finding supports the hypothesis based on anatomical comparisons that the choriocapillaris/Bruch's membrane/retinal pigment epithelial complex may respond to disease in a similar way to the glomerulus. The complex interrelationship between the eye and kidney in disease processes is already well recognised (889).
Fig. IV28. Fluorescein angiogram of a patient with end stage renal failure and diabetes, showing multiple hyperfluorescent spots, but no diabetic retinopathy.
The fundus abnormalities seen in glomerular disease can be broadly divided into those associated with hypertension, those associated with vasculitis causing glomerulonephritis, those associated with hyperviscosity, those resulting from treatment of the renal lesion and those considered to be specifically related to the renal lesion (260). In systemic hypertension, the fundus abnormalities are well recognised, and are described in renal patients. The blood retinal barrier is known to be defective (165,654) even in the absence of clinical evidence of hypertensive retinopathy. In experimental animals this lesion is confirmed and is reversed by blood pressure control (251), but the site of the lesion is unknown. In accelerated hypertension, infarcts of the retinal pigment epithelium, termed Elschnig’s spots, are described (492,624), but differ from the lesions we document in that those we describe are much more widespread and are not associated with the focal pigment clumping seen in Elschnig’s spots. In addition, there is no history of visual disturbance in any of our patients, whereas if there were such widespread infarction of the retinal pigment epithelium, symptoms of neuroretinal dysfunction would be expected, probably with neurosensory retinal detachment.
A series of patients with glomerulonephritis with and without hypertension have been studied ophthalmologically (815). None of these showed any fluorescein angiography abnormality, although the type of glomerulonephritis was not classified in the report.

Vasculitis, such as is seen in systemic lupus erythematosus, may involve the renal circulation as well as the retinal and choroidal circulation, giving rise to cotton-wool spots, haemorrhages, swelling of the optic nerve head, and vascular occlusion (83, 199, 200, 427, 494, 557, 558, 576, 673). Hyperviscosity syndrome may be a manifestation of renal disease. The ophthalmic findings are dilated retinal veins, haemorrhage, exudate and retinal vein occlusion (40, 159, 880). In the cases we have studied, no features of vasculitis were present.

Ocular complications of chronic renal disease include hypertensive retinopathy (334), exudative retinal detachment (125) and crystals of cystine in the cornea and retina (585). In cystinosis, intracellular crystals are present in the RPE and choroid (990). The complications of treatment include cataract which is independent of treatment with steroids or
antimetabolites (64,509) raised intraocular pressure,
opportunistic retinitis (533,676,929) and retinal microaneurysms.

I know of only one publication in which renal pathology is compared to eye pathology, and which describes microaneurysms in the glomerulus in diabetes (836).

The comparison has been made in reverse, also in diabetes mellitus, in which lesions likened to Kimmelsteil Wilson nodules were described in the choroid (508).

Partial lipodystrophy is very close associated with MCGN II but renal function is normal in some cases (63,1039). The biochemical defect is hypocomplementaemia. It is hypothesised that because of the defect, the alternative pathway of complement activation operates and in some way predisposes to the renal lesion (1039).

A number of familial disorders are described which affect the eye and the kidney. Those which involve the retina and choroid include Alstrom's syndrome (18,434,801,1018) which comprises pigmentary retinopathy, obesity, diabetes mellitus and nerve deafness, often associated with renal insufficiency, and
Alport’s syndrome (218,433,910,934) which is characterised by lenticconus and spherophakia (1052) sensori-neural deafness and a hereditary nephropathy. The literature on Alport’s syndrome has recently been reviewed (284). In the fundus a pigmentary change may be seen in the periphery (218) and yellow white intraretinal deposits at the macula are reported (439,904,1109). These deposits are at the level of both Bruch’s membrane and the inner limiting membrane (439,1109). Alport’s syndrome is now known to be due to a defect in basement membrane metabolism (462,757,1055) and the retinal flecks are considered to be focal basement membrane lesions (408,439,1109).

Pigmentary retinopathy is also a feature of polycystic (286) and medullary cystic kidney disease (923,1020) as well as other rare familial nephropathies (28,50,262,715,1010,1021).

Recently an early case of MCGN type II has been studied histopathologically (998). It is interesting that the early lesion, prior to the appearance of the dense deposit, is a lamellation of the lamina densa of the glomerular basement membrane, very reminiscent of the appearance seen in Alport’s syndrome which is indisputably associated with a chorioretinal lesion.
To my knowledge, there is no previous description of the lesion in the fundus which is described here. Only two other cases showed a similar picture, and those were in benign monoclonal gammopathy (830, 852). In one of these (852) a less striking drusen-like appearance was reported. These findings suggest that in patients with type II MCGN and partial lipodystrophy, chorioretinal changes may parallel those found in the kidney. Since in all five cases, the fundus changes are very similar, but the duration of renal disease ranges from seven months to thirty-one years, the lesion is likely to be static. There is undoubtedly a structural and pathological comparison to be drawn between the eye and the kidney, and investigation of patients with glomerular disease may shed light on the pathophysiological responses of the choriocapillaris/Bruch's membrane/retinal pigment epithelial complex. Similarly, study of the ocular responses may contribute to the understanding of the basis of the renal lesion.
Chapter V

Conclusions

In this thesis, I have attempted to study disease processes at the macula with a new approach based on clues gleaned from individual clinicopathological case studies.

Cellular responses within Bruch's membrane hitherto have been described in a nonsystematic way, and strict criteria for identification of cell populations have not been applied. I have described the contributions of cells from the choriocapillaris, retinal pigment epithelium, and from the circulating mononuclear phagocytic system to disease processes and aging changes. This approach helps in providing a better basis for understanding the pathophysiological responses. The criteria used for cellular identification are summarised in table V 1 and represented diagramatically in Fig V 1.
<table>
<thead>
<tr>
<th></th>
<th>Pericytes</th>
<th>Monocyte/Macrophage</th>
<th>RPE</th>
<th>Endothelial Cell</th>
<th>Activated Pericyte</th>
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<tr>
<td>Nucleus</td>
<td>Oval/Round</td>
<td>Indented Round</td>
<td>Round</td>
<td>Spindle</td>
<td>Oval/Round</td>
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<tr>
<td>Cytoplasm</td>
<td>Watery few</td>
<td>Many organelles</td>
<td>Packed organelles</td>
<td>Electron dense Many organelles</td>
<td>Watery or dense Variable organelles</td>
</tr>
<tr>
<td>Smooth Endoplasmic Reticulum</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rough Endoplasmic Reticulum</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Filaments</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+/+++</td>
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<td>-</td>
<td>++/++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Lysosomes</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-/+</td>
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<tr>
<td>Focal Cytoplasmic Membrane Densaification</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/+++</td>
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<tr>
<td>Pinocytotic Vesicles</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+++</td>
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<td>Basement Membrane</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-/+</td>
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<td>long/complex</td>
<td>short</td>
<td>short</td>
<td>long</td>
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- Absent  + Scanty  ++ Moderate  +++ Abundant
Fig V1. Diagram showing cytological features of cell types found in Bruch's membrane.

A. Pericyte with filaments, pinocytotic vesicles, lysosomes, rough endoplasmic reticulum, and a basement membrane and envelope.

B. Macrophages with smooth and rough endoplasmic reticulum, pigment granules and mitochondria.

C. RPE with smooth endoplasmic reticulum, pigment granules, mitochondria and a basement membrane.

D. Endothelial cell with smooth and rough endoplasmic reticulum, filaments, mitochondria, pinocytotic vesicles and a basement membrane.

E. Activated pericyte with filaments, mitochondria, cytoplasmic membrane densities, pinocytotic vesicles and a partial basement membrane envelope.
Figure V 1

A: Pericyte

B: Macrophage

C: RPE

D: Endothelial cell

E: Activated pericyte
In addition, the recognition of comparisons in morphology between the kidney and the chorioretinal juncture opens up new avenues for collaboration between researchers working on these two tissues. Ophthalmic researchers have the advantage over renal pathologists in being able to make direct clinical observations of the effects of disease by ophthalmoscopy, fluorescein angiography and vitreous fluorophotometry, while renal pathologists have the advantage of being able to obtain tissue for study more readily because of the relative technical ease of renal biopsy.

From these studies, I am now able to speculate on the pathophysiology of macular disease.

The possible sites of a lesion causing a disturbance of macular function are the choriocapillaris, Bruch’s membrane, and the pigment epithelium. Obviously, lesions of the neurosensory retina cannot be dismissed, but they have not been the subject of this study.

1. Choriocapillaris. The two cells involved in cellular responses are the endothelial cell and the pericyte. Thirdly, mononuclear cells are carried into the tissues through the choroidal circulation. If the circulation is interrupted acutely by for example
thrombosis of the posterior ciliary vessels, the area of supply of the affected lobules will be infarcted. Although the neurosensory retina may receive its blood supply from the retinal circulation, the retinal pigment epithelium will be infarcted and the neurosensory retina may detach, because of failure of the retinal pigment epithelium to evacuate the subretinal space. Chronic reduction in chorionicapillary blood flow causes less recognisable clinical effects because the flow is normally far in excess of that required to supply oxygen to the tissues, and is presumed to bear some other function, such as to offer a buffer against injury, and to carry away the heat created by the phototransduction process. A point frequently made in the literature is that the choriocapillaris is patent and appears healthy in the majority of eye with age-related macular degeneration. Although clinically, the patient is often offered the explanation that his vision is failing because of poor circulation. Chronic insufficiency of the choriocapillaris probably contributes to the atrophic form of age related macular degeneration (Fig V 2).

Endothelial cell proliferation is a very important component of vision threatening age related change. This was seen in Chapter II cases 1 and 2, and in the experimental study 2. The role of pericytes in this
Fig V2. Diagramatic representation of the contribution of the choriocapillaris to macular disease.
**Figure V.2**

A. Normal

B. Acute chorio-capillary insufficiency

C. Chronic chorio-capillary insufficiency

D. Cellular response

- Pericyte
- Endothelial cell
- Monocyte
process has been studied by Archer (32) and merits further investigation. The recognition that pericytes have an active role in physiology and pathophysiology of the choriocapillaris is, I believe, an important new observation. Previously, pericytes have been considered static and inert cells, having a supportive function for the endothelium of the choriocapillaris. I propose that they are chemotactically attracted to abnormal deposits in Bruch’s membrane and remove filtered debris, allowing the free passage of metabolites to continue unhindered. In aged cells, the volume of filtered debris exceeds the scavenging ability of the pericytes, or the pericytes are less active than in youth, and material deposits and accumulates. It may then be that pericytes are still chemotactically attracted by the debris, but carry with them their endothelial cells with which they are intimately related, and neovascularisation occurs. Mononuclear phagocytes which are found in normal choriocapillaris, may also participate in this system, but to a greater extent in acute lesions. Circulating monocytes leave the circulation in the choriocapillaris, attracted out of the blood stream by a variety of well recognised factors. Their presence in Bruch’s membrane in eyes with subretinal neovascularisation has been implicated as evidence of
their involvement in the neovascular process. A parallel can be drawn between these macrophages, well recognised in ocular pathology, and the more recently recognised macrophages from the circulating pool of monocytes present in the glomerulus, where the morphologists more easily recognise mesangial cells of pericytic type.

The contribution of the pericyte is an interesting new avenue to develop in ophthalmic pathology. For example, in preretinal membranes, the fibroblastic component and the cause of contraction is unknown (456). Could it be pericytic?

2. Bruch's membrane deposits which may be the exciting stimulus for neovascularization (559,616,648,728,819) may either arise from the retinal pigment epithelium or the choriocapillaris. The choriocapillaris is freely permeable and Bruch's membrane is semipermeable becoming less so with age. The reabsorption of transudate from the choriocapillaris depends on the oncotic pressure in the capillary. It may be that abnormal extracellular matrix deposits which are hydrophobic (754) interfere with the reabsorption by disturbing the balance of oncotic pressure (Fig. V. 3). Once material accumulates under the retinal pigment epithelium, it will remain as there is no recognised mechanism to remove it, as there
Fig. V3. Diagram of possible origins of deposits on Bruch's membrane.
choriocapillary exudate

RPE degenerative product

Colloid osmotic pressure

? NODULAR (Type I)

? BASAL LINEAR (Type II)

? RPE DETACHMENT (Type III)

Figure V 3
is for material in the subretinal space which is cleared by the RPE pump. It may be that the altered oncotic pressure caused by the existence of such materials draws fluid in from the choriocapillaris giving the clinical appearance of retinal pigment epithelial detachment. The case described in Chapter II 3 proves that the distribution of nodular deposits can at least be mimicked by leakage of material from the choriocapillaris. There is no such definitive evidence of their deposition in a strictly RPE disease. It may be that the vascular theory of drusen formation of the nodular type is indeed correct.

The only means for removing abnormal deposits is by mononuclear cells from the choriocapillaris, by metaplastic retinal pigment epithelial cells, or possibly by the activity of choriocapillary pericytes.

3. The retinal pigment epithelium also makes a contribution to the material accumulated in Bruch's membrane. Diseased retinal pigment epithelium tends to produce excessive quantities of extracellular material at its base. It may be diseased because of an intrinsic metabolic defect, possibly by a defect caused by light damage, or from poor oxygen supply because of a wide diffusion barrier presented by a thickened Bruch's membrane between it and its blood supply in the
choriocapillaris.

The RPE is an inhibitor of neovascularisation, and it may be that in age related macular degeneration the primary defect is in the RPE possibly due to lipofuscin accumulation (107) and it fails to prevent vessels in the choriocapillaris from proliferating. In young patients, as for example in myopes with Fuch's spot, it is recognised clinically that a neovascular frond at the macula carries a far less serious prognosis for vision than does a frond in age related macular degeneration. In Fuch's spot, the RPE cells proliferate exuberantly round the new vessels and prevent progression.

Similarly, subhuman primate models of sub retinal pigment epithelial neovascularisation do not behave like those in human age related degeneration (805,806,807).

The cellular responses which I have described, and the analogy with the kidney which I have drawn, emphasise a complex interaction among the endothelial cells and pericytes of the choriocapillaris, the retinal pigment epithelium and circulating monocytes.

The next stage in investigating these pathological processes would be to find ways of reliably identifying the cell types using cell markers, since their morphological characteristics change in different circumstances. While cells cannot always be reliably
identified on purely morphological grounds other means of defining cells for example, surface markers may not be available or possible to execute in diagnostic specimens. The criteria I have drawn up are helpful in studying biopsy and autopsy cases, but the physiology and roles in pathological responses of the cells require to be further studied using experimental methods.

The concept that Bruch's membrane is an inert collagenous structure should be cast aside. All the components of it are constantly being turned over, albeit slowly, it is bathed on its outer aspect by a fluid almost identical with plasma and on its inner side is presented with quantities of RPE breakdown products. The flow of fluid across it is large. Taking all this into account, it is facile of us to think of lesions of Bruch's membrane in terms of the relatively static deposits we describe clinically.

Looking to the future, perhaps taking this cellular approach, it will be possible to influence the functions of the participating cells pharmacologically, possibly with the aid of the technique of tagging active agents to photosensitising drugs, since the macula is an ideal site for such a mode of treatment (700).
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