

Ageing and degeneration in the macular region: a clinico-pathological study

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Certain changes at the macula can be attributed to normal ageing. Metabolic waste accumulates in the cells of the retinal pigment epithelium. Connective tissue, especially altered collagenous fibres, increases in Bruch's membrane, and vascular changes inherent in the vessels themselves can be shown in the choroid. Which of these ageing processes is implicated in the pathogenesis of senile macular degeneration or at what stage they become pathological is uncertain. Most cases of senile macular degeneration are believed to be due to sclerosis and obliteration of the choriocapillaris in the central area (Duke-Elder, 1966), while electron microscopic studies by Hogan (1967, 1972) emphasized the role of ageing changes in Bruch's membrane and the retinal pigment epithelium.

Senile macular degeneration shows a wide spectrum of clinical appearances, reflecting the different anatomical levels predominantly affected at the time. Thus the fundus may present a disturbance of retinal pigmentation, exposure and abnormality of the choroidal vessels, drusen of various appearances, evidence of exudation, haemorrhage or neovascularization from the choroid, and intraretinal and preretinal changes. This has resulted in the recognition of many distinct and generally unrelated entities since the disease was originally described by Haab (1885). The most significant advance in recent years stems from the original demonstration by Verhoeff and Grossman (1937) that senile disciform degeneration results from the organization of haemorrhage beneath the retinal pigment epithelium. The cause of this haemorrhage was investigated by subsequent observers, notably by Maumenee (1965), and by Gass (1967), who formulated our current knowledge of the predisciform state when he proposed that neovascularization from the choroid may occur in response to the accumulation of abnormal deposits beneath the pigment epithelium and that this may precede haemorrhage.

Current interest therefore centres on the recogni-

tion of the predisciform state and the use of photo-coagulation to prevent the complications of sub-retinal neovascularization. A definitive form of treatment has thus been evolved, although applicable to only a limited number of patients suffering from an advanced degree of degeneration. Further, it has been difficult to rationalize and to evaluate this treatment because the natural history of the disease remains poorly understood (Gass, 1973). Not surprisingly, therefore, the majority of ophthalmologists regard degenerative disease of the retina and the macula as the most difficult to treat and the most in need of research (Hammond and Spalter, 1973).

The present investigation reports the results of clinical and pathological examination of 378 eyes. The aim of this study was to identify the age-related changes in the retinal pigment epithelium, Bruch's membrane, and choriocapillaris which could be regarded as normal and to relate the progression of these changes to the evolution of senile macular degeneration.

Material and methods

Histological examination was performed on 378 eyes in which the macula had presented a variety of clinical appearances ranging from normal to the late manifestations of senile macular degeneration. This series did not include eyes suffering from degenerative myopia, retinal vascular disease affecting vision, advanced simple glaucoma, or eyes in which an adequate view of the macula had not been obtained clinically. The 378 eyes were collected during the period 1966-75 from 216 patients, 199 men and 17 women, whose ages ranged from 43 to 97 years. All patients had been admitted to Lidcombe Hospital, generally for long-term care, and a full ocular examination was performed at intervals. Fundus photographs were taken whenever possible and selected patients were submitted to fluorescein angiography. The average interval between the last clinical examination and the time of death was 16.4 months.

When eyes became available after death they were fixed in Lillie's buffered formalin. They were opened in the horizontal plane and examined macroscopically. The position on the sclera corresponding to the macula was localized by observing the tip of a fine probe during transillumination, and the spot was marked with con-

centrated Harris's haematoxylin solution. The eyes were then double embedded (Tait Smith, 1976). Serial sections 8 μm thick were cut horizontally through the disc and the macula. Every tenth section was stained by the picro-Mallory method as modified by Lendrum, Fraser, Slidders, and Henderson (1962) and examined histologically. This stain was selected for routine use as it distinguishes fibrin (red), collagen (blue), and neural tissue (pink). In areas of interest the intervening sections were examined after staining with the following: haematoxylin and eosin, luxol fast blue, periodic acid-Schiff, Verhoeff's elastic stain, chloranilic acid, Wilder's silver stain, Mallory's PTAH, and congo red.

Results

Histological changes associated with ageing were detected at the level of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris before clinical abnormality became apparent. Subsequent changes in these tissues also correlated closely with the clinical progress of senile macular degeneration. In the present investigation the ageing and degenerative changes at the macula were therefore classified according to the histology.

The age-related changes in Bruch's membrane comprised thickening, hyalinization, patchy basophilia, and precipitation of calcium crystals with chloranilic acid. These changes were first seen beneath the macula and adjacent to the disc and remained most advanced in these regions. An arbitrary assessment of the findings was made in sections beneath the fovea. The thickness of a representative segment of the membrane was compared to the vertical diameter of the underlying choroidal capillary. The thickness was then expressed according to whether Bruch's membrane: choriocapillaris was one-quarter or thinner, one-third, or one-half or thicker (Fig. 1).

Hyalinization of the membrane was indicated by increased periodic acid-Schiff positivity and a change from blue to red staining with the picro-

Mallory method. The extent was noted to the nearest half disc diameter and four grades were recognized. Grade 1 referred to small patches which appeared in the fifth decade and later became continuous. Grade 2 hyalinization extended into the intercapillary pillars (Fig. 2) and grade 3 hyalinization reached the level of the outer surface of the choriocapillaris (Fig. 3). Hyalinization completely surrounding several choroidal capillaries was occasionally observed (grade 4).

Two types of drusen were noted on Bruch's membrane. Some deposits were hyalinized and globular in shape, others were dome-shaped and had a granular structure. These drusen could also be distinguished on clinical examination, the former appearing round and discrete while the latter showed greater variation in size and shape with ill-defined outlines.

The earliest light microscopic evidence of disturbance to the pigment epithelium was associated with the appearance of a finely granular deposit at the base of the cells. This material was eosinophilic, was unstained with luxol fast blue, was only moderately positive to periodic acid-Schiff, but stained blue with the picro-Mallory method. The formation of this basal linear deposit beneath the macula proved the most reliable histological criterion of the stage of the disease and correlated most closely with the clinical findings, although this was influenced to some extent by the time interval between clinical and histological examinations.

HISTOLOGICAL GROUPS

The eyes were divided into six groups according to the degree of histological abnormality (Fig. 4). The first four groups reflected the progressive development of the basal linear deposit and the visual acuity recorded in these eyes is shown in Table I. Groups V and VI represented the late stages of geographical atrophy and disciform

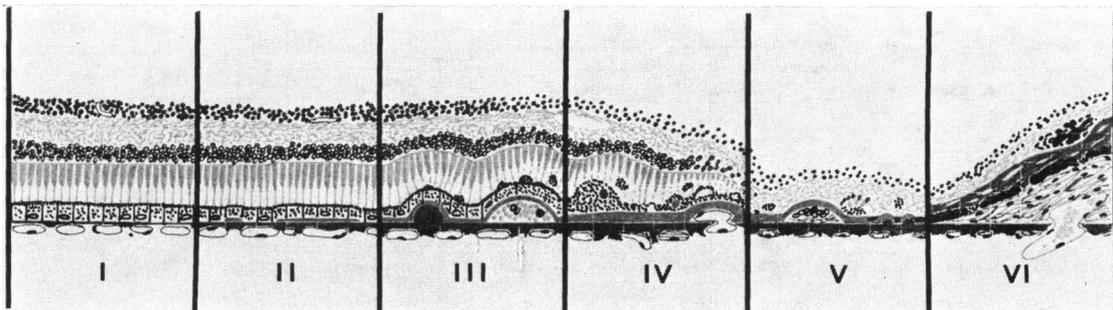


FIG. 4. Diagram illustrating histological classification of 378 eyes according to development of basal linear deposit under retinal pigment epithelium

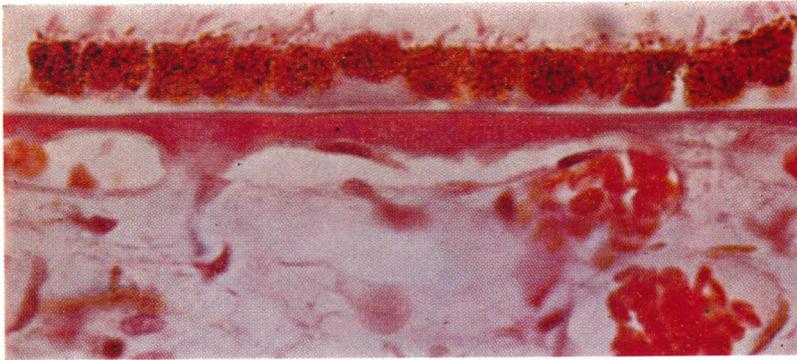


FIG. 1 Example of Group II. Section passing through macular region of patient aged 86 with normal fundus and 6/12 vision. Marked thickening of Bruch's membrane encroaching on choroidal capillary, ratio thickness membrane : capillary lumen almost 1:1. Localized deposit of blue staining finely granular material related to thickened membrane. Picro-Mallory. $\times 500$

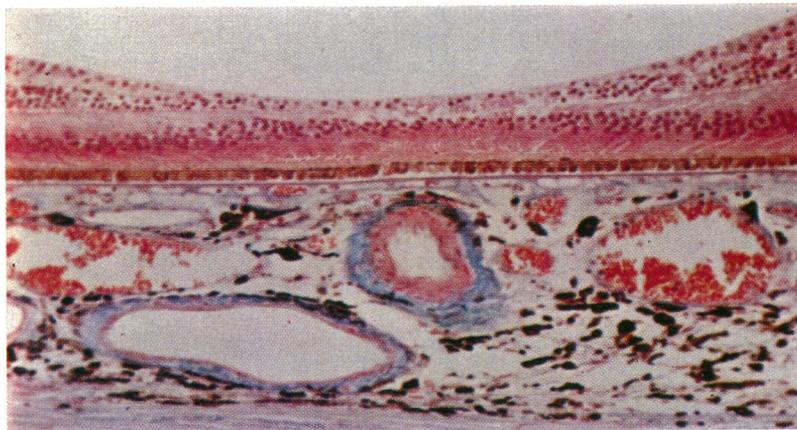


FIG. 2 Example of Group I. Section through normal macula of left eye of patient whose right fundus is illustrated in Fig. 5. Bruch's membrane shows grade 2 hyalinization and there is no evidence of basal material under retinal pigment epithelium. The pigmented choroid is of normal thickness and vessels are normal. Picro-Mallory. $\times 150$

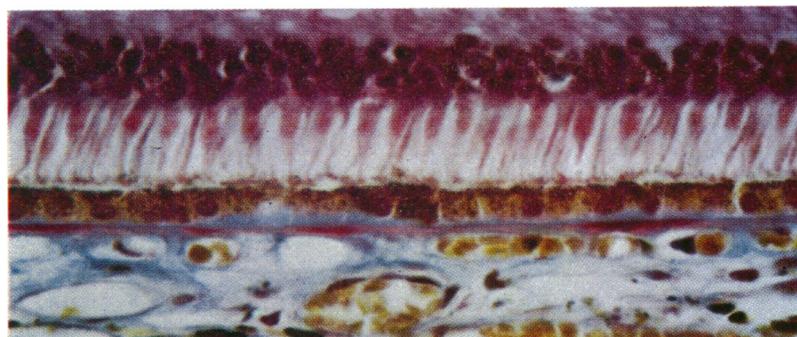


FIG. 6 Example of Group II. Section through paramacular area of left eye of 72-year-old man with 6/6 vision and normal fundus. Beneath retinal pigment epithelium localized deposits of finely granular material are related to deeply staining segments of Bruch's membrane. These segments were basophilic with haematoxylin and eosin stain. Picro-Mallory. $\times 500$

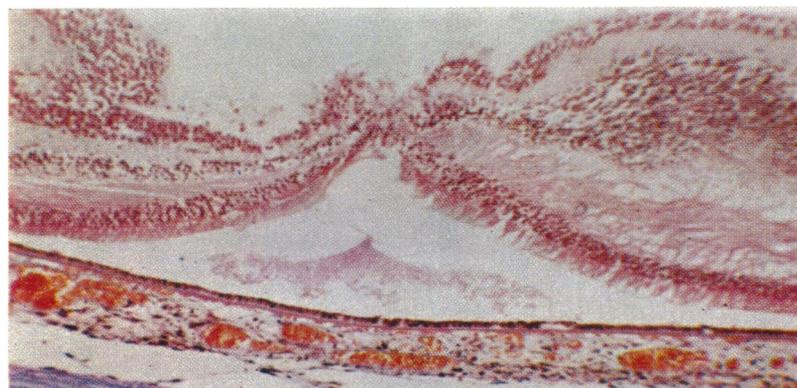


FIG. 7 Example of Group III. Section through macula of 79-year-old man whose fundus had appeared normal with 6/9 vision. Basal linear deposit now forms thin continuous layer and Bruch's membrane shows widespread grade 3 hyalinization extending into the intercapillary pillars to the level of outer surface of choriocapillaris. Picro-Mallory. $\times 75$

FIG. 3 Example of Group IV, showing thick basal linear deposit related to grade 3 hyalinization of Bruch's membrane. Section of eye shown in Fig. 11. Picro-Mallory. $\times 500$

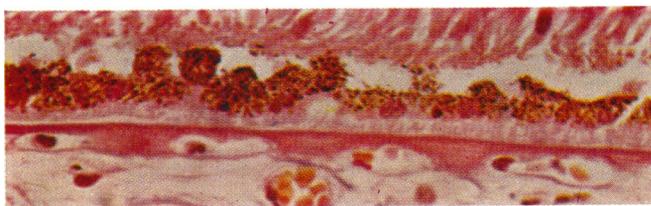


FIG. 8 Example of Group IV. Section through macula of 83-year-old man whose fundus had shown coarse pigmentary disturbance although vision had remained 6/9. Note thick continuous basal linear deposit and degeneration of overlying pigment epithelium with liberation of pigment-laden cells into subretinal space. Bruch's membrane shows thickening and pillars of grade 3 hyalinization. Picro-Mallory. $\times 150$

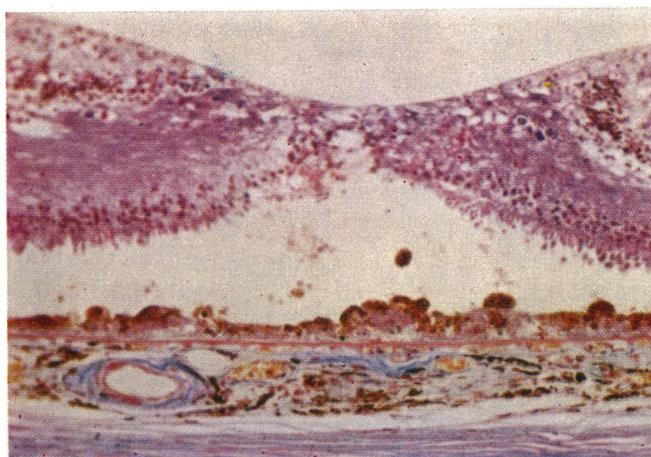


FIG. 17 Example of Group IV progressing to Group V. Sections passing through macula of eye in Fig. 16. Basal linear deposit forms continuous hyalinized and very thickened layer under macula. Pigment epithelium shows marked attenuation and seems about to disappear. Top: periodic acid-Schiff. $\times 45$. Bottom: Picro-Mallory. $\times 150$

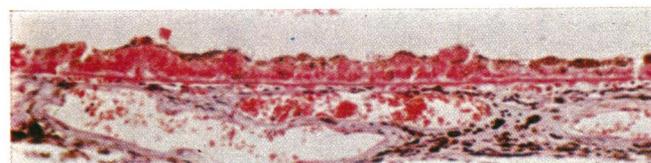
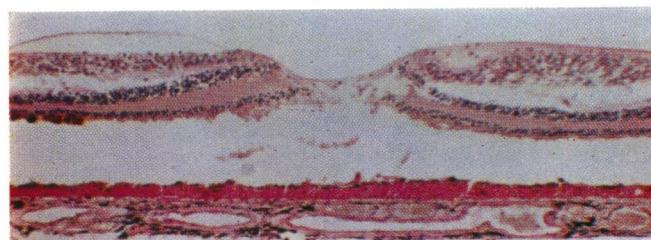
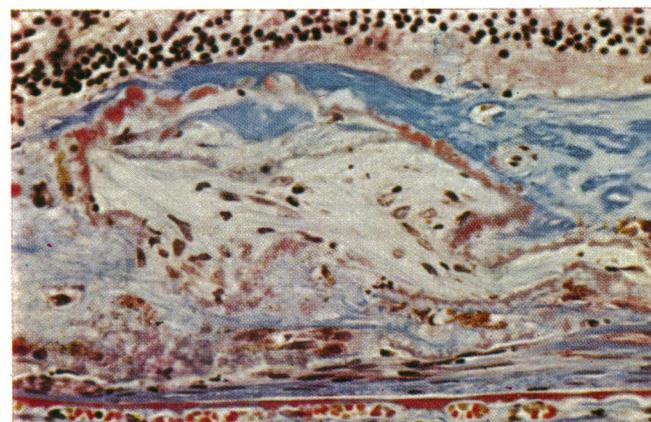


FIG. 22 Example of Group VI. Section passing through disciform scar in eye of 80-year-old patient. Hyalinized basal linear deposit has been folded into the mass by successive waves of fibrous tissue. Picro-Mallory. $\times 300$



degeneration in which vision was greatly reduced when the fovea was involved. Table II shows the associated histological and clinical findings, and Table III shows the age distribution of the 216 patients.

Group I (No basal linear deposit)

In this group (120 eyes) there was no trace of the basal linear deposit and the retinal pigment epithelium appeared normal. The average extent of grade 2 hyalinization of Bruch's membrane was 2.0 disc diameters, and even eyes from patients in the 40 to 50 year age group showed some evidence of grade 1 hyalinization. Small drusen of the hya-

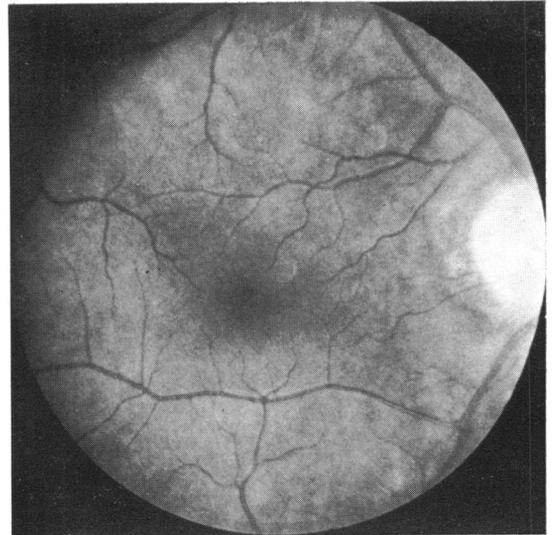


FIG. 5 Normal right fundus of man aged 67. Left fundus was identical. Vision 6/6 in both eyes

Table I *Visual acuity recorded in Groups I-IV (333 eyes)*

Visual acuity	Group I	Group II	Group III	Group IV
6/6	66 (55.0)	29 (26.1)	6 (10.0)	2 (4.8)
6/9	17 (14.2)	32 (28.9)	23 (38.3)	2 (4.8)
6/12	6 (5.0)	18 (16.2)	12 (20.0)	8 (19.0)
6/18-6/24	4 (3.3)	9 (8.1)	12 (20.0)	17 (40.5)
<6/24	2 (1.7)	1 (0.9)	1 (1.7)	10 (23.8)
Unknown	25 (20.8)	22 (19.8)	6 (10.0)	3 (7.1)
Total	120	111	60	42

Percentages are shown in parentheses

linized globular variety were noted in 23 eyes but had no detectable effect on vision, although none was located at the fovea.

The average age of patients in this group was 67.5 years and no pigmentary changes were noted on clinical examination. Figs 2 and 5 illustrate these normal findings. 6/6 vision was recorded in

Table II *Clinical and histological findings in 378 eyes, grouped according to appearance of basal linear deposit*

	Group I	Group II	Group III	Group IV	Group V	Group VI
No. of eyes	120	111	60	42	24	21
Basal linear deposit	Absent	Patchy	Thin continuous	Thick continuous	Persists after loss of pigment	Incorporated into scar
Bruch's membrane/choriocapillaris						
(a) Average limits of hyalinization in disc diameters						
Grade 2	2.0	2.5	3.0	3.9	5.1	5.7
Grade 3	Nil	odd pillars	1.0	3.0	3.7	3.3
(b) Thickness of membrane*						
capillary lumen	1	1	1	1	1	1
	3.7	3.4	2.9	2.3	2.2	2.4
Incidence of subretinal neovascularization (percentage)	0	0	0	14.3	41.7	100
Clinical disturbance of pigmentation (percentage)						
Nil	100	96.4	41.6	4.7	Geographic atrophy	Disciform degeneration
Fine	0	3.6	46.7	16.7		
Coarse	0	0	11.7	78.6		
Average age of patients (years)	67.5	75.3	81.9	84.0	85.6	81.9

*Average

Table III Age distribution of patients according to histological classification of 378 eyes

Age group	Group I		Group II	Group III	Group IV	Group V	Group VI	Total
	Vision 6/6	Vision < 6/6						
-59	16	15	2	0	0	0	0	33
60-69	29	7	25	4	0	0	0	65
70-79	21	17	43	14	11	2	7	115
80-89	0	15	38	34	22	20	14	143
90+	0	0	3	8	9	2	0	22
Total	66	54	111	60	42	24	21	378

only 66 of the 120 eyes, and in none of the eyes of patients aged 80 years and over (Table III). In most eyes the lowered visual acuity was ascribed to hazy media or to failure of concentration, but in others no cause was apparent.

Group II (Patchy basal linear deposit)

In this group (111 eyes) the basal linear deposit appeared in patches beneath three to eight retinal pigment cells, which showed slight distortion. The average extent of grade 2 hyalinization of Bruch's membrane was 2.5 disc diameters with occasional pillars of grade 3 hyalinization. Grade 3 hyalinization was associated with widening of some pillars and also with thickening of the membrane, resulting in encroachment on the choriocapillaris. It was at this stage that degenerative changes in the overlying pigment epithelium were first observed (Figs 1, 6). Drusen were present in the macular region in 22 eyes and were predominantly of the hyalinized globular variety.

The average age of patients in this group was 75.5 years and nearly all eyes showed no clinical disturbance of pigmentation (Table II). The most commonly recorded visual acuity was 6/9 (Table I), with an about equal incidence of eyes in which vision was better (26.1 per cent) and worse (25.2 per cent).

Group III (Thin continuous basal linear deposit)

In this group (60 eyes) the linear deposit formed a thin continuous layer under the macula. The average extent of grade 3 hyalinization was 1.0 disc diameter but the deposit sometimes extended more widely, becoming patchy before petering out (Fig. 7). The overlying pigment cells were irregular and the outline of individual cells was less distinct so that they appeared fused together. The rod and cone processes were generally separated from the pigment epithelium at the macula and some appeared stunted. Drusen were present in 25 eyes

with an about equal incidence of the hyalinized and granular varieties.

The average age of patients in this group was 81.9 years. The most common visual acuity was again 6/9, but 6/6 vision was recorded in only 10 per cent of the eyes. More than half the eyes showed a clinical disturbance of pigmentation, predominantly a fine clumping of pigment (Table II), and this included 23 of the 25 eyes with histological evidence of drusen. The incidence of fundus abnormality is probably underestimated owing to the interval after the clinical examination.

Group IV (Thick continuous basal linear deposit)

This group (42 eyes) showed thickening of the basal linear deposit, sometimes to about the height of normal pigment epithelium (Fig. 8). Globules of hyalinized material and small foci of calcification were sometimes demonstrated in the material. The pigment epithelium appeared as an attenuated layer in which cell outlines were lost and nuclei were few. In some areas proliferative changes were observed, large pigment-laden cells being shed into the subretinal space, and occasional cells contained hyalinized material or developed cystic changes. Localized mounds of pigment granules were also noted. The photoreceptors, which were sometimes absent over the mounds of pigment granules, showed a greater degree of retraction and distortion in this group. The basal linear deposit attained its maximum thickness over grade 3 hyalinization of Bruch's membrane, the average extent of which was 3.0 disc diameters. The underlying choroidal capillaries were wide-spaced and often narrowed, so that the average ratio of membrane thickness to capillary lumen was almost 1:2. This was due not only to encroachment by the thickened membrane but also to reduction of the capillary lumen by surrounding fibrous tissue. Drusen were present in 15 eyes. They were mainly of the granular type and several were undergoing calcification.

Six of the 42 eyes (14.3 per cent) showed thin

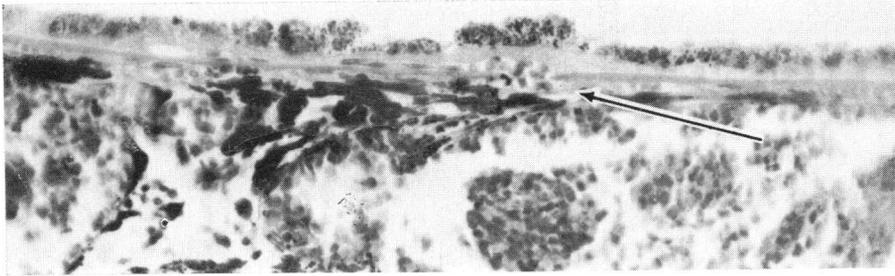


FIG. 9 Section through macular area of 72-year-old man whose fundus had shown coarse pigmentary disturbance, vision 6/18. Capillary (arrow) passes through small gap in Bruch's membrane to invade basal linear deposit. Picro-Mallory. $\times 300$

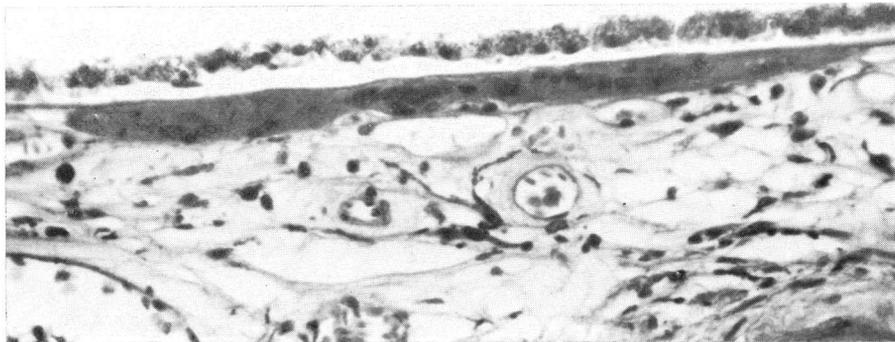


FIG. 10 Section showing giant cell beneath thinned segment of Bruch's membrane in eye from 77-year-old man. There were several areas of fibrovascular invasion but serial sections did not show break in Bruch's membrane at site of giant cell. Picro-Mallory. $\times 500$

capillary membranes passing through gaps in Bruch's membrane and spreading beneath the retinal pigment epithelium in the macular region for up to half a disc diameter. Drusen were a conspicuous feature in two of these eyes but were not immediately related to the breaks in the membrane, the capillaries invading the basal linear deposit (Fig. 9). Giant cells were often prominent near the gaps in the membrane but were also found in relation to thinned segments of the membrane where serial sections did not show a break in the immediate vicinity (Fig. 10).

The average age of patients in this group was 84 years and the youngest was aged 70. The most commonly recorded visual acuity was 6/24 and almost all eyes showed a clinical disturbance of pigmentation which was predominantly coarse. Fig. 11 shows the tigroid fundus of a 90-year-old man with fine pigmentary changes and 6/9 vision. The basal linear deposit was widespread under the macula (Figs 12, 13) and was appreciably thickened over grade 3 hyalinization (Fig. 3). An electron microscopic section was taken from the paraffin block in this area. This technique is unsatisfactory for fine detail but shows the thick deposit lying on Bruch's membrane (Fig. 14). The hyalinized membrane and the intercapillary pillars contain irregular-banded collagen, vesicles, and tube-like structures. The electron micrograph (Fig. 15) represents the macular region of a man aged 71 who showed coarse pigmentary mottling in both eyes, and

histological examination of the fellow eye showed a thick layer of basal material. The deposit contains banded material lying between the plasma infoldings of the retinal pigment epithelium and the basement membrane.

Fig. 16 shows the tigroid fundus of an 80-year-

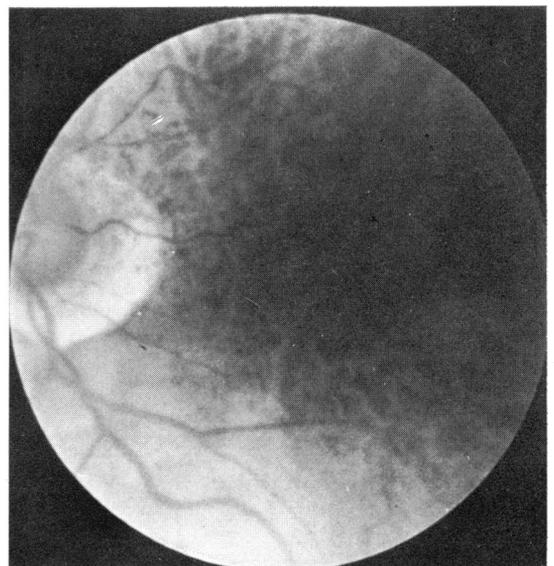


FIG. 11 Tigroid fundus of 90-year-old man. Macula showed fine pigmentary disturbance. Vision 6/9



FIG. 12 Section through macula of eye shown in Fig. 11. Note thinning of choroid accentuating prominence of larger vessels. Picro-Mallory. $\times 90$

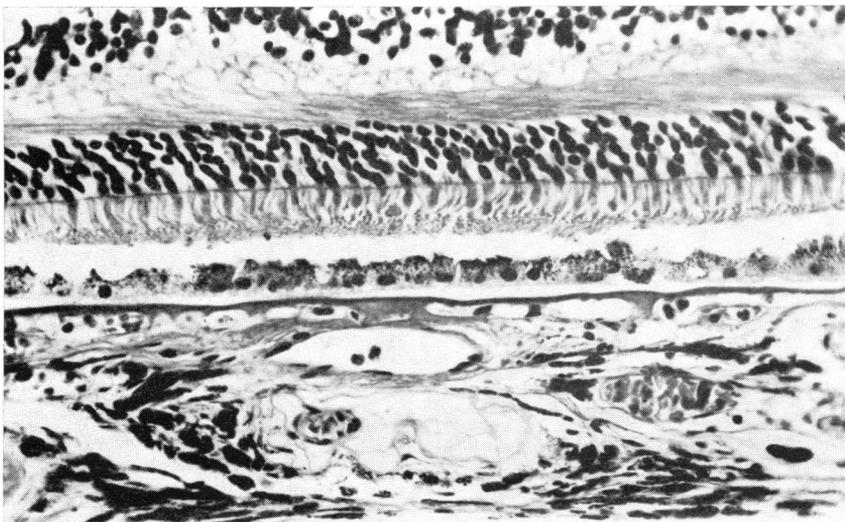


FIG. 13 Section through paramacular area of same eye showing grade 3 hyalinization of Bruch's membrane and continuous basal linear deposit. Pigment cells show irregularity, cystic spaces, and indistinct cell outlines. In a choroidal artery there is replacement of muscle by fibrillar fibrous tissue. Picro-Mallory. $\times 300$

old man. Coarse clumps of pigment were distributed around a central hypopigmented area. Sections through this area showed the basal linear deposit to be much thickened and hyalinized, while the pigment epithelium remained only as a very attenuated layer and seemed about to disappear (Fig. 17). This was the most extreme example of thickening of the deposit found in Group IV, as in the other eyes it did not exceed the height of the normal pigment epithelium. Further, this group included three eyes in which the deposit did not show thickening although the pigment epithelium was similarly attenuated and formed occasional mounds of pigment granules. In these eyes the deposit was not hyalinized and appeared to have faded with the pigment epithelium.

Group V (Basal linear deposit with loss of overlying pigment)

In this group (24 eyes) loss of the retinal pigment epithelium produced areas of geographical atrophy visible clinically (Fig. 18). On histological examina-

tion the hyalinized basal linear deposit could be traced throughout the depigmented area in most eyes. The deposit also extended for some distance beneath the adjacent pigment epithelium, which showed the same changes as noted in Group IV. At the edge of the depigmented area the histological changes were constant. The pigment epithelium often ended in a group of proliferated cells, while the photoreceptors showed progressive degeneration as they approached the atrophic area in which they disappeared. The external limiting membrane ended in a curved line and the outer nuclear layer also disappeared so that the outer plexiform layer rested directly on the basal material (Fig. 19). Occasionally an island of persisting photoreceptors converged on a cluster of degenerating pigment cells. The choroid was often more atrophic in these eyes and many choroidal capillaries showed partial obliteration by fibrous tissue in the depigmented area. The narrowing of the capillaries often occurred abruptly where the pigment epithelium ended (Fig. 20). In relation to these capillaries Bruch's membrane appeared disproportionately

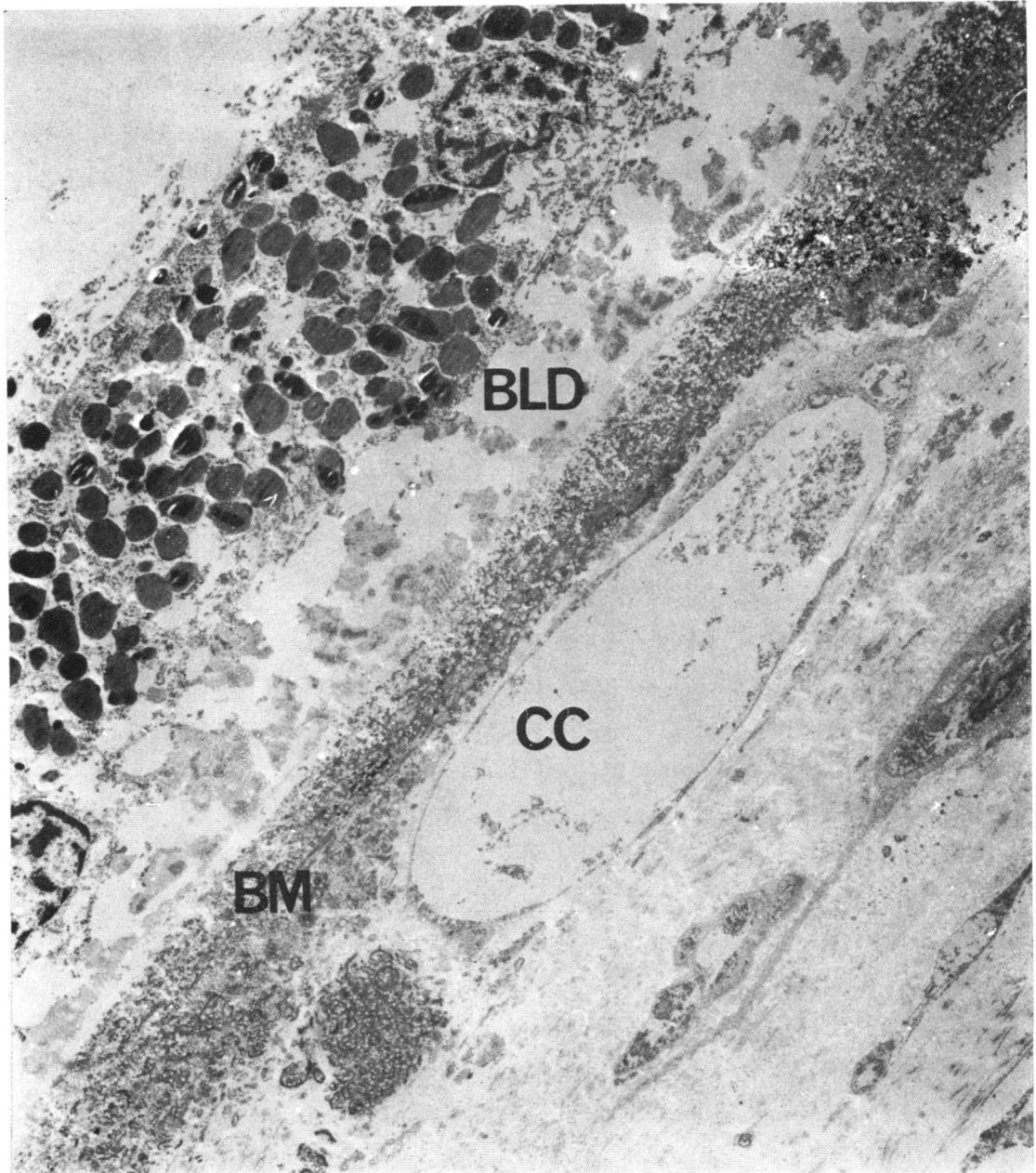


FIG. 14 *Electron micrograph of eye in Fig. 11. Section taken from area of basal linear deposit depicted in Fig. 3. This technique is unsuitable for fine detail but shows a thick layer of amorphous material (BLD) lying on Bruch's membrane (BM). The material in intercapillary pillars extends to level of outer surface of choriocapillaris (CC) and consists of irregular-banded collagen, vesicles, and tube-like structures. $\times 6820$*

thick but in actual measurements the membrane was often thinner than in Group IV, particularly in those eyes in which clinical observation had confirmed the loss of the pigment epithelium to be of long standing (Fig. 21).

Fifteen eyes showed drusen of both types. All of the granular variety showed calcification and some also contained avascular fibrous tissue. Neovascularization from the choroid was demonstrated in 10 eyes, including six of the eyes with drusen,

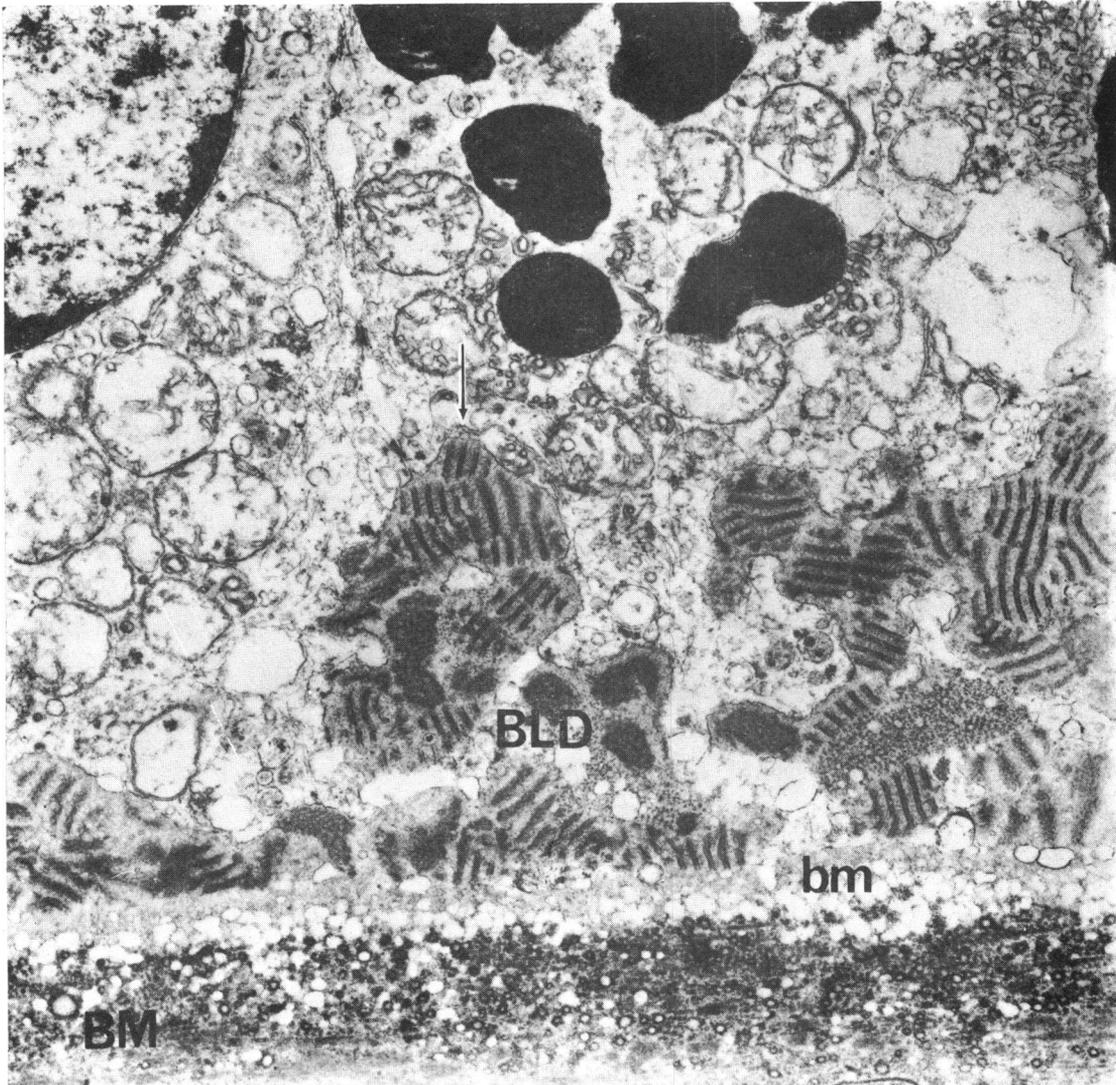


FIG. 15 *Electron micrograph from macular region of man aged 71 whose fundus had shown coarse pigmentary changes. Histological examination of the fellow eye revealed thick basal linear deposit. The deposit (BLD) contains banded material lying between plasma infoldings of retinal pigment epithelium (arrow) and the basement membrane (bm). BM = Bruch's membrane. $\times 19\ 250$*

and in seven eyes the breaks in Bruch's membrane were multiple. The fibrovascular tissue was more extensive than in Group IV but did not obscure the underlying choroid on clinical examination, unlike the thicker scars of disciform degeneration.

The areas of geographical atrophy were either present at the time of the first clinical examination or were observed to develop gradually within an area of coarse pigmentary mottling. The average age of patients in this group was 85.6 years and the most commonly recorded visual acuity when the fovea was involved was 3/60.

Group VI (Disciform degeneration)

In this group of 21 eyes fibrovascular invasion from the choroid resulted in clinically visible scars of varying size. The basal linear deposit remained identifiable as a hyalinized layer folded into the mass, sometimes separating fibrous tissue of different ages (Fig. 22). The deposit also extended for some distance beyond the scar and was attended by corresponding changes in the pigment epithelium and Bruch's membrane. Under the scar the choroid was generally thicker than in Group V and the arteries showed more pronounced sclerosis.

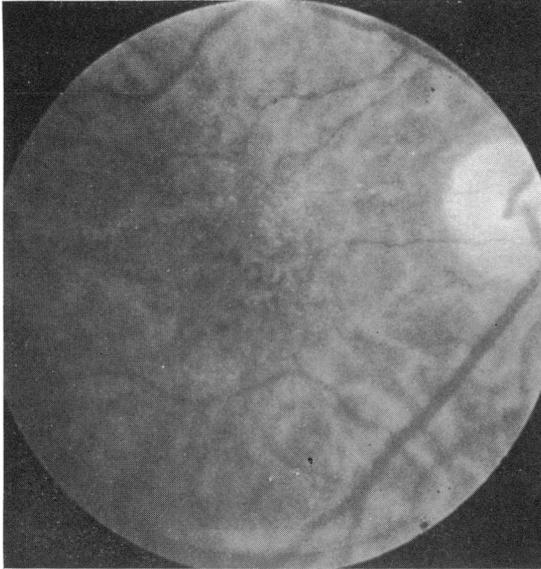


FIG. 16 *Tigroid fundus of 80-year-old man. Macula shows coarse clumps of pigment distributed around central hypopigmented area. Vision 6/24*

The average age of the 14 patients in this group was 81.9 years. Disciform degeneration was bilateral in seven patients while in four the second eye showed geographical atrophy which was also associated with new vessels. Although serous detachments of the retinal pigment epithelium were noted clinically during the evolution of disciform degeneration, only one eye subsequently showed such detachment on histological examina-

tion (Fig. 23). Fibrin was demonstrated in the serous fluid and vessels appeared to be extending into the serous detachment from an adjacent mound of fibrovascular tissue.

Cuticular material was occasionally observed in the scars, lying between rows or clusters of proliferating retinal pigment cells (Fig. 24). This material was eosinophilic, intensely positive to periodic acid-Schiff, and of hyaline appearance but stained blue with picro-Mallory, unlike the hyalinization of Bruch's membrane or of the basal linear deposit, which both showed a change in staining reactions to red with this method.

SENILE CHANGES IN CHOROID

The frequency with which the fundus presented a tigroid appearance rose sharply after the age of 75 years. This picture differed from the tigroid fundus seen in younger patients in that the choroidal vessels became visible beneath the macula and their margins were clear-cut. The senile halo was often pronounced (Fig. 11).

Although a pigmentary disturbance was commonly associated, the senile tigroid fundus was also observed in eyes in which the macula was otherwise normal. Histological examination confirmed that the clinical prominence of the vessels was due to thinning of the choroid, due particularly to loss of the middle layer, so that the larger vessels occupied almost the full thickness of the choroid (Fig. 12). Degenerative changes were also noted in some choroidal arteries similar to those seen in cerebral vessels, particularly in the choroid plexus. The vessels were shrunken and showed

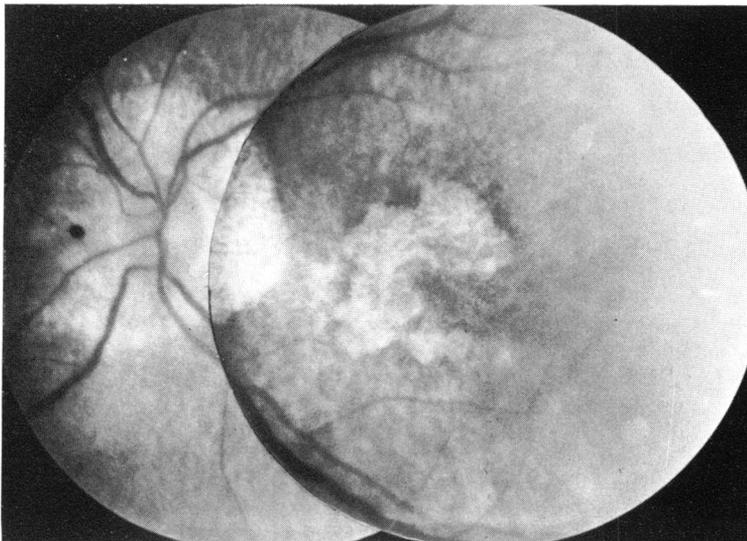


FIG. 18 *Left fundus of 84-year-old man first seen four years previously when fundus showed only peripapillary choroidal sclerosis and fine pigmentary disturbance at the macula. He gradually developed area of depigmentation nasal to the fovea, vision falling from 6/9 to 6/24 during this period*

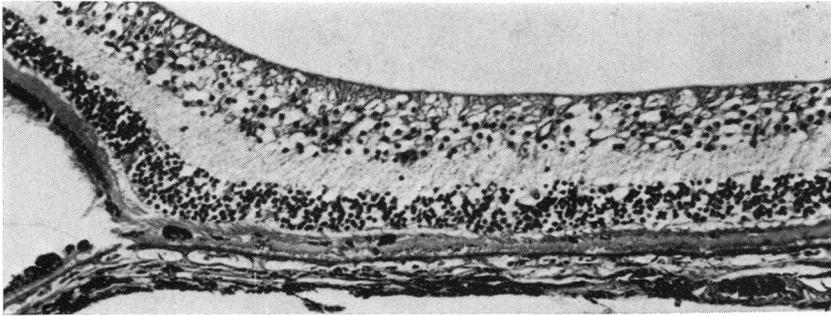


FIG. 19 Section between macula (at left) and disc of eye in Fig. 18. There is loss of pigment epithelium, rod and cone processes, external limiting membrane, and outer nuclear layer. Outer plexiform layer rests directly on hyalinized basal linear deposit. Picro-Mallory. $\times 150$

replacement of muscle by fibrillar fibrous tissue (Fig. 13). The remains of occluded vessels with collapsed fibrous walls were also seen. The majority of the vessels, however, showed only fibrous replacement of the media with the retention of

wide lumina. In normotensive patients hyalinization was observed only in extreme old age affecting the small vessels near the disc.

Discussion

In the elderly the macula typically shows loss of the foveal reflex, fine granularity of the retinal pigment, increased visibility of the choroidal vessels, and a few discrete drusen. These changes are considered to lie within normal limits, but in the present investigation 6/6 vision was recorded in fewer than half of the eyes showing these appearances and in none of such eyes belonging to patients aged 80 years and over. In most eyes this could be attributed to a failure of co-operation or to hazy media, but in others no cause was apparent. This decline in visual acuity with age was first noted by Donders (1864), and Weale (1975) calculated that the deterioration could be explained if the rate of cell fall-out found in the cerebellum was applied to the visual pathways. It follows that the limits of normal ageing are difficult to define in terms of fundal appearances or visual acuity.

The natural history of senile macular degeneration is similarly difficult to predict from clinical observation. Some cases show a progressive disturbance of retinal pigmentation, with or without prominent drusen, and culminate in geographical atrophy. During the evolution of the disease, however, the appearance of the choroidal vessels may become sufficiently abnormal to lead to the recognition of senile choroidal atrophy as a separate

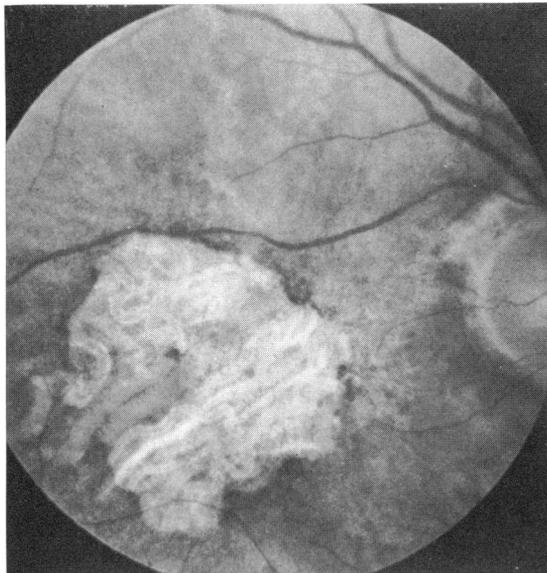


FIG. 20 Right fundus of 83-year-old man suffering from central choroidal atrophy in both eyes. The areas increased slowly in size over period of six years. Note large vein which retains normal blood column. Vision was counting fingers in both eyes

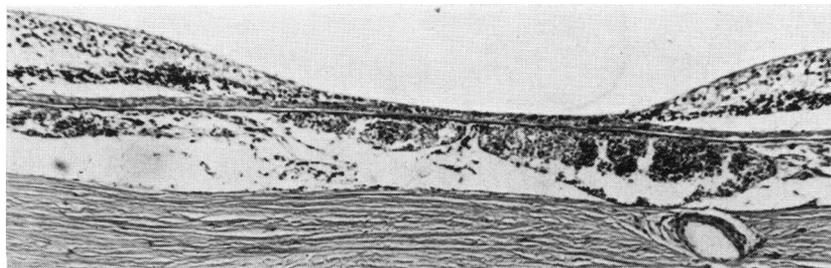


FIG. 21 Section through macula of eye in Fig. 20. There is loss of retinal pigment epithelium and photoreceptors but basal linear deposit can be traced across depigmented area. The choriocapillaris is absent and dilated thin-walled vein occupies full thickness of choroid. Picro-Mallory. $\times 75$

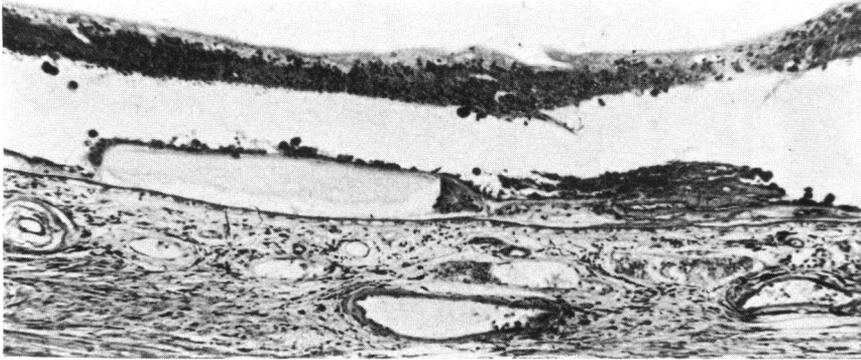


FIG. 23 *Right eye of 86-year-old man suffering from disciform degeneration. Section shows serous detachment of retinal pigment epithelium containing fibrovascular tissue, and an adjacent mound of cuticular material and proliferating pigment cells. Break in Bruch's membrane was remote from the detachment. Picro-Mallory. $\times 75$*

catity. At other times subretinal exudation, haemorrhage, and neovascularization may occur to alter the clinical picture and influence the prognosis. In the present clinicopathological investigation, therefore, the changes associated with ageing and degeneration of the macula were recorded according to the degree of histological abnormality occurring at the level of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris.

BRUCH'S MEMBRANE

The age-related changes in Bruch's membrane comprised thickening and hyalinization, increased periodic acid-Schiff positivity, and basophilic staining. The use of the term hyalinization requires explanation, since it merely denotes that the membrane appears glassy or without structure. In the present discussion the term has been retained

and has been applied when the membrane showed a change in staining properties from blue to red with the picro-Mallory method, increased periodic acid-Schiff positivity, and green staining with luxol fast blue. Picro-Mallory was one of several staining methods developed by Lendrum and others (1962) for the demonstration of fibrin, and Garner (1975) has suggested that the thickening of the membrane is due to the accumulation of plasma constituents secondary to undue permeability of the endothelium of the choriocapillaris. Staining with Mallory's PTAH, however, does not produce the dark blue appearance characteristic of fibrin, nor does the membrane subsequently develop the staining properties which Lendrum, Slidders, and Fraser (1972) found to accompany the ageing of fibrin. The change from blue to red staining of the membrane may be due to a reduction in the size of the intermicellar pores so that they accept only

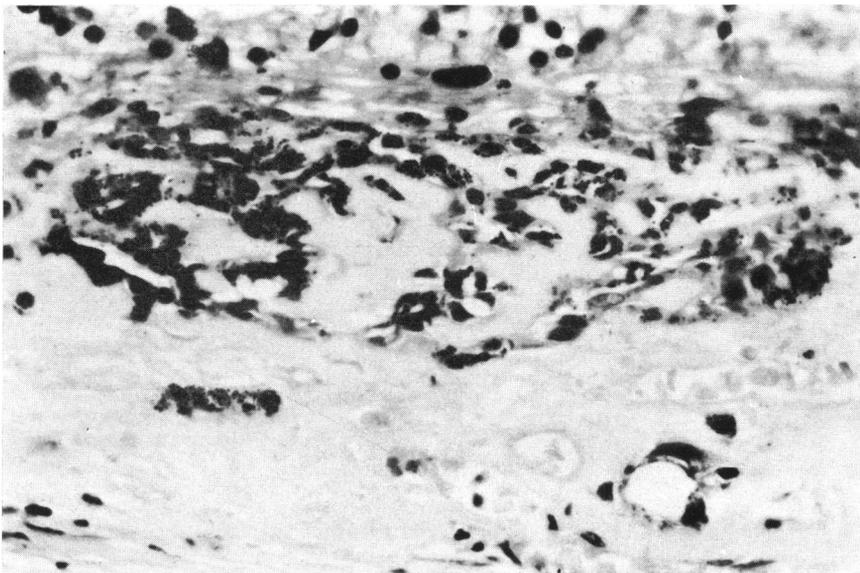


FIG. 24 *Section through eye of 75-year-old patient suffering from disciform degeneration. An irregular mass of hyaline cuticular material surrounded on all aspects by abnormal retinal pigment cells lies on inner aspect of fibrous tissue. Picro-Mallory. $\times 500$*

the smaller molecule of the acid fuchsin dye. This explanation is suggested by the electron microscopic demonstration of increasing density of the membrane.

The electron microscopic changes which develop in the membrane with age appear to fall into two main groups. The accumulation of vesicular, granular, and filamentous material begins in the inner collagenous zone at around the age of 20 (Hogan, 1967). Residual bodies and undigested outer rod segments have been identified in this material which represents debris derived from the retinal pigment epithelium. On the other hand, after the age of 40 changes develop in the collagen and elastic fibres of the membrane. There is an increase of normal and intermediate collagen and of fibres resembling long-spacing collagen. Hogan, Alvarado, and Weddell (1971) also described long, coiled osmiophilic fibres which they suggested may be altered collagen fibrils on which an electron-dense substance is deposited. The elastic fibres also show increasing density and undergo calcification.

RETINAL PIGMENT EPITHELIUM AND BASAL LINEAR DEPOSIT

The earliest light microscopic evidence of degeneration of the retinal pigment epithelium was associated with the development of a finely granular deposit beneath the cells, although hyalinization of Bruch's membrane was already established. This material was simply described as a basal linear deposit in order to distinguish it from drusen. The deposit contrasted with the hyalinized membrane by staining blue with picro-Mallory, being only moderately periodic acid-Schiff positive and remaining unstained with luxol fast blue. Gass (1967) described this deposition as an eosinophilic granular material and noted that it stained blue with Masson's stain, suggesting a collagenous component to its composition. The electron microscopic findings (Figs 14, 15) show this deposit to lie between the basal plasma infoldings and the basement membrane of the retinal pigment epithelium and to consist mainly of spindle-shaped deposits, often embedded in a granular material. These deposits contained structures with widely-spaced striations with a periodicity of 120 nm, which Hogan (1972) considers to resemble short-segment, long-spacing collagen such as is obtained by the *in-vitro* precipitation of tropocollagen (Gross, 1957). Basement membrane is collagenous in nature and may briefly be defined as tropocollagen in carbohydrate-rich mucoprotein (Ashton, 1974). Tripathi (1974) suggested that under certain conditions long-spacing collagen may originate

from a direct polymerization of basement membrane material.

Long-spacing collagen fibres have also been described in other tissues, notably in Descemet's membrane (Jakus, 1962), where they appeared to be the result of abortive attempts to form normal membrane (Hogan, Wood, and Fine, 1974), in the cortical zone of the trabecular beams (Garron, Feeney, Hogan, and McEwen, 1958), and in association with the basement membrane of the neuroepithelium of the utricular macula (Friedmann, Cawthorne, and Bird, 1965). Present indications are that these deposits which accumulate in the region of the basement membrane are a manifestation of gradual degeneration of the associated cells.

INTERPRETATION OF AGEING AND DEGENERATION IN MACULAR REGION ACCORDING TO BASAL LINEAR DEPOSIT

The development of the basal linear deposit beneath the retinal pigment epithelium appeared to be the most reliable histological criterion of the degree of degeneration of the overlying cells. The eyes were therefore classified according to the histological appearance of this deposit. Groups I and II broadly represented normal ageing, Groups III and IV represented the development and progress of degeneration, and Groups V and VI showed the subsequent end-results.

Groups I and II

In Group I the deposit could not be demonstrated although ageing of Bruch's membrane was already in evidence, starting in the fifth decade as patches of hyalinization under the macula and adjacent to the disc. With advancing age hyalinization and thickening spread over a wider area and also extended into the intercapillary pillars. The basal linear deposit first appeared in Group II in relation to thickened or basophilic segments of the membrane, or over the occasional widened intercapillary pillar showing hyalinization extending to the level of the outer surface of the choriocapillaris (grade 3). Nearly all eyes in these two groups retained a normal fundus appearance, often with 6/6 vision, and the histological changes were considered to be within the limits of normal ageing.

Groups III and IV

In Group III the basal deposit became a thin continuous layer and grade 3 hyalinization of Bruch's membrane extended for almost one disc diameter under the macula. These changes were considered to have become pathological, since

more than half the eyes had developed a clinical disturbance of pigmentation and in most vision was reduced. In Group IV clinical abnormality was well established, manifest predominantly as coarse pigmentary clumping. This group was characterized by thickening of the basal deposit and more pronounced degenerative and proliferative changes in the pigment epithelium. Gradual disappearance of the cells led to the circumscribed areas of depigmentation which characterized Group V. A number of eyes appeared to show this transition, since they contained only a thin layer of pigment. In several eyes the deposit appeared to fade as the pigment epithelium disappeared, but in most it remained as a thickened hyalinized layer.

Neovascularization was first detected in Group IV, in which six of the 42 eyes (14.3 per cent) showed capillary membranes growing beneath the pigment epithelium in the macular region. These capillaries were found to be invading the basal linear deposit, and Gass (1967) also described capillaries coursing through this eosinophilic material in two cases. None of the eyes in Group IV showed evidence of a serous detachment of the pigment epithelium with which new vessels are commonly associated (Teeters and Bird, 1973*a, b*). The present series therefore appears to confirm the suggestion by the same authors that blood vessels may grow into the subpigment epithelial space without previous detachment of the pigment epithelium. The retinal pigment epithelium is normally firmly anchored to the choroid by fine filaments of the basement membrane which extend from its inner and outer surfaces to join the cell membrane and the inner collagenous zone of Bruch's membrane (Hogan and others, 1971), and probably the basal linear deposit disturbs this attachment. This may allow spontaneous detachment of the pigment epithelium to occur and may also predispose to the ingress and spread of new vessels. Further, the demonstration of macrophages and giant cells in relation to thinned but unbroken segments of Bruch's membrane suggests that there may be an attempt at organization, since in other tissues these cells may precede the appearance of granulation tissue.

Groups V and VI

In the later stages of macular degeneration the basal linear deposit becomes hyalinized and assumes the same staining properties as hyalinized Bruch's membrane. The deposit generally remains after the pigment epithelium has disappeared and traces of the deposit could be found in the depigmented area of all eyes belonging to Group V.

Commenting on the aetiology of these areas of geographical atrophy, Gass (1973) observed that

most cases followed the fading of drusen but noted that this appearance could also result from the collapse of a serous detachment of the pigment epithelium. The latter mechanism was also proposed by Blair (1975), who thought that ischaemic changes in the underlying choriocapillaris would be less likely to produce such a well-demarcated area of atrophy. However, geographical atrophy was clinically observed to develop gradually within an area of coarse pigmentary mottling in several eyes in the present series. The histological studies also suggest that these depigmented areas evolve through the stages outlined, and in this respect to be determined by the initial changes in Bruch's membrane, retinal pigment epithelium, and choriocapillaris.

Neovascularization was demonstrated in 10 of the 24 eyes (41.7 per cent) in Group V. The fibrovascular invasion was more extensive than in Group IV but had not obscured the underlying choroid on clinical examination, unlike the thicker scars of disciform degeneration. The clinical picture is therefore determined by the extent of the neovascular response and different manifestations may occur in the two eyes. The more limited fibrovascular invasion associated with geographical atrophy may be related to the tendency for such eyes to show a greater degree of atrophy of all layers of the choroid, although it is more likely that the final result is dependent upon exudation and haemorrhage from the initial capillary membranes. Gass (1973) believed that geographical atrophy did not signify a basic difference from serous or haemorrhagic detachment of the retinal pigment epithelium and noted that disciform detachment sometimes occurred in the other eye. In the absence of neovascularization it is probable that geographical atrophy is the natural end-result and that this picture only becomes modified by an excessive degree of scarring.

In disciform degeneration the basal linear deposit becomes incorporated into the fibrovascular scar and the original derivation of the material is not readily apparent. Thus Green and Gass (1971) referred to the separation of the basal linear deposit from Bruch's membrane by fibrovascular tissue as a splitting of Bruch's membrane. The segments of hyalinized basal material which become enveloped by scar tissue and which no longer show any trace of the pigment epithelium are distinct from the laminated cuticular deposits found between rows of proliferating retinal pigment cells. The latter material is also eosinophilic and strongly periodic acid-Schiff positive, but is of more hyaline appearance and stains blue with picro-Mallory. Cuticular material has been described in senile disciform degeneration (Verhoeff and Grossman, 1937; Frayer, 1955; Klien, 1951), fundus dystrophy

(Ashton and Sorsby, 1951), melanosis of the retina (Parsons, 1904), ringschweile of the ora in long-standing retinal detachment (Hogan and Zimmerman, 1962) and reactive proliferation of the retinal pigment epithelium (Tso and Albert, 1972), where the authors referred to it as basement membrane-like material. In several eyes in the present series the basal linear deposit resembled cuticular material, and the two deposits appear related.

DRUSEN

The incidence of eyes containing drusen in the macular region rose from 19.2 per cent in Group I to 52.5 per cent in Group V, due mainly to an increase in the granular variety. In the first three groups the drusen did not appear to affect vision, although none was located at the fovea. In Group IV, however, degeneration of the pigment epithelium was sometimes more pronounced over the larger deposits.

Drusen are a common clinical manifestation of the predisciform stage, but this investigation failed to find any histological evidence that drusen predispose to neovascularization. The drusen were not immediately related to the breaks in Bruch's membrane and any drusen in the vicinity of the new vessels appeared to be only the result of chance. Instead the vessels ramified within the basal linear deposit, and the drusen may simply be an independent manifestation of degeneration of the pigment epithelium. However, this series did not provide any information upon the relationship between drusen and pigment epithelial detachments.

In Group V drusen within the depigmented areas were observed clinically to become less prominent or to develop glistening foci of calcification. Gass (1973) noted that drusen in such an area may fade, and disappearance of some drusen was noted in the present series. Most, however, remained as calcified deposits, often partly replaced by avascular fibrous tissue.

CHOROID

Thinning of the choroid, interpreted as senile choroidal atrophy, became more common with advancing age. Clinically this was manifest as the senile tigroid fundus, the incidence of which rises sharply after the age of 75 (Sarks, 1974). This appearance has been termed depigmentation—*in situ* (Klien, 1958) and benign choroidal sclerosis (Archer, Krill, and Newell, 1971), the increased visibility of the choroidal vessels being attributed to disturbance of the overlying pigment epithelium. However, although degenerative changes in the pigment epithelium were commonly associated,

the present investigation confirmed that the prominent choroidal pattern resulted when the larger vessels occupied a greater proportion of the attenuated choroid.

Senile choroidal atrophy was noted in all groups in this series and modified the clinical picture accordingly. This was particularly evident in Group V, in which the exposed vessels sometimes remained pink and at other times showed sheathing by white lines or appeared as solid white cords. The white lines of sheathing were caused by the disproportionate thickening of the lateral walls of the vessels which were flattened in the thinned choroid. The macroscopic dissection of several specimens showed that the vessels retained sufficient transparency for any contained blood column to become visible, suggesting that vessels which appeared as solid white cords no longer contained blood. Although degenerative changes were found in some choroidal arteries identical to those found in the ageing brain, most vessels showed only normal ageing changes with the retention of wide lumina.

Comment

Although senile macular degeneration seems inextricably bound to the ageing process the lack of universality suggests it is not essential to ageing. However, the mechanisms proposed to explain normal ageing can also be applied to the degenerative changes. Hogan (1972) believes there is a gradual run-down in the metabolic activity of the retinal pigment epithelium leading to the accumulation of metabolic waste in Bruch's membrane and consequent decrease in its permeability. The basal linear deposit subsequently develops over the more abnormal segments of the membrane and at this stage histological changes can be demonstrated in the retinal pigment cells. Clinical evidence of senile macular degeneration, however, does not develop until the changes become continuous under the macula.

Thickening of the basal linear deposit is associated with progressive degeneration of the pigment epithelium. If neovascularization does not develop, or if the fibrovascular response is limited, the natural end-result of this process is geographic atrophy. Since this is an uncommon manifestation and evolves slowly, useful vision may be retained for many years. Visual loss is accelerated when new vessels lead to complications, and treatment is therefore directed to their prevention or obliteration. However, since the histological abnormalities may extend over several disc diameters, the disciform response can be multifocal and particularly endangers the fovea where the changes are generally most severe.

Prophylactic photocoagulation may come into increasing use but as Bird (1974) points out, there are as yet no means of identifying those eyes at high risk from those at low risk. Drusen have been implicated in initiating the disciform response and in this study these were noted more frequently at the stage when neovascularization occurs, but the drusen were not related to the new vessels and may represent an independent expression of the metabolic failure of the pigment epithelium. The present investigation merely indicated that the eyes most prone to neovascularization were those with a coarse pigmentary disturbance and moderate visual loss whether drusen were present or not, and that the new vessels may also develop in the absence of pigment epithelial detachments.

Summary

Clinical and pathological examination was performed on 378 eyes from 216 patients aged 43 to 97 years. This series represented eyes in which the fundi were normal or showed various manifestations of senile macular degeneration. The eyes were divided into six groups according to the histological appearance of a linear deposit at the base of the retinal pigment cells. Groups I and II were considered to represent normal ageing, Groups III and IV the progressive development of senile macular degeneration, and Groups V and VI the end-results.

Group I showed no basal linear deposit. Thickening and hyalinization of Bruch's membrane was noted as early as the fifth decade. Group II showed patchy development of the basal linear deposit in relation to thickened or basophilic segments of Bruch's membrane, or over intercapillary hyalinization extending to the level of the outer surface of the choriocapillaris. Almost all eyes in these two groups retained a normal fundus appearance but visual acuity declined with age even in the absence of other causes. In Group III the basal deposit formed a thin continuous layer associated with moderate degeneration of the retinal pigment epithelium. More than half the eyes had developed a clinical disturbance of pigmentation and in most

vision was reduced. Group IV was characterized by thickening of the deposit and more pronounced disturbance of the pigment epithelium. Clinically most eyes showed coarse pigmentary changes and vision was in the order of 6/24. 14.3 per cent of eyes in this group showed early neovascularization from the choroid. In Group V the pigment epithelium disappeared to produce circumscribed areas of depigmentation. The basal linear deposit could be traced throughout the depigmented area in most eyes. Thin fibrovascular sheets were found beneath the pigment epithelium in 41.7 per cent of eyes. Group VI represented disciform degeneration. The basal linear deposit could often be demonstrated as a disrupted hyalinized layer incorporated into the scar. Disciform degeneration was an alternative end-result to geographical atrophy. In each group the clinical and histological findings may be modified by the presence of drusen or by atrophy of the choroid.

The basal linear deposit consisted of banded fibres embedded in granular material lying between the plasma infoldings and the basement membrane of the retinal pigment epithelium. This deposit seems to be a manifestation of gradual failure of the pigment epithelium and proved to be the most suitable criterion by which to study the natural history of senile macular degeneration.

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