

SENILE MACULAR DEGENERATION: A HISTOPATHOLOGIC STUDY*

BY *W. Richard Green*, MD

AND (BY INVITATION) *Samuel N. Key, III*, MD

NUMEROUS OBSERVERS HAVE DESCRIBED THE CLINICAL ASSOCIATION OF DRUSEN with disciform degeneration of the macula.¹⁻⁷ Others have noted that retinal pigment epithelial atrophy (areolar atrophy) also occurs with drusen in the macula.⁸⁻¹⁰ Such observations support the proposition by Gass that atrophic and exudative forms of senile macular degeneration are part of the same basic process.⁵ We undertook this histopathologic study to determine whether drusen, areolar retinal pigment epithelial atrophy, sub-retinal pigment epithelial neovascularization, and disciform degeneration coexist in eyes of patients with senile macular degeneration.

MATERIAL AND METHODS

The files of the Eye Pathology Laboratory of the Wilmer Institute were searched for adult cases of macular degeneration. Eyes with any of the following histopathologic features in the macular area were accepted as having senile macular degeneration: confluent areas of atrophy of the retinal pigment epithelium (defined as areolar or geographic atrophy), neovascularization beneath the retinal pigment epithelium or retina, drusen with serous or hemorrhagic detachment of the pigment epithelium or retina with evidence of chronicity such as degenerative changes in these structures, and fibrous tissue proliferation beneath the pigment epithelium or retina (defined as disciform degeneration).

Extramacular lesions and cases with historical or histopathologic evidence of high myopia, angioid streaks, trauma, or choroidal neoplasm in the macula were excluded. No cases with peripapillary and peripheral chorioretinal scarring, compatible with the ocular histoplasmosis syndrome, were included. Eyes with only serous fluid beneath the pigment epithelium or retina, without evidence of degeneration, were con-

*From the Eye Pathology Laboratory, Wilmer Institute and Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland. This study was supported in part by Research Grant 1R01 EY 01684-01 from the National Eye Institute, U.S.P.H.S.

sidered to have agonal changes and were excluded. Eyes with "senile macular hole" formation were not considered in this review, except when such holes were coexistent with features of senile macular degeneration.

RESULTS

We found evidence of senile macular degeneration in 176 of 211 eyes obtained from 115 cases from the following sources: 96 autopsy cases with both eyes, 8 surgical cases with one eye each and 11 autopsy cases with only 1 eye each. Most of the eyes were obtained from autopsies performed at The Johns Hopkins Hospital or from several other hospitals in the Chesapeake Bay region participating in the program of the Medical Eye Bank of Maryland. Eight eyes were surgical specimens, enucleated because of absolute glaucoma or suspicion of an intraocular neoplasm. These eyes were received during the period from 1929 through April, 1977, at the Wilmer Institute. Approximately 95% are from the period between 1968 and 1977.

Most of these eyes had been routinely processed to show the optic nerve head, macula, and pupil. Forty-seven eyes were studied further with serial sections of the macula. Five additional eyes were studied with stepped-sections through the macula at 0.1 mm intervals. Two-dimensional reconstruction maps of the macular areas of 9 eyes were prepared from the study of serial sections using an ocular micrometer, after the method of Frank, Green and Pollack,¹¹ and Small and coworkers.¹² Electron microscopic studies were conducted in five eyes. Clinical pathologic correlation was possible in 11 cases (19 eyes).

Characteristics of the 115 cases with senile macular degeneration are listed in Table 1. Men and women were affected in about equal numbers. Whites greatly outnumbered blacks, despite the fact that 42% of patients over the age of 50 autopsied at The Johns Hopkins Hospital from 1960 through 1975 were black. Most cases had bilateral macular involvement, and most of the cases with unilateral degeneration had prominent drusen in the other eye.

TABLE I: SENILE MACULAR DEGENERATION: 115 CASES
EYE PATHOLOGY LABORATORY, WILMER INSTITUTE

Sex:	66 Male, 49 Female
Race:	White, 86 Cases
	Black, 15 Cases
	Not Listed, 14 cases
Bilateral:	61 Cases
Unilateral: [*]	35 Cases (25 had only drusen in fellow eye)

*In another 19 cases, only one eye was obtained.

TABLE II: SENILE MACULAR DEGENERATION EYE PATHOLOGY LABORATORY
WILMER INSTITUTE TOTAL OF 176 EYES*

Stage of Degeneration	Number	Age Range	Median
Areolar atrophy	69 eyes	46-92	77 years
Sub-RPE neovascularization	46 eyes	47-97	79 years
Disciform degeneration	51 eyes	41-102	80 years

*Does not include 6 eyes with drusen and serous retinal and/or RPE detachment.

Distribution of the various stages of senile macular degeneration is given in Table II. This does not include 6 eyes (from 4 patients) with drusen associated with serous detachment of the retinal pigment epithelium. Over half of the eyes (97 of 172, 56.3%) had neovascularization beneath the pigment epithelium or in disciform scars. Forty-six of these 97 eyes (47.4%) might be considered to have predisciform lesions, because the new vessels beneath pigment epithelium were not associated with fibrous tissue production. Eyes with both areolar atrophy and choroidal neovascularization were counted only in the neovascular groups.

The distribution of various morphologic stages of senile macular degeneration among 96 cases in which both eyes were available for study is shown in Table III. The coexistence of the various morphologic forms of macular degeneration in the same patient is quite apparent. Out of 63 cases with choroidal neovascularization beneath the retinal pigment epithelium with or without a disciform lesion, 23 (36.5%) had drusen and choroidal neovascularization in the fellow eye. Twenty-two (34.9%) had drusen and areolar atrophy, and 14 (22.2%) only had drusen in the fellow eye. Four fellow eyes (6.3%) had no changes in the macula. In the remaining 33 cases, drusen and areolar atrophy were observed in the first eye. The fellow eyes in this group of 33 cases had drusen and areolar atrophy in 16 (48.4%) and only drusen in 11 (33.3%). The fellow eye was normal in 6 cases (18.1%).

The results of this study support the observations of Gass⁴ that persons with drusen in the macular area are prone to the development of

TABLE III: DISTRIBUTION OF MORPHOLOGIC STAGES OF SENILE MACULAR DEGENERATION
IN 96 CASES IN WHICH BOTH EYES WERE STUDIED

Findings in One Eye	Findings in Fellow Eye
Drusen and choroidal neovascularization with or without disciform lesions (63 cases)	Drusen and choroidal neovascularization 23 Drusen and areolar atrophy 22 Drusen only 14 Negative 4
Drusen and areolar atrophy (33 cases)	Drusen and areolar atrophy 16 Drusen only 11 Negative 6

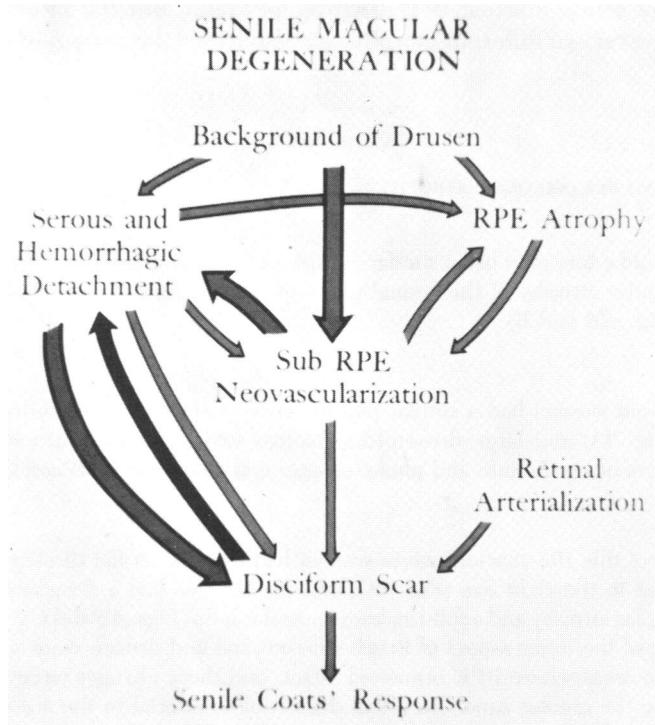


FIGURE 1

Flow diagram of the interrelationships of the different morphologic forms of senile macular degeneration. The larger and darker arrows indicate the more common pathway from drusen to disciform scarring. The smaller and lighter arrows indicate other pathways and associated features that may be observed. Older persons with drusen and diffuse thickening of the inner aspect of Bruch's membrane may develop "wet" sequelae including serous or hemorrhagic detachment of the retina and/or retinal pigment epithelium. Such persons may also develop retinal pigment epithelial (areolar) atrophy. Usually this occurs without associated serous or hemorrhagic detachment. Areolar atrophy and sub-RPE neovascularization frequently coexist, thus the arrows in both directions between these two categories. Sub-RPE neovascularization leads to serous and hemorrhagic detachment of the retinal pigment epithelium and/or the retina and this, in turn, may lead to disciform scarring. Retinal vascular contribution to the disciform lesion may occur. The new vasculature of some disciform lesions leaks profusely and produces marked intra- and subretinal exudation which may be rich in lipid material ("exudative senile maculopathy," "senile Coats' response").

areolar atrophy alone or in combination with subretinal pigment epithelial neovascularization. A scheme to illustrate the interrelationships of the various features of senile macular degeneration is illustrated in Fig. 1. Illustrations of the following selected cases demonstrate the various

features of senile macular degeneration and point out the interrelationships of the various different morphologic features of this proposed scheme.

CASE REPORTS

DRUSEN AND RPE (AREOLAR) ATROPHY

CASE 1

A 74-year-old white man had a similar picture in both eyes that included a central area of areolar atrophy of the retinal pigment epithelium (RPE) surrounded by drusen (Figs. 2A and B).

CASE 2

A 65-year-old woman had a similar picture in both eyes which included typical drusen (Fig. 3A) and large drusen-like changes with associated atrophy of the retinal pigment epithelium and photoreceptor cell layer (Figs. 3B and C).

CASE 3

Both eyes of this 102-year-old white woman had drusen. A flat disciform lesion was present in the right eye (Fig. 4A), and the left eye had a doughnut-shaped area of areolar atrophy and a full-thickness macular hole (Figs. 4B and C). Curious thickening of the inner aspect of Bruch's membrane and drusen were most conspicuous in areas where RPE remained intact, and these changes were less conspicuous in the areolar zone. Residual drusen-like material in the areolar areas suggests that drusen were previously present (Fig. 4D).

CASE 4

A 72-year-old white man had drusen in both eyes, an irregular area of areolar atrophy in the right eye and a doughnut-shaped area of areolar atrophy in the left eye. The foveal area was intact and the vision was 20/20 in both eyes. He had been seen by an ophthalmologist on numerous occasions, but unfortunately no photographs or fluorescein studies were obtained. His last examination was 8 months before his death. In the area of areolar atrophy there was loss of the RPE and photoreceptor cell layer (Figs. 5A and B). The inner nuclear layer and inner portion of the outer plexiform layer remained intact. A light scattering of lymphocytes was present in the subjacent choroid, and the choriocapillaris remained relatively intact (Fig. 5B).

CASE 5

A 93-year-old white woman had a central area of areolar atrophy. Bruch's membrane was thickened and the basement membrane of the RPE had separated from the remainder of Bruch's membrane (Figs. 6A and B). A glial preretinal membrane was present (Fig. 6B) and extended from the retina through a discontinuity in the internal limiting membrane.

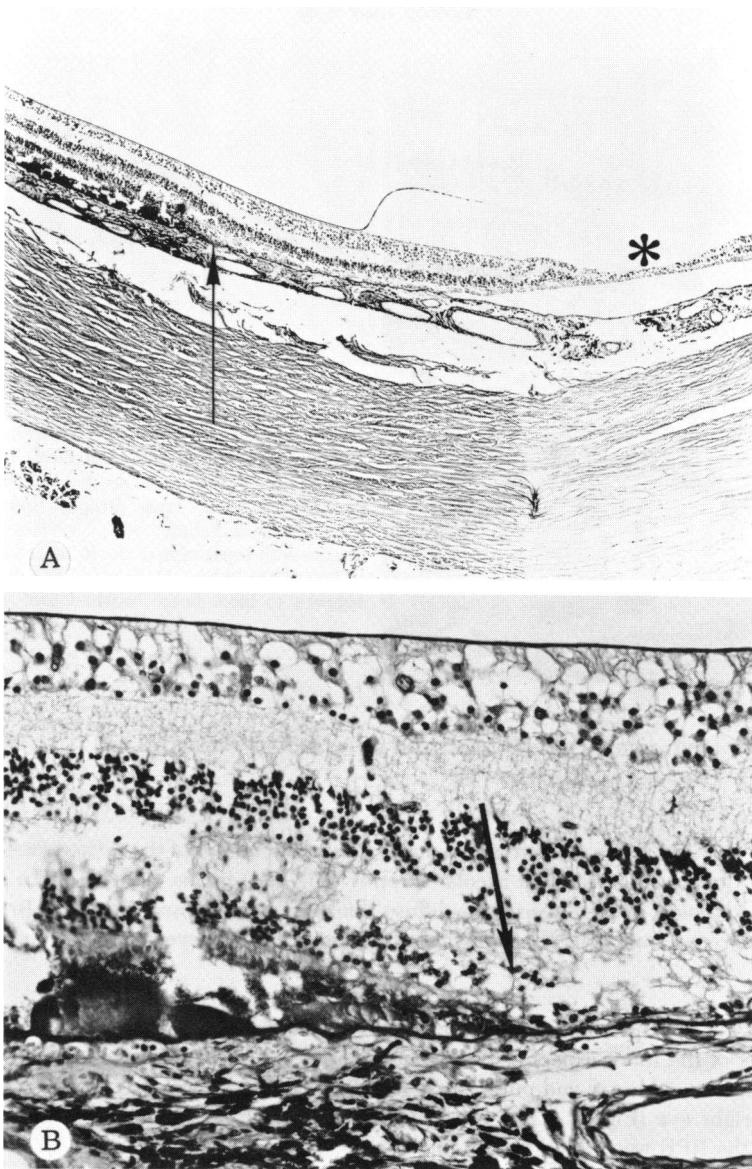


FIGURE 2

Case 1. A: Section through the foveola (asterisk) of the left eye showing RPE areolar atrophy and drusen outside the area of atrophy where RPE and retina are intact. There is total loss of the photoreceptor cell layer in the area of areolar atrophy. The arrow marks the junction between the drusen area (to the left) and areolar atrophy (to the right) (Periodic-acid Schiff, $\times 40$). B: Higher power of abrupt junction (arrow) between areolar and drusen areas (Periodic-acid Schiff, $\times 240$).

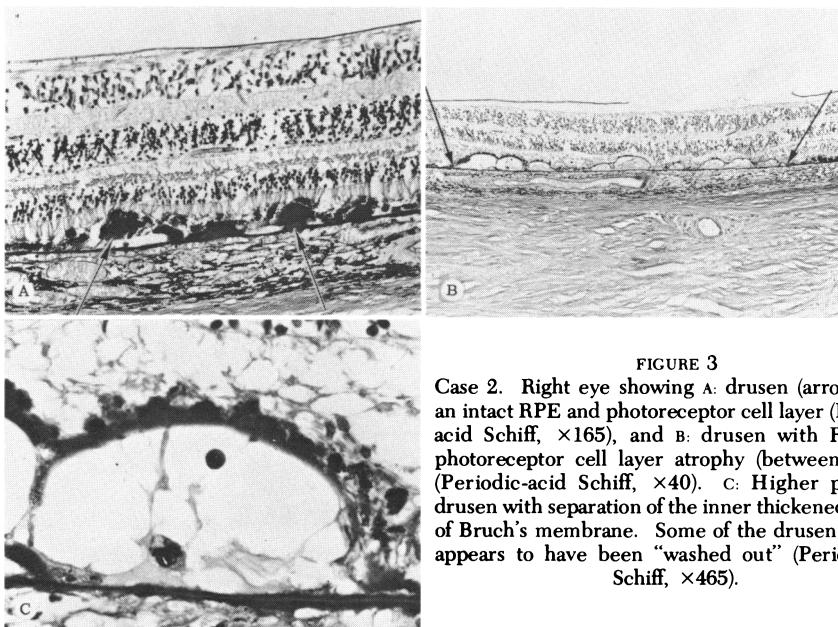


FIGURE 3

Case 2. Right eye showing A: drusen (arrows) with an intact RPE and photoreceptor cell layer (Periodic-acid Schiff, $\times 165$), and B: drusen with RPE and photoreceptor cell layer atrophy (between arrows) (Periodic-acid Schiff, $\times 40$). C: Higher power of drusen with separation of the inner thickened portion of Bruch's membrane. Some of the drusen material appears to have been "washed out" (Periodic-acid Schiff, $\times 465$).

DRUSEN AND SEROUS OR HEMORRHAGIC DETACHMENT OF RETINA OR RETINAL PIGMENT EPITHELIUM

CASE 6

A 76-year-old white woman had a small serous detachment of the retina associated with drusen (Fig. 7A) and areolar atrophy (Fig. 7B) in the right eye. In addition to typical drusen, there was diffuse thickening of the inner aspect of Bruch's membrane, areolar RPE atrophy, and drusen in the left eye.

CASE 7

Both eyes of this 88-year-old woman disclosed typical drusen and marked thickening of the inner aspect of Bruch's membrane. A serous detachment between the thickened inner and outer portion of Bruch's membrane was also present in the right eye (Fig. 8). The photoreceptor cell layer was partially degenerated and the RPE was intact, but attenuated.

CASE 8

The left eye of this 49-year-old white man was enucleated because of the suspicion of a malignant melanoma in the macular area with some subretinal hemorrhage. Numerous drusen were observed in the posterior pole of both eyes by several ophthalmologists. Microscopic examination disclosed a hemorrhagic detachment of the retinal pigment epithelium (Fig. 9A). Numerous

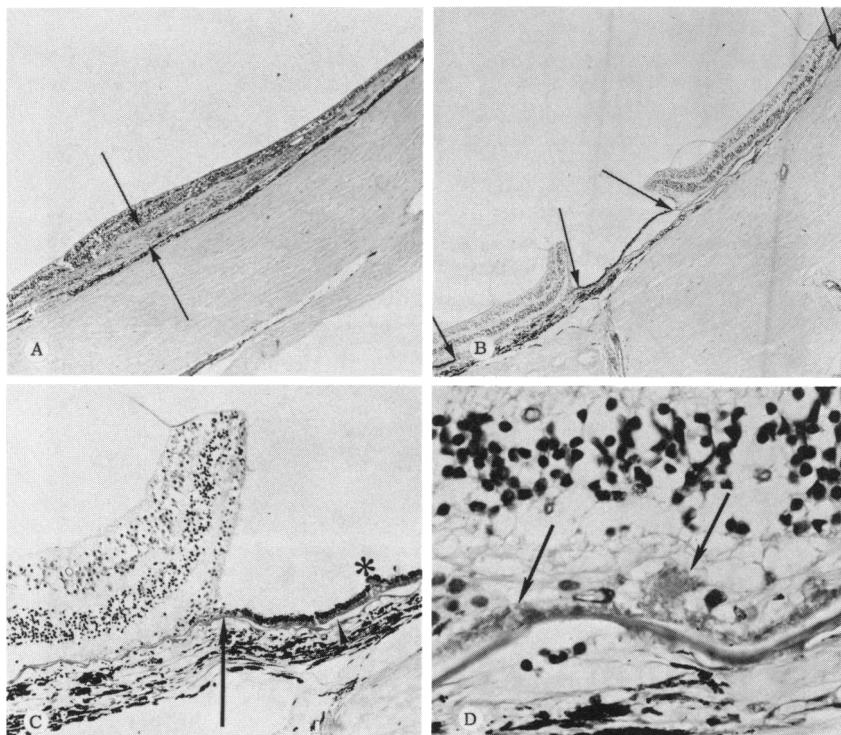


FIGURE 4

Case 3. A: Flat disciform lesion (between arrows) of the right eye (Hematoxylin and eosin, $\times 19$). B: Doughnut-shaped area of areolar atrophy of retinal pigment epithelium and photoreceptor cell layer (between arrows). A macular hole is present in the foveola where the retinal pigment epithelium is intact (Periodic-acid Schiff, $\times 19$). C: Higher power of junction (arrow) between areolar area and central zone where retinal pigment epithelium is intact and there is prominent thickening of the inner aspect of Bruch's membrane (arrowhead) and drusen (asterisks) (Periodic-acid Schiff, $\times 100$). D: Areolar area showing residual drusen-like material (arrows) (Periodic-acid Schiff, $\times 385$).

drusen were present, and of particular interest was the presence of drusen that were detached along with the retinal pigment epithelium (Fig. 9B). No disciform process was present. Serial sections were not obtained and the break in Bruch's membrane was not identified.

CASE 9

The left eye of this 81-year-old black woman with opaque media was enucleated because of blindness and pain from neovascular glaucoma. There were many other abnormalities seen, but the interesting feature in this context was a hemorrhagic intra-Bruch's-membrane detachment in the macular area. Drusen are present, along with the detached retinal pigment epithelium (Fig. 10).

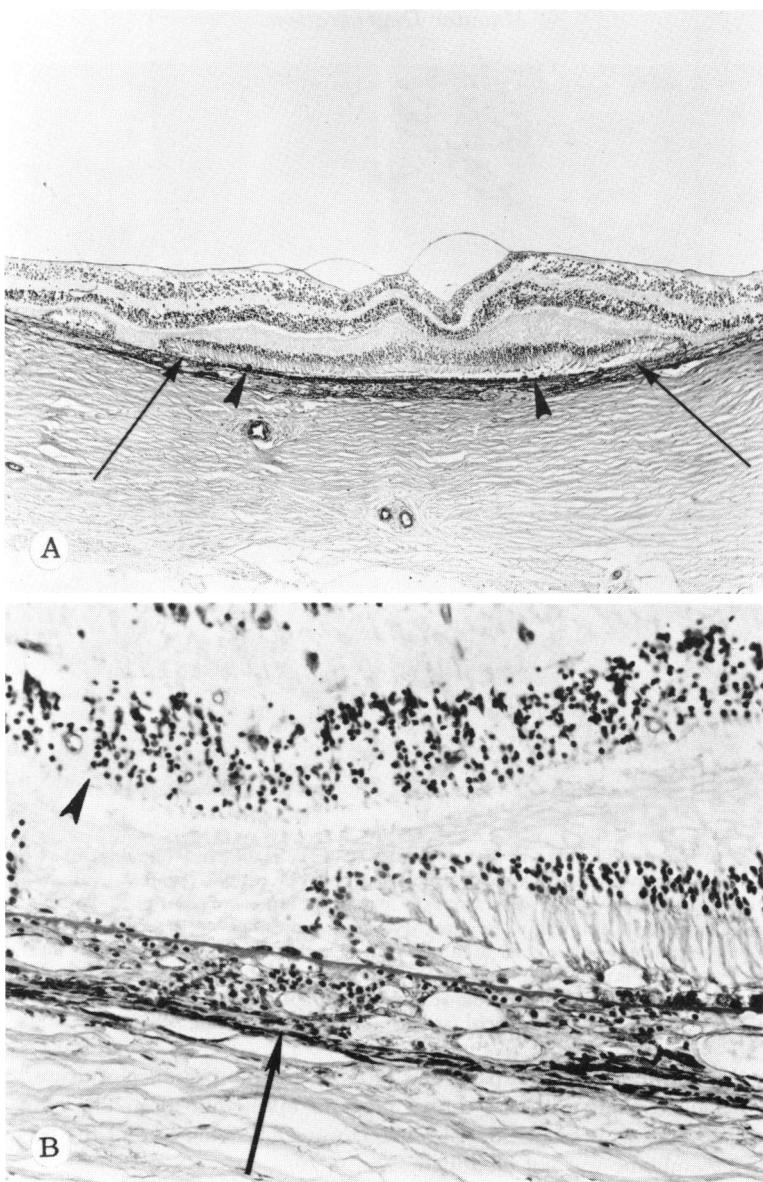


FIGURE 5

Case 4. A: Ring-shaped area of areolar atrophy of retinal pigment epithelial and photoreceptor cell layer. Centrally (between arrows) the retinal pigment epithelium and photoreceptor cell layers are intact, except for an occasional druse (arrowhead) (Periodic-acid Schiff, $\times 40$). B: Higher power of abrupt junction between areolar area and central intact zone. The inner nuclear layer is intact in the areolar area (arrowhead) and a lymphocytic infiltration is present in the choroid (arrow) (Periodic-acid Schiff, $\times 240$).

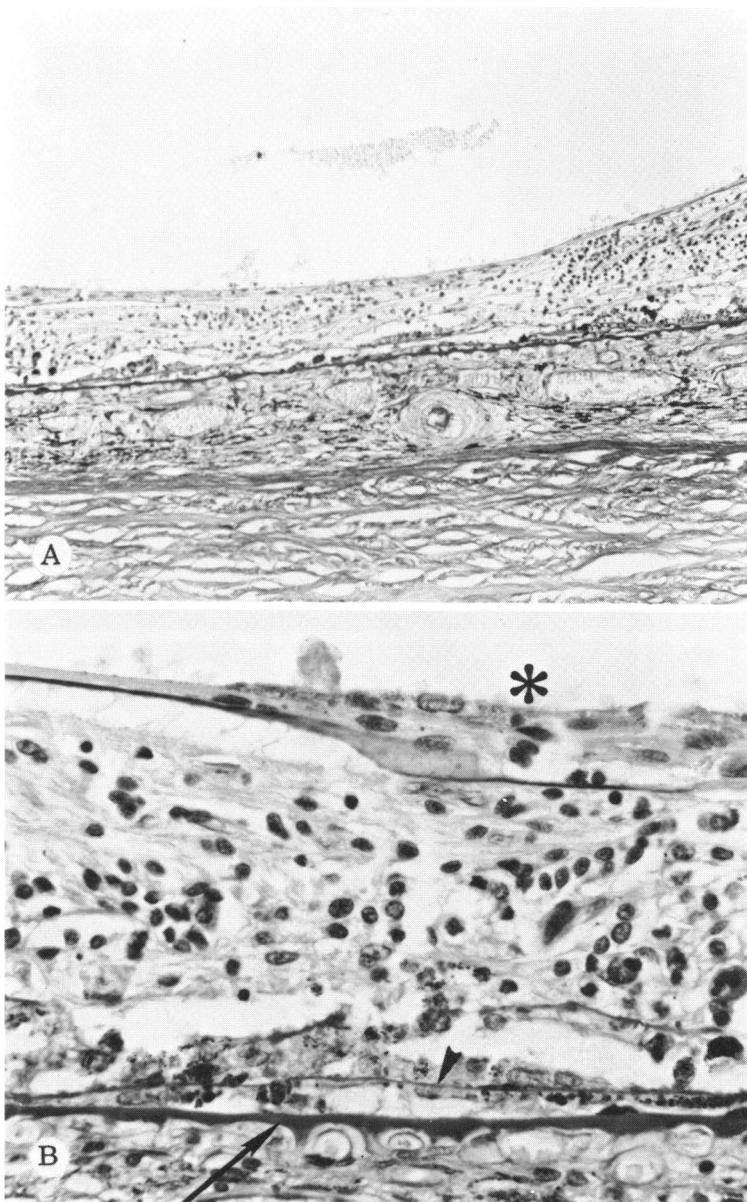


FIGURE 6

Case 5. A: Central area of areolar atrophy (Periodic-acid Schiff, $\times 120$). B: Higher power showing prominent thickening of Bruch's membrane (arrow) and separation of the basement membrane of the retinal pigment epithelium (arrowhead) from the remainder of the membrane. A glial cell preretinal membrane (asterisk) is present (Periodic-acid Schiff, $\times 500$).

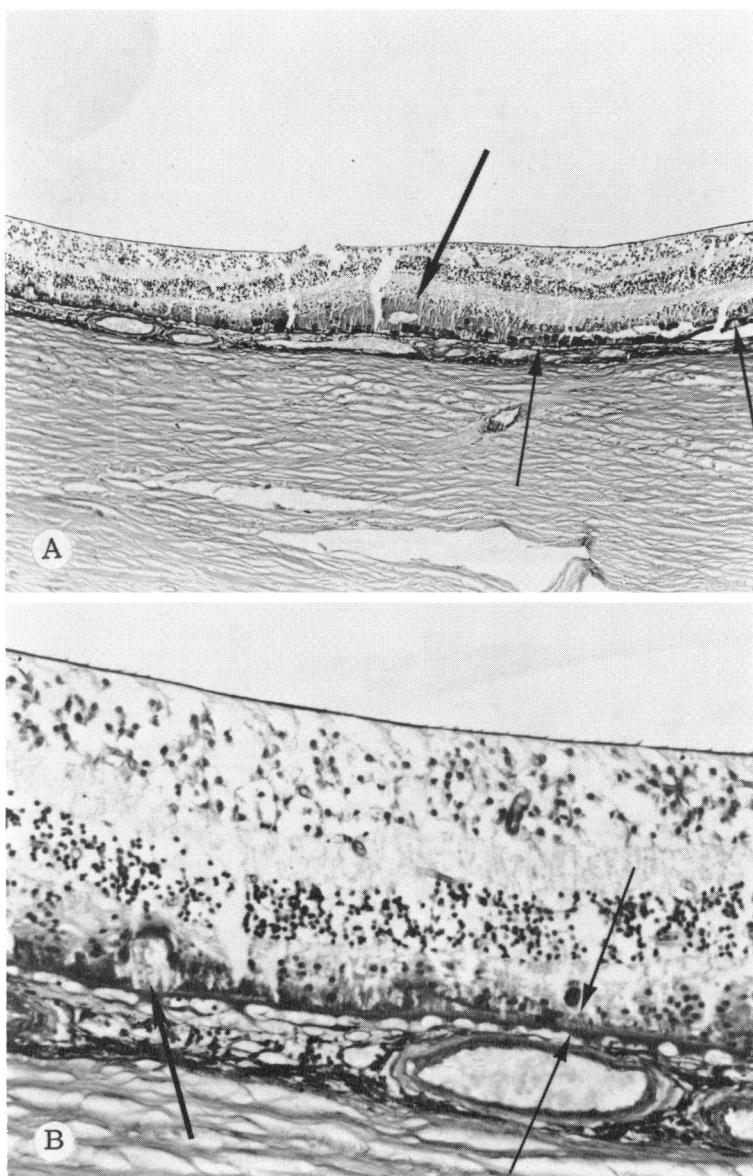


FIGURE 7

Case 6. A: Small serous detachment of retina (large arrow) associated with drusen (small arrows) (Periodic-acid Schiff, $\times 40$). B: Adjacent area showing drusen (large arrow), thickening of Bruch's membrane (between small arrows), and atrophy of retinal pigment epithelium and the photoreceptor cell layer (Periodic-acid Schiff, $\times 210$).

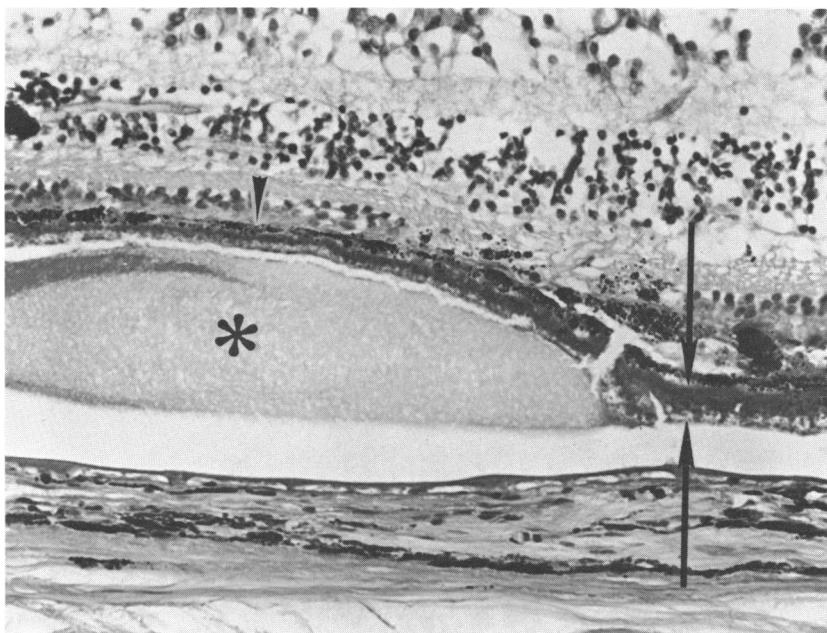


FIGURE 8

Case 7. Macular area of right eye showing marked thickening of the inner aspect of Bruch's membrane (between arrows), and a serous intra-Bruch's-membrane (subretinal pigment epithelial) detachment. The overlying retinal pigment epithelium (arrowhead) is intact, but attenuated. There is thinning of the photoreceptor cell layer (Periodic-acid Schiff, $\times 245$).

CASE 10

An 81-year-old woman had been followed for many years for senile macular degeneration. Drusen in the posterior pole of both eyes had been observed. There had been no ophthalmologic examination in the last several years of her life. Serial sections were prepared through the macular area of the left eye, and through a portion of the right eye. Portions of the macular area of the right eye were studied by electron microscopy. A single, moderately large serous detachment of the retinal pigment epithelium was present within the parafoveal area of the left eye (Fig. 11). A two-dimensional reconstruction prepared from a study of serial sections illustrates the location, size and shape of the large serous detachment of the RPE (Fig. 12). Retinal pigment epithelial hyperplasia and migration into the retina were present in one area (Fig. 13A). There was diffuse thickening of the inner aspect of Bruch's membrane, as well as nodular drusen-like appearances. The serous material was located between the thickened inner aspect and the remaining portion of Bruch's membrane. Nodular drusen-like

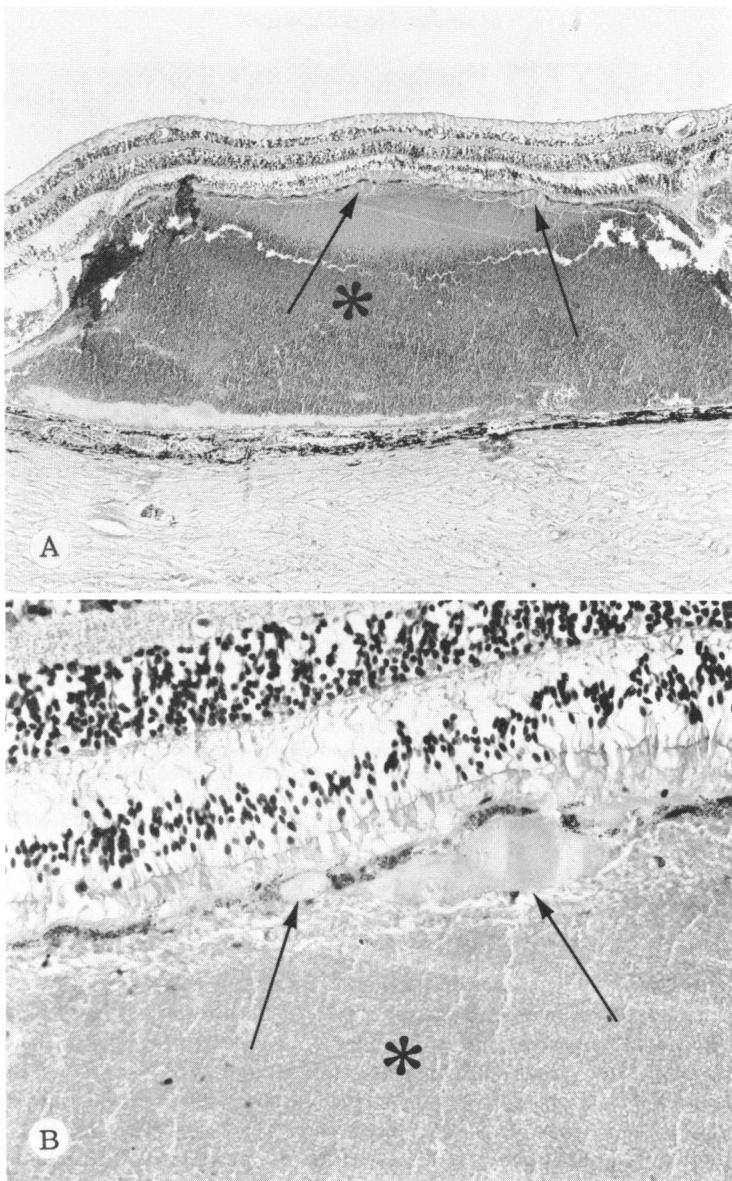


FIGURE 9

Case 8. A: Hemorrhagic detachment of retinal pigment epithelium (asterisk) in an eye that was considered to have a malignant melanoma. Drusen are detached (arrows) along with the retinal pigment epithelium (Hematoxylin and eosin, $\times 40$). B: Higher power illustrating drusen (arrows) along with retinal pigment epithelium that have been detached by hemorrhage (asterisk). The retinal pigment epithelium is intact but attenuated, and the photoreceptor cell layer is generally intact (Hematoxylin and eosin, $\times 240$).

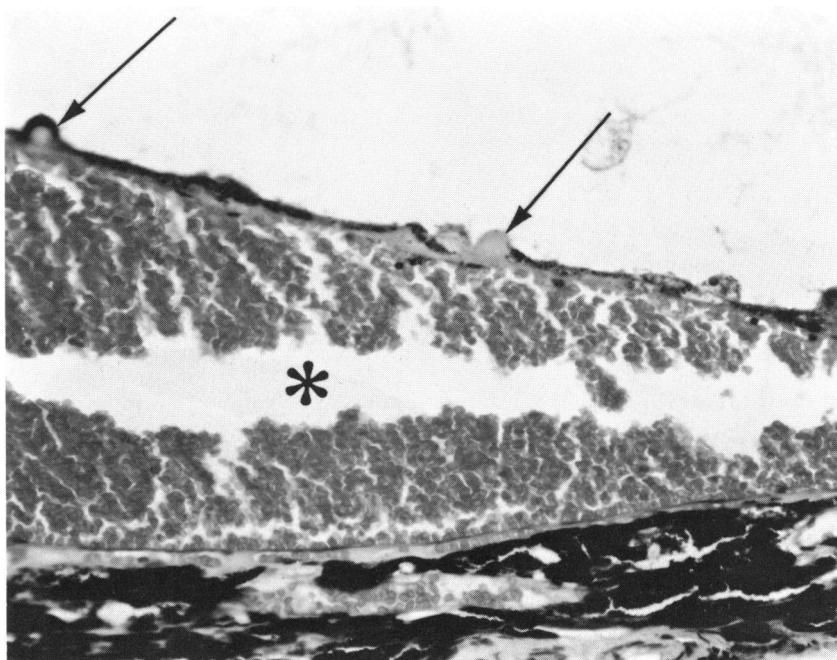


FIGURE 10

Case 9. Hemorrhagic intra-Bruch's membrane detachment (asterisk). Drusen (arrows) and retinal pigment epithelium are detached (Hematoxylin and eosin, $\times 240$).

lesions are detached along with the markedly thickened inner aspect of Bruch's membrane (Fig. 13B). Localized areas of calcification were present within the larger area of serous detachment of the retinal pigment epithelium (Fig. 13C), as well as within several individual drusen (Fig. 13D).

Electron microscopic study disclosed the retinal pigment epithelium to have a normal basement membrane. The inner collagenous zone of Bruch's membrane was markedly thickened due to accumulation of small vesicles, small electron-dense particles and frequent fibrils. The elastic layer of Bruch's membrane was essentially normal. The outer collagenous zone showed mild thickening with accumulation of similar structures as noted above. This accumulation was prominent in some areas, resulting in broadening of the intercapillary septae. In some areas, a few deposits of wide-spaced collagen were noted in the thickened inner portion of Bruch's membrane. The serous detachment occurred within the thickened inner collagenous zone of Bruch's membrane and contained fragments of cellular debris, membranous structures and electron-dense material, but no disks of the outer segments (Fig. 14).

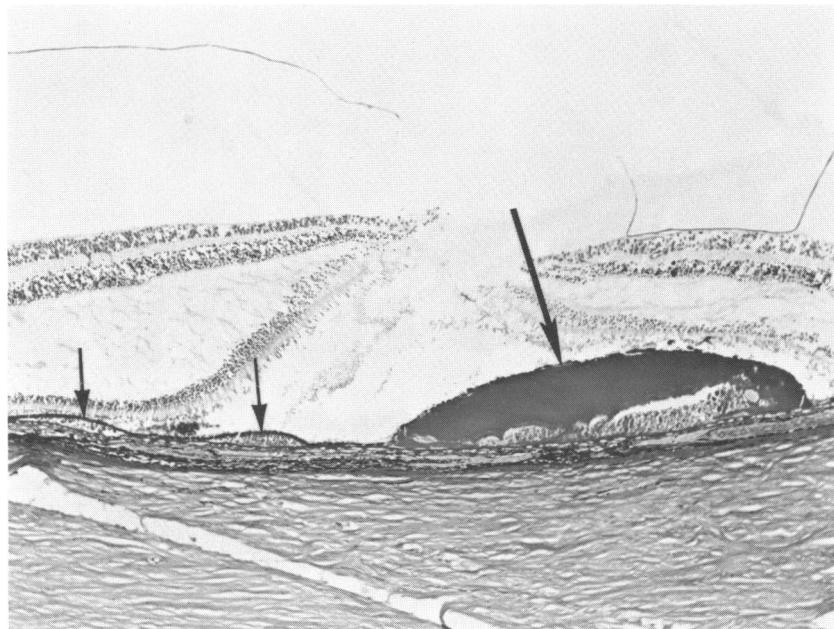


FIGURE 11

Case 10. One large (large arrow) and two smaller areas (small arrows) of serous detachment of the retinal pigment epithelium in the macula of the left eye (Periodic-acid Schiff, $\times 50$).

DRUSEN AND SUBRETINAL PIGMENT EPITHELIAL NEOVASCULARIZATION

CASE 11

Both eyes of this 87-year-old white man had drusen in the posterior pole. In addition, there was areolar atrophy in the right eye and subretinal pigment epithelial neovascularization in the left eye (Fig. 15).

CASE 12

This 78-year-old white man had many drusen in the left eye (Fig. 16) and drusen with subretinal pigment epithelial neovascularization in the right eye (Figs. 17A and B). Two-dimensional reconstruction from study of serial sections through most of the lesion illustrates the relationship of three breaks in Bruch's membrane, sub-RPE neovascularization and retinal pigment epithelial changes (Fig. 18).

DRUSEN, AREOLAR ATROPHY AND SUBRETINAL PIGMENT EPITHELIAL NEOVASCULARIZATION

CASE 13

Both eyes of this 78-year-old black woman disclosed similar changes, including drusen (Figs. 19A and B), a break in Bruch's membrane (Figs. 19B and D), sub-

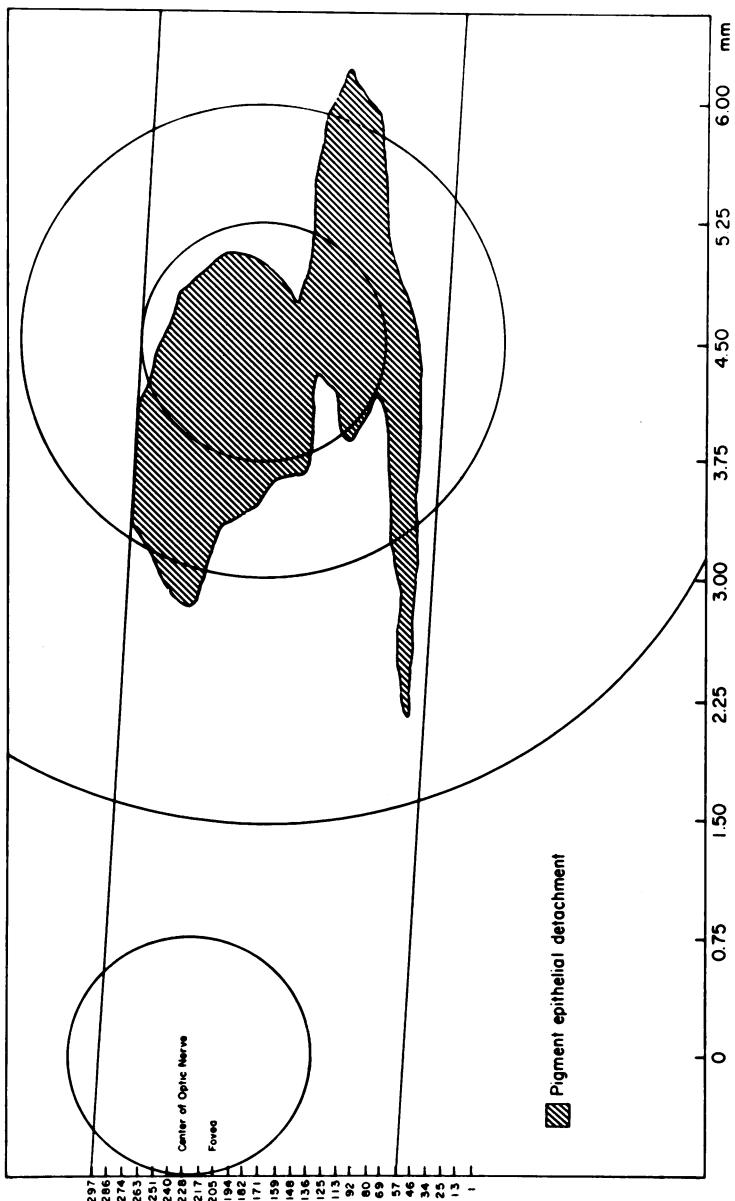


FIGURE 12
Case 10. Two-dimensional reconstruction from study of serial sections showing the size and location of the large serous detachment of the retinal pigment epithelium.

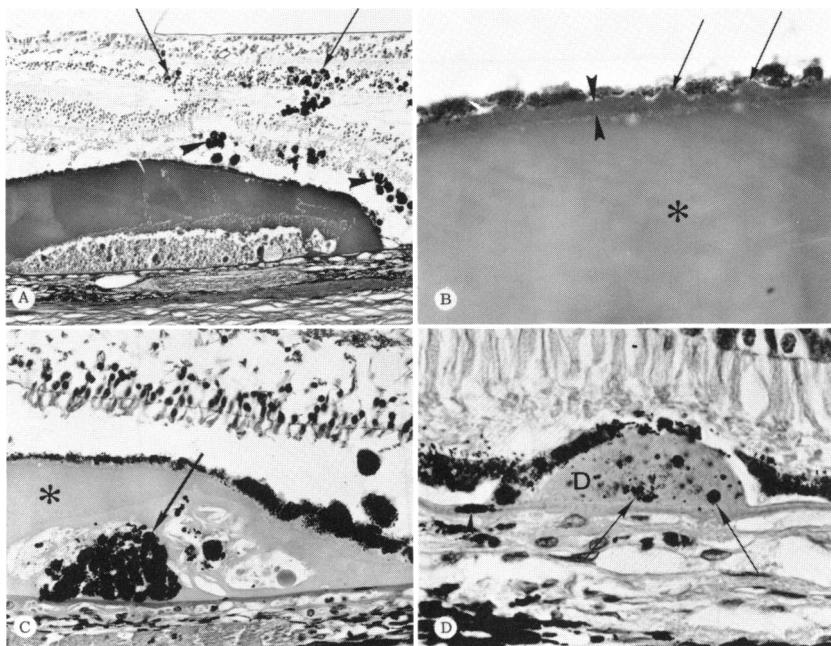


FIGURE 13

Case 10. A: Different level of serous retinal pigment epithelial detachment showing rounded-up pigment-containing cells that are located in the subretinal space (arrowheads) and have migrated into the retina (arrows) (Periodic-acid Schiff, $\times 95$). B: Higher power illustrating the markedly thickened and detached inner portion of Bruch's membrane (between arrowheads). Nodular areas or drusen (arrows) are also detached by a dense proteinaceous material (asterisk) located between the two layers of Bruch's membrane (Periodic-acid Schiff, $\times 390$). C: Different level of the large serous detachment of the retinal pigment epithelium (asterisk) showing a nodular aggregate of calcium (arrow). (Von Kossa, $\times 170$). D: Partially calcified druse (D) near large serous detachment of the retinal pigment epithelium. The small black-staining particles in the druse are calcium (arrows). Spotty calcification of Bruch's membrane is also present (arrowhead) (Von Kossa, $\times 440$).

retinal pigment epithelial neovascularization (Figs. 19B, C, and D), and areolar atrophy (Figs. 19B, D, and E).

CASE 14

This 70-year-old man had drusen in the posterior pole of both eyes in association with a break in Bruch's membrane and choroidal neovascularization. Areolar atrophy of the retinal pigment epithelium was present over portions of this new vascular membrane in both eyes (Fig. 20).

CASE 15

Both eyes of this 74-year-old white man disclosed senile macular degeneration with marked thickening of the inner aspect of Bruch's membrane associated

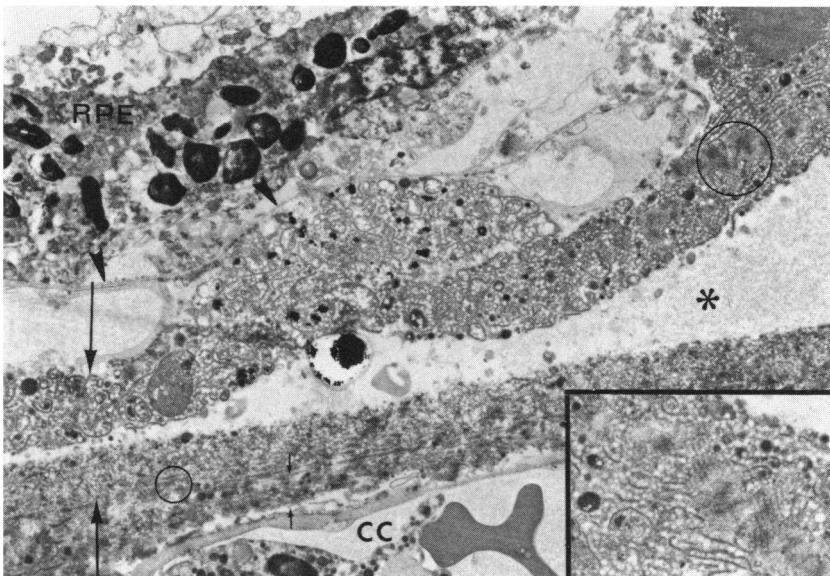


FIGURE 14

Case 10. Electron microscopic appearance of Bruch's membrane in the right eye. The retinal pigment epithelial basement membrane is intact and normal (arrowheads). The inner collagenous zone of Bruch's membrane is greatly thickened (between larger arrows) by the accumulation of small vesicles, electron-dense particles, fibrils, and clusters of widely-spaced collagen (large circle and inset). The middle-elastic layer of Bruch's membrane (small circle) is essentially normal. The outer collagenous zone (between smaller arrows) is mildly thickened with accumulation of material similar to that seen in the inner zone. Splitting of the thickened inner collagenous zone (asterisk) has occurred with the accumulation of a finely granular material, membranous structures, and electron-dense particles (CC—choriocapillaris) ($\times 3,950$, inset $\times 6,560$).

with areolar atrophy of the retinal pigment epithelium (Figs. 21A and B). Intra-Bruch's-membrane neovascularization was present in the right eye in an area of areolar RPE atrophy (Fig. 21C).

CASE 16

The following clinicopathologic correlation also illustrates the coexistence of areolar atrophy and subretinal pigment epithelial neovascularization. This 84-year-old white man was first seen at the Wilmer Institute in December, 1974, because of a spontaneous conjunctival hemorrhage. At that time, his visual acuity was 20/50 in the right eye and 20/40 in the left. Open-angle glaucoma was diagnosed, and he was followed for that reason. Both fundi showed extensive peripapillary atrophy and areolar atrophy in the parafoveal regions (Figs. 22A and B). Neovascularization was neither suspected clinically nor shown angiographically (perhaps because only late frames were taken). In April, 1975, four months after

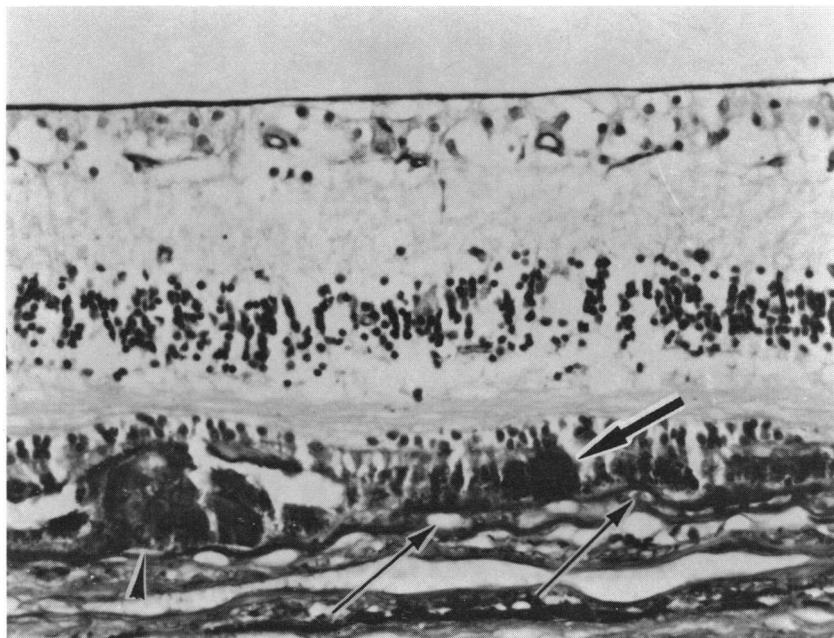


FIGURE 15

Case 11. Left eye showing drusen (arrowhead) and subretinal-pigment-epithelial (intra-Bruch's membrane) neovascularization (smaller arrows). The retinal pigment epithelium is intact, but shows some clumping (larger arrow) (Periodic-acid Schiff, $\times 280$).

the photographs and angiograms, he died following a stroke. Both eyes were obtained at autopsy.

Microscopic examination of the right eye disclosed atrophy of the chorio-capillaris, retinal pigment epithelium, photoreceptors, and outer plexiform layer of the retina around the optic nerve head and near the fovea (Fig. 23A). Bruch's membrane was diffusely calcified, with numerous artifactitious breaks. Scattered drusen were located in the midperiphery. In areas of residual choriocapillaris and pigment epithelium, there were small neovascular membranes, supplied through tiny breaks in Bruch's membrane, located in the perifoveal region and nasal to the optic nerve head (Fig. 23B). The relationships of these findings are depicted in the reconstruction map (Fig. 24).

The left eye showed the same atrophic changes around the optic nerve head and near the fovea, as shown in the map (Fig. 25). Within the zone of atrophy nasally, multiple large breaks in Bruch's membrane were present (Fig. 23C). No neovascularization had occurred, presumably due to the loss of subjacent choroid.

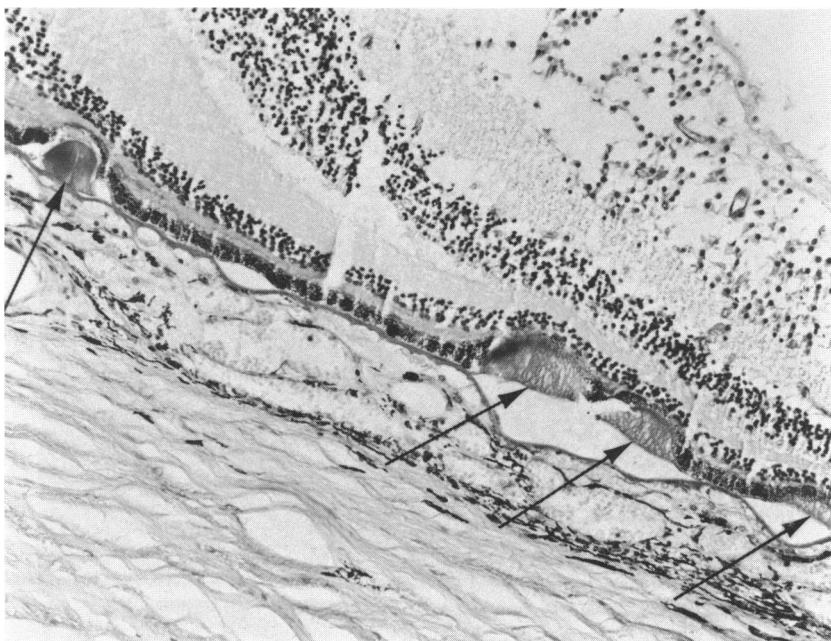


FIGURE 16

Case 12. Section of the left eye showing drusen (arrows) (Periodic-acid Schiff, $\times 180$).

DRUSEN, SUBRETINAL PIGMENT EPITHELIAL NEOVASCULARIZATION AND SEROUS AND/OR HEMORRHAGIC RETINAL DETACHMENT

CASE 17

This case illustrates the development of subretinal pigment epithelial neovascularization in the context of confluent drusen in the macula and the development of serosanguinous detachment of the retina. In 1968, this white woman complained of decreased vision, at the age of 56 years. Unfortunately, the physician's records were destroyed, so that her visual acuity is not known. She was found to have scattered drusen in the posterior pole of both eyes. The right eye had confluent drusen and several small hemorrhages around the fovea (Fig. 26). Fluorescein angiography (1968) demonstrated drusen and either confluent drusen or small serous detachments of the pigment epithelium (Figs. 27A and B). Although neovascularization was to be expected due to the presence of hemorrhage, the angiogram failed to show it, perhaps because the blood blocked fluorescence. The left eye also had confluent drusen in the macula (Fig. 28). Angiographically, these showed up as transmission defects, with late staining (Figs. 29A and B).

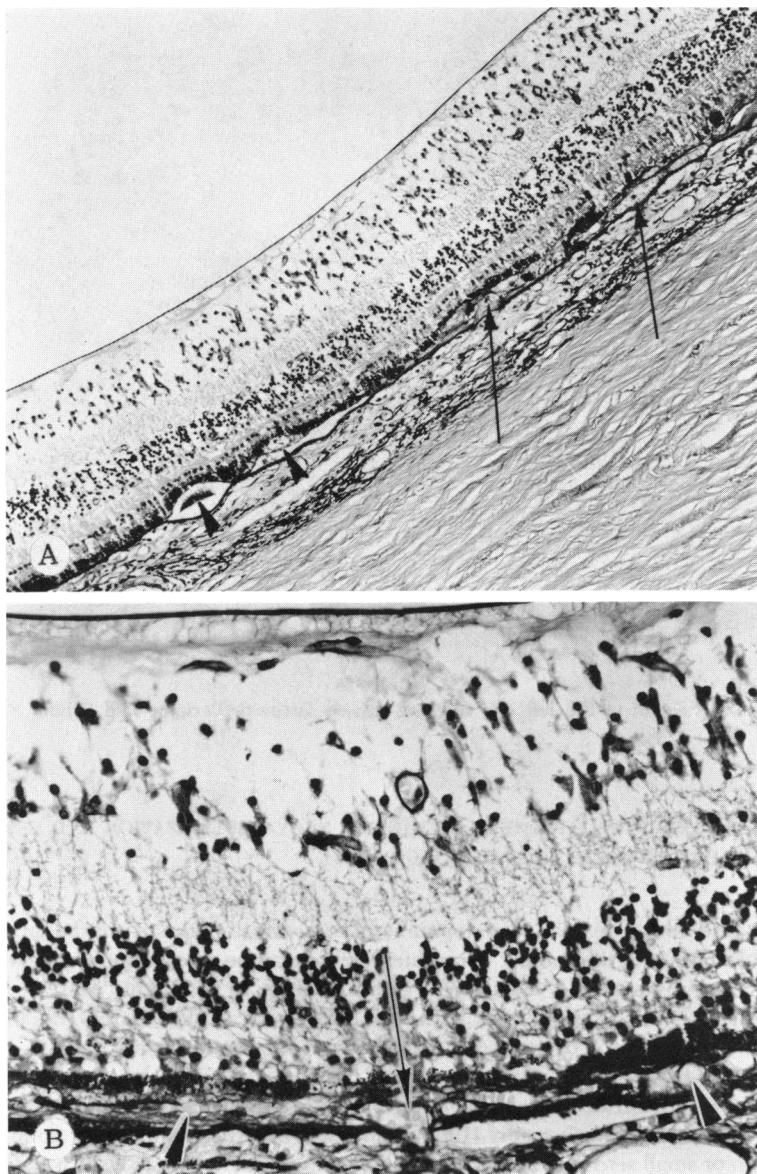


FIGURE 17

Case 12. A: Right eye with drusen (arrowheads) and subretinal-pigment-epithelial neovascularization (arrows) (Periodic-acid Schiff, $\times 105$). B: One of three breaks (arrow) in Bruch's membrane through which choroidal vessels extend to form the subretinal pigment epithelium vascular membrane (arrowheads) (Periodic-acid Schiff, $\times 290$).

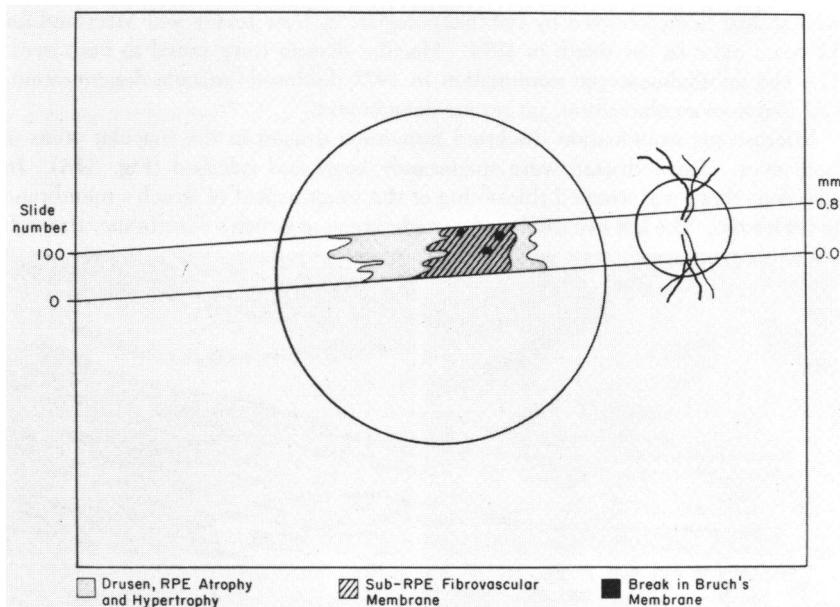


FIGURE 18

Case 12. Two-dimensional reconstruction of the macular lesion of the right eye from the study and mapping of serial sections. It illustrates the relative size and location of the breaks in Bruch's membrane, subretinal pigment epithelial neovascularization and retinal pigment epithelial changes.

Four years later, at the age of 60, she died of leukemia. An autopsy was performed, and the eyes were obtained for histopathologic examination. Neither eye had leukemia involvement. Both eyes had, by this time, subretinal pigment epithelial neovascularization with exudative detachment of the macula.

An extensive subretinal pigment epithelial neovascular membrane was present in the right eye and was associated with a serosanguinous retinal detachment (Fig. 30A). Drusen were present in adjacent areas (Fig. 30B). Serial sections through a portion of the lesion were prepared. Two-dimensional reconstruction of the lesion is shown in Fig. 31. The break in Bruch's membrane was not included in these sections.

Serial sections through the macular area of the left eye disclosed a similar extensive subretinal pigment epithelial vascular membrane and serosanguinous retinal detachment (Fig. 32A). A single break in Bruch's membrane was found, through which choroidal vessels traversed (Fig. 32B). The relationships of these features are depicted in the two-dimensional reconstruction from study of the serial sections (Fig. 33).

CASE 18

The following case illustrates the coexistence of drusen, intra-Bruch's-membrane neovascularization, and serous detachment of the retina. This 84-year-old white

woman had been followed by ophthalmologists in New Jersey and Maryland for 15 years prior to her death in 1974. Macular drusen were noted in both eyes. The last ophthalmoscopic examination in 1972 disclosed "macula degeneration, OU (No neovascularization, no serous detachment)."

Microscopic examination disclosed numerous drusen in the macular areas of both eyes. Some drusen were moderately large and calcified (Fig. 34A). In addition, there was marked thickening of the inner aspect of Bruch's membrane in both eyes. The left eye disclosed a single break in Bruch's membrane, through

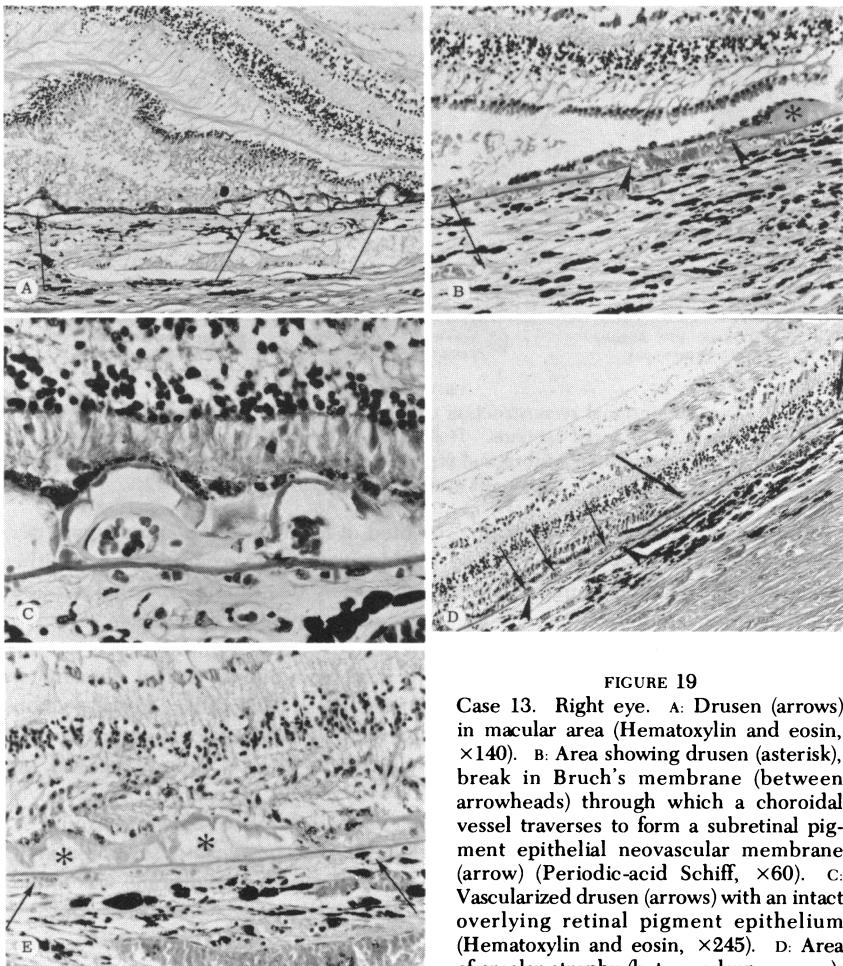


FIGURE 19

Case 13. Right eye. A: Drusen (arrows) in macular area (Hematoxylin and eosin, $\times 140$). B: Area showing drusen (asterisk), break in Bruch's membrane (between arrowheads) through which a choroidal vessel traverses to form a subretinal pigment epithelial neovascular membrane (arrow) (Periodic-acid Schiff, $\times 60$). C: Vascularized drusen (arrows) with an intact overlying retinal pigment epithelium (Hematoxylin and eosin, $\times 245$). D: Area of areolar atrophy (between large arrows), break in Bruch's membrane (between arrowheads) and subretinal pigment epithelial neovascularization (small arrows) (Masson trichrome, $\times 65$). E: Areolar atrophy in an area of drusen (asterisks). Photoreceptor cell layer is markedly degenerated, but the inner nuclear layer and the choriocapillaris (between arrows) are intact (Masson trichrome, $\times 245$).

break in Bruch's membrane (between arrowheads) and subretinal pigment epithelial neovascularization (small arrows) (Masson trichrome, $\times 65$). E: Areolar atrophy in an area of drusen (asterisks). Photoreceptor cell layer is markedly degenerated, but the inner nuclear layer and the choriocapillaris (between arrows) are intact (Masson trichrome, $\times 245$).

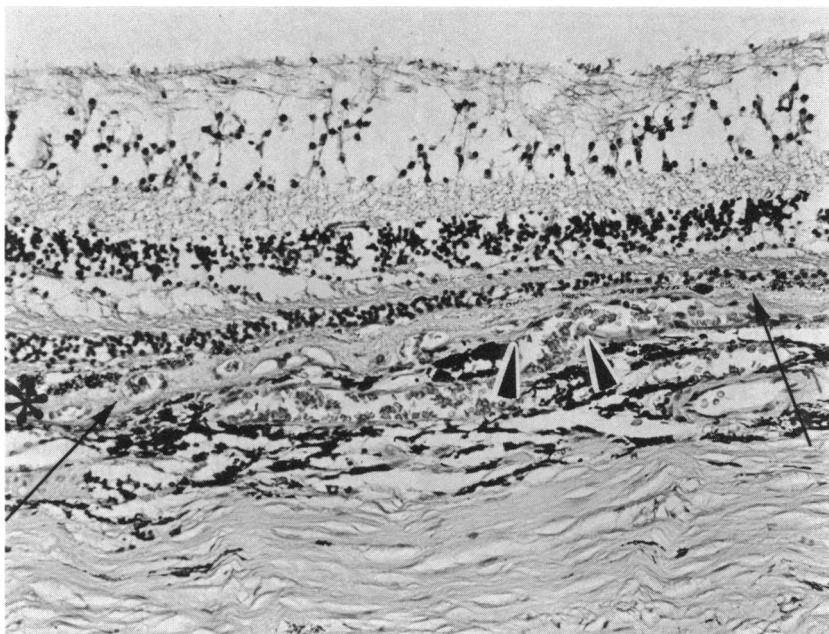


FIGURE 20

CASE 14. Areolar atrophy of retinal pigment epithelium over a choroidal neovascular membrane (arrows). Section also shows a break in Bruch's membrane (arrowheads) through which a choroidal vessel traverses to form the subretinal and subretinal pigment epithelial vascular membrane (asterisk) (Hematoxylin and eosin, $\times 150$).

which choroidal vessels traversed (Fig. 34B) and formed an extensive web of intra-Bruch's-membrane neovascularization. The retinal pigment epithelium was generally intact over the neovascularization, but displayed areas of partial drop-out and some clumping of pigment. In addition, a large area of serous detachment of the foveal area, similar to that seen in central serous retinopathy, was present (Fig. 34C).

CASE 19

This 74-year-old white man was found to have what grossly was thought to be a small disciform lesion in the fovea of the right eye (Fig. 35A). Serial sections through most of the lesion disclosed a serous detachment of the fovea (Figs. 35B and C) associated with a small area of subretinal pigment epithelial neovascularization (Fig. 35C) and a single small break in Bruch's membrane (Fig. 35D). A small area of serous detachment of the retinal pigment epithelium was present. At that point there was a discontinuity in the retinal pigment epithelium with proteinaceous material in continuity between the subretinal and

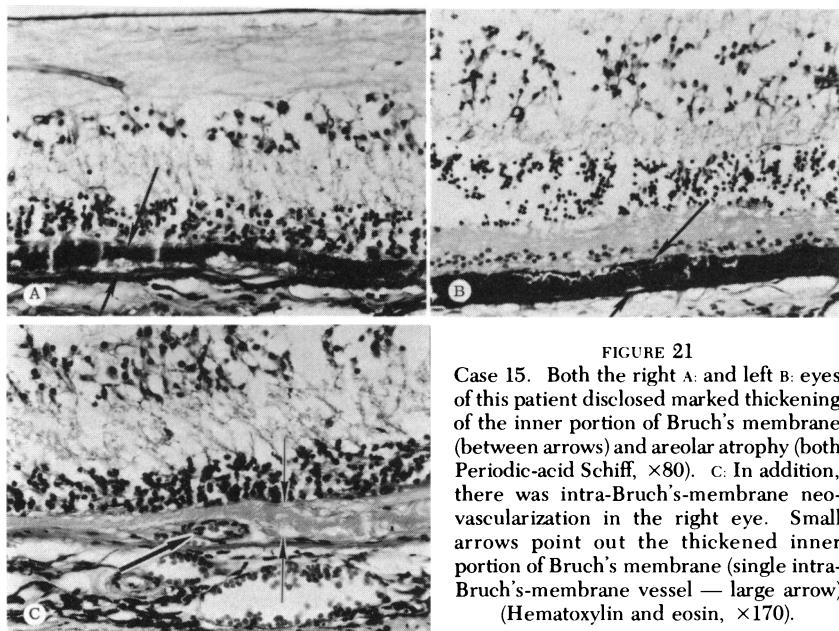


FIGURE 21

Case 15. Both the right A. and left B. eyes of this patient disclosed marked thickening of the inner portion of Bruch's membrane (between arrows) and areolar atrophy (both Periodic-acid Schiff, $\times 80$). C. In addition, there was intra-Bruch's-membrane neovascularization in the right eye. Small arrows point out the thickened inner portion of Bruch's membrane (single intra-Bruch's-membrane vessel — large arrow) (Hematoxylin and eosin, $\times 170$).

subretinal pigment epithelial areas (Fig. 35E). Two-dimensional reconstruction of the macular lesion (Fig. 35F) disclosed the relative size and relationship of these features. Rare drusen were present in the right eye and the left eye was not remarkable, except for moderate thickening of Bruch's membrane.

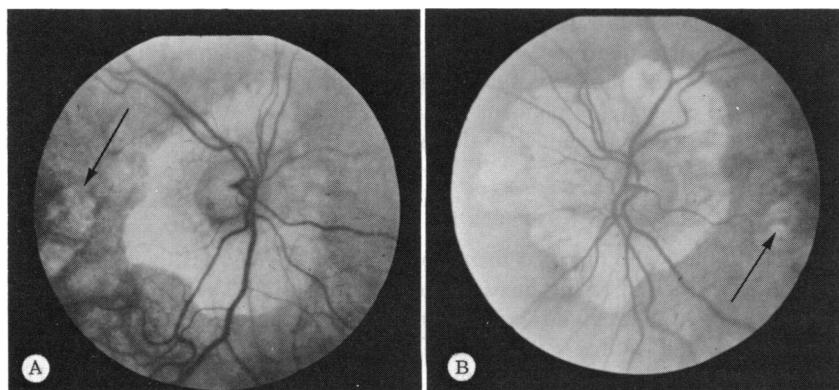


FIGURE 22

Case 16. Right A. and left B. eyes showing peripapillary atrophy and areolar atrophy in the macula of both eyes (arrow).

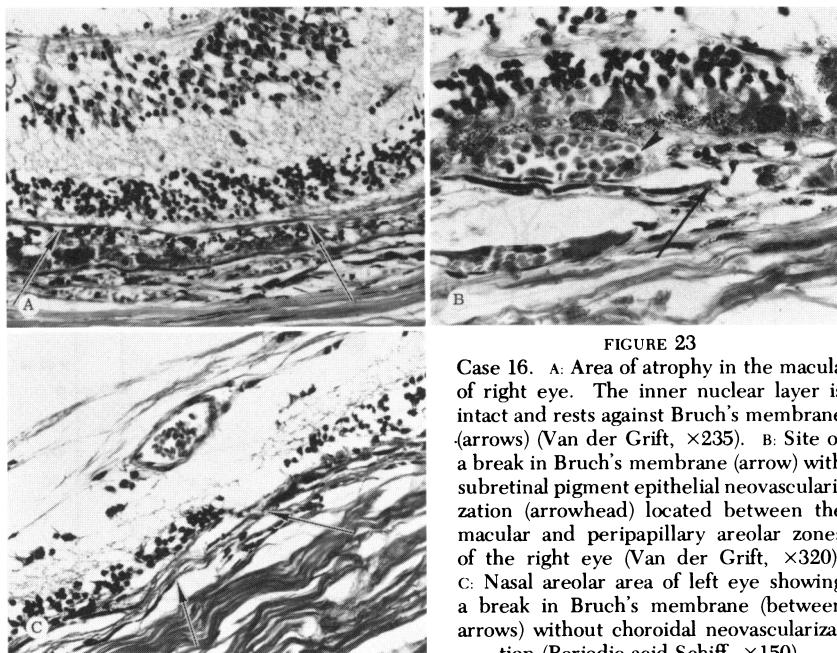


FIGURE 23

Case 16. A: Area of atrophy in the macula of right eye. The inner nuclear layer is intact and rests against Bruch's membrane (arrows) (Van der Grift, $\times 235$). B: Site of a break in Bruch's membrane (arrow) with subretinal pigment epithelial neovascularization (arrowhead) located between the macular and peripapillary areolar zones of the right eye (Van der Grift, $\times 320$). C: Nasal areolar area of left eye showing a break in Bruch's membrane (between arrows) without choroidal neovascularization (Periodic-acid Schiff, $\times 150$).

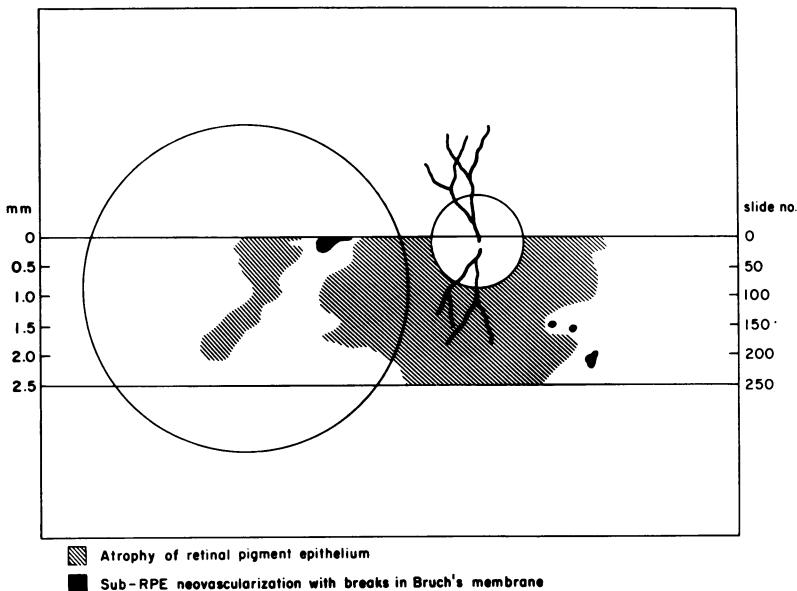


FIGURE 24

Case 16. Two-dimensional reconstruction of the right eye mapping the macular and peripapillary lesions and breaks in Bruch's membrane.

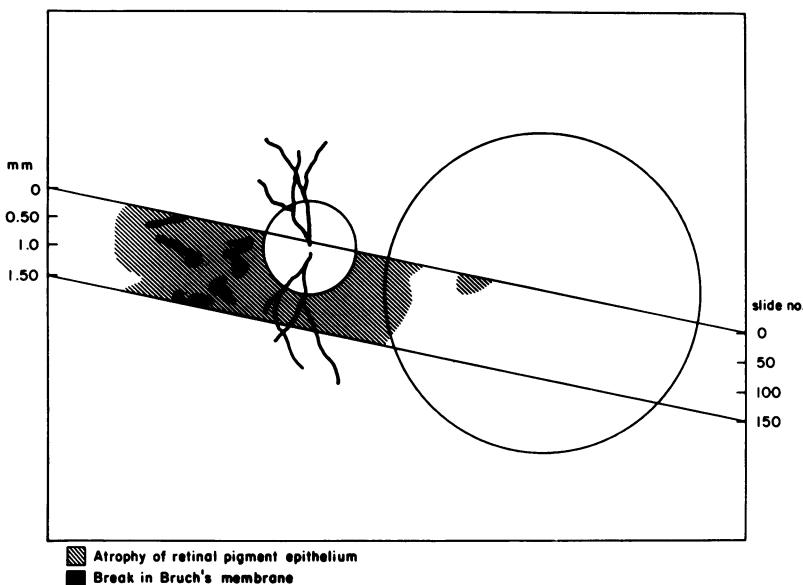


FIGURE 25

Case 16. Two-dimensional reconstruction of macular and peripapillary lesions of the left eye showing the size and location of the macular and peripapillary areolar atrophy and breaks in Bruch's membrane nasally.

DRUSEN, SUBRETINAL PIGMENT EPITHELIAL NEOVASCULARIZATION, AND SEROUS DETACHMENT OF RPE

CASE 20

This case illustrates the association of drusen, subretinal pigment epithelial neovascularization and serous detachment of the retinal pigment epithelium.

This previously reported case¹² was a 72-year-old man who had been examined periodically by his ophthalmologist for seven years preceding his death. The left eye had been successfully operated on for cataract and was medically controlled for open-angle glaucoma. The right eye was normal until May, 1973, when metamorphopsia and loss of the foveal reflex marked the typical onset of senile macular degeneration. It progressed rapidly, so that in July ophthalmoscopic examination showed a large serous detachment of the RPE in the lower temporal area of the macula and areas of RPE hypertrophy and defects centrally, as shown in the fundus photograph (Fig. 36). Fluorescein angiography (Figs. 37A and B) disclosed a web of early fluorescence and late staining, characteristic of choroidal neovascularization and a contiguous area of RPE serous detachment. This was the patient's last eye examination before he died one month later, following operation for lung cancer.

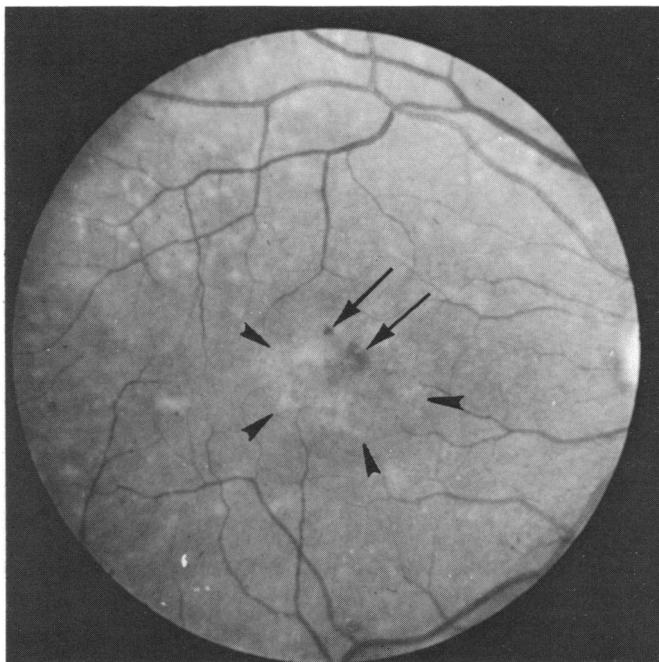


FIGURE 26

Case 17. Ophthalmoscopic appearance of right macular area in 1968. There are numerous drusen, several small hemorrhages (arrows) and a ring-like hazy area (arrowheads).

Microscopic examination showed moderately thickened Bruch's membrane, and some thickening of the intercapillary pillars of the choriocapillaris in the foveal and perifoveal areas. A large area of sub-RPE neovascularization was located in the foveal and perifoveal areas (Fig. 38A). A single break in Bruch's membrane with a traversing choroidal vessel was present (Figs. 38A and B). Inferiorly, the subretinal neovascular membrane merged with a large, relatively flat serous detachment of the RPE (Figs. 38A and C). A small serous detachment of the sensory retina adjoined the neovascularized zone also. Two-dimensional reconstruction from study of serial sections shows the relationships of the various components of the macular degeneration (Fig. 39).

DRUSEN, SUBRETINAL PIGMENT EPITHELIAL NEOVASCULARIZATION AND DISCIFORM SCAR

CASE 21

The findings in this patient disclose the evolution of drusen and subretinal pigment epithelial neovascularization to a disciform process.

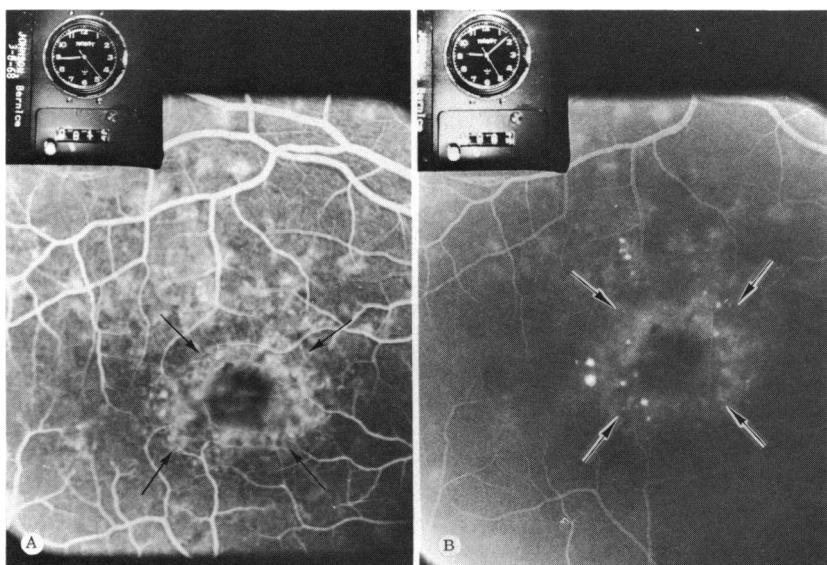


FIGURE 27

Case 17. Fluorescein angiography of the right eye taken in 1968. A: At 12 seconds there are several drusen and a ring-shaped area of lacy fluorescence (arrows). Fluorescence is blocked in the center of this ring. B: At 84 seconds several large drusen or small subretinal pigment epithelial detachments are present. There is also a residual ring-shaped area of fluorescence (arrows).

This previously reported¹² 62-year-old woman had had regular and frequent eye examinations for seven years preceding her death. Mild diabetic retinopathy, with 20/20 vision, was present in both eyes, until the onset of senile macular degeneration in the left eye was noted on Oct. 5, 1968, and in the right eye two years later.

The onset, four years and three months prior to her death, was marked by failing vision (20/60) and the presence of drusen, macular mottling, and the loss of the foveal reflex in the left eye. One year and eight months later (May 26, 1970) macular edema was seen. The visual acuity was 20/200. Two months later (July 16), visual acuity was 20/400. There were perifoveal exudates in a circinate pattern, a pigment ring, and more pigment changes in the macula. Eighteen days later (Aug. 3), a fluorescein angiogram of the left eye disclosed many drusen, early fluorescence, and late staining, the configuration of which was interpreted as choroidal neovascularization (Figs. 40A, B, and C). This angiogram was taken two years and five months before the patient died. On Dec. 10, 1970, slit-lamp contact lens examination showed pigmentary changes in the macula and retinal thickening in the perifoveal region. Visual acuity gradually decreased to counting fingers at 2 feet. Fundus examinations every three months in 1971 showed no

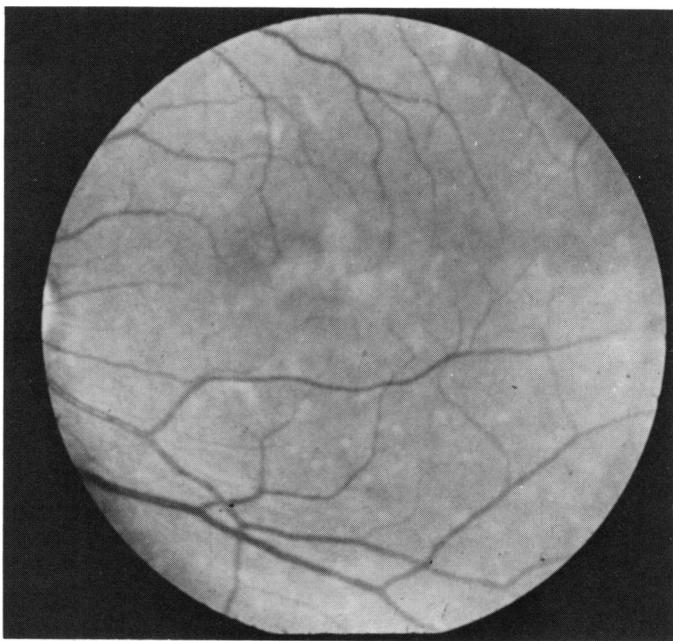


FIGURE 28

Case 17. Ophthalmoscopic appearance of the left eye in 1968. There are numerous drusen and several large confluent drusen or small detachments of the retinal pigment epithelium.

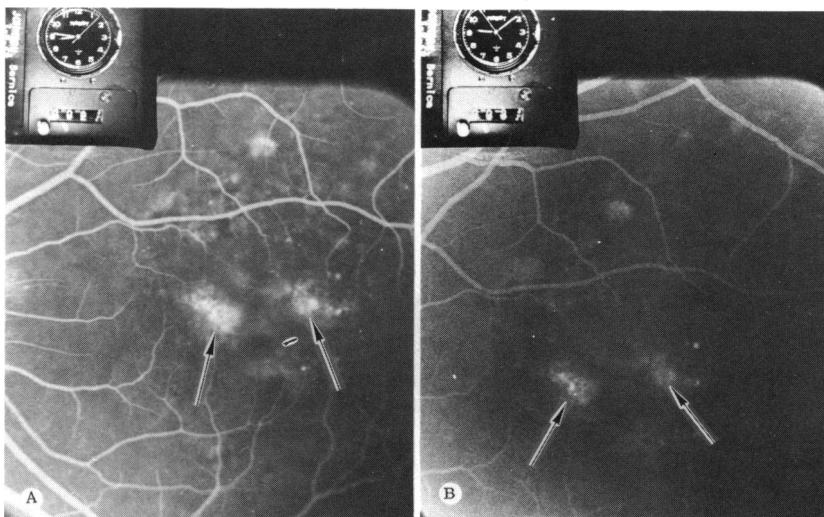


FIGURE 29

Case 17. Fluorescein angiography of the left eye in 1968. A: At 21 seconds there are several drusen and two nondiscrete areas of hyperfluorescence (arrows). B: These two areas of lacy, ill-defined areas of staining persist at 87 seconds (arrows).

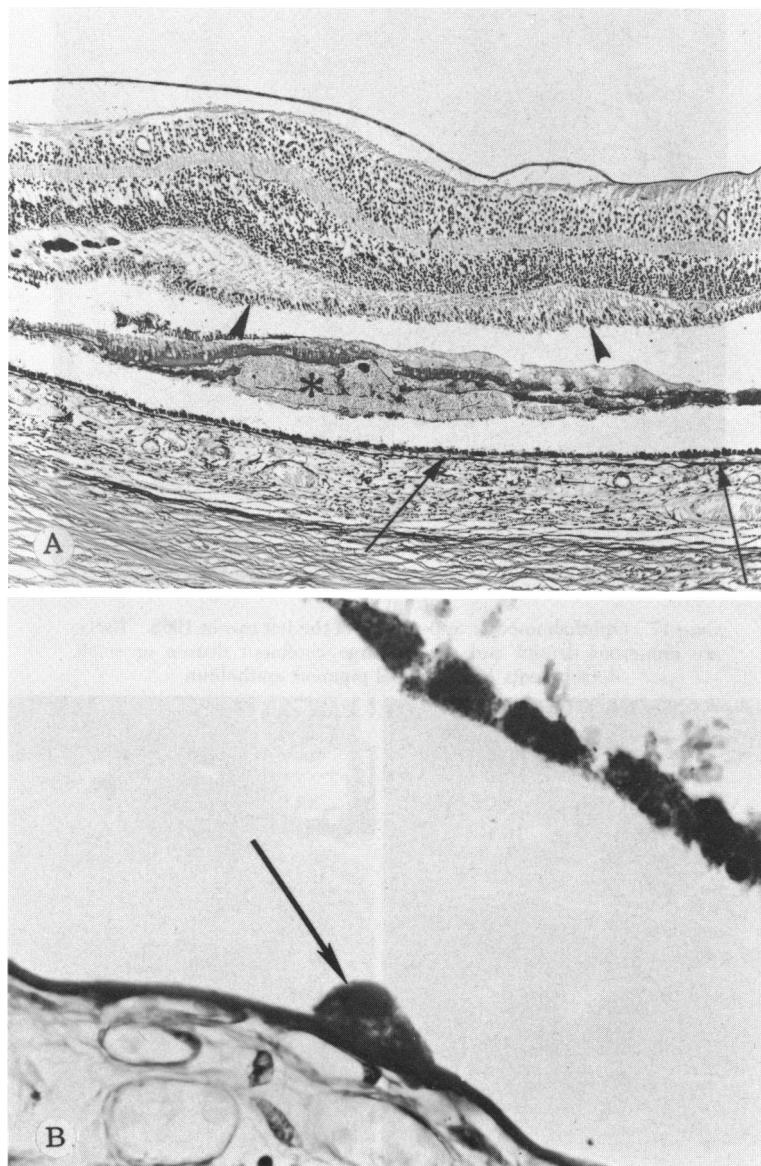


FIGURE 30

Case 17. A: Macular area of right eye showing extensive subretinal pigment epithelial neovascularization (arrows) and a serosanguinous retinal detachment (asterisk). Some thinning of the photoreceptor cell layer is present (arrowheads) (Periodic-acid Schiff, $\times 60$).

B: Druse (arrow) near the macular area (Periodic-acid Schiff, $\times 700$).

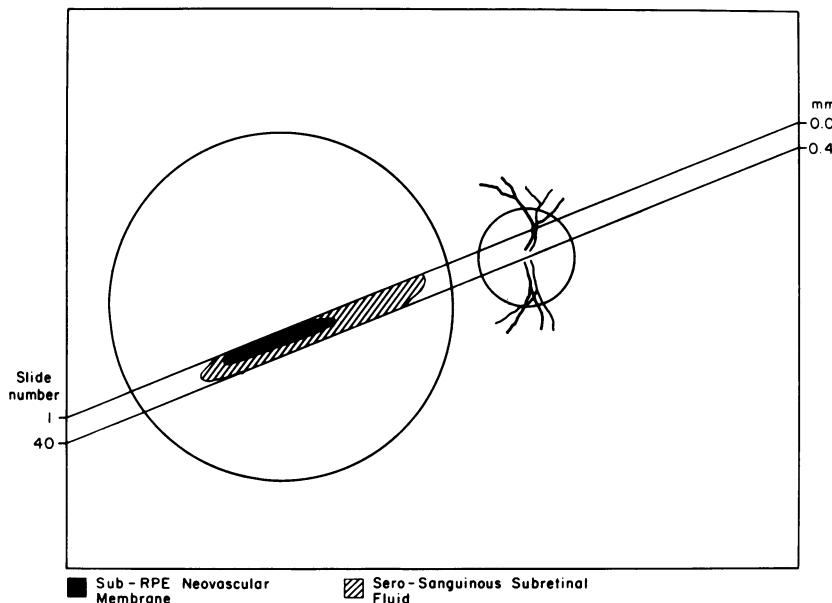


FIGURE 31

Case 17. Two-dimensional reconstruction of macular lesion of right eye from study of serial sections showing size and location of the subretinal pigment epithelial neovascular membrane and the serosanguinous retinal detachment.

further change until December, when the macula had a white scar. On Nov. 15, 1972, two months before death, ophthalmoscopy showed two pigmented scars in the macula. This was the last fundus examination before the patient died of complications of diabetes mellitus on Jan. 9, 1973. Both eyes were obtained postmortem.

The left eye was unremarkable grossly, except for a thickened retina in the macular area. Microscopic examination disclosed an extensive area of sub-RPE neovascularization (Fig. 41A) and a central area of a subretinal fibrovascular disiform process (Fig. 41B), with conspicuous retinal arterialization. At the upper border of the neovascularized area, there was a small serous detachment of the sensory retina. Many drusen were present throughout the fundus. No definite break in Bruch's membrane was found in serial sections of the macular area available for study. One break was present nasal to the disk in an additional area of sub-RPE neovascularization. Another small break with neovascularization of a druse was present nasally (Fig. 41C). Two-dimensional reconstruction of the lesions from the study of serial sections is depicted in Fig. 42 and shows the relationship of the various features. We presume that the break in Bruch's membrane is in that portion where sections were not obtained, near the center of the lesion.

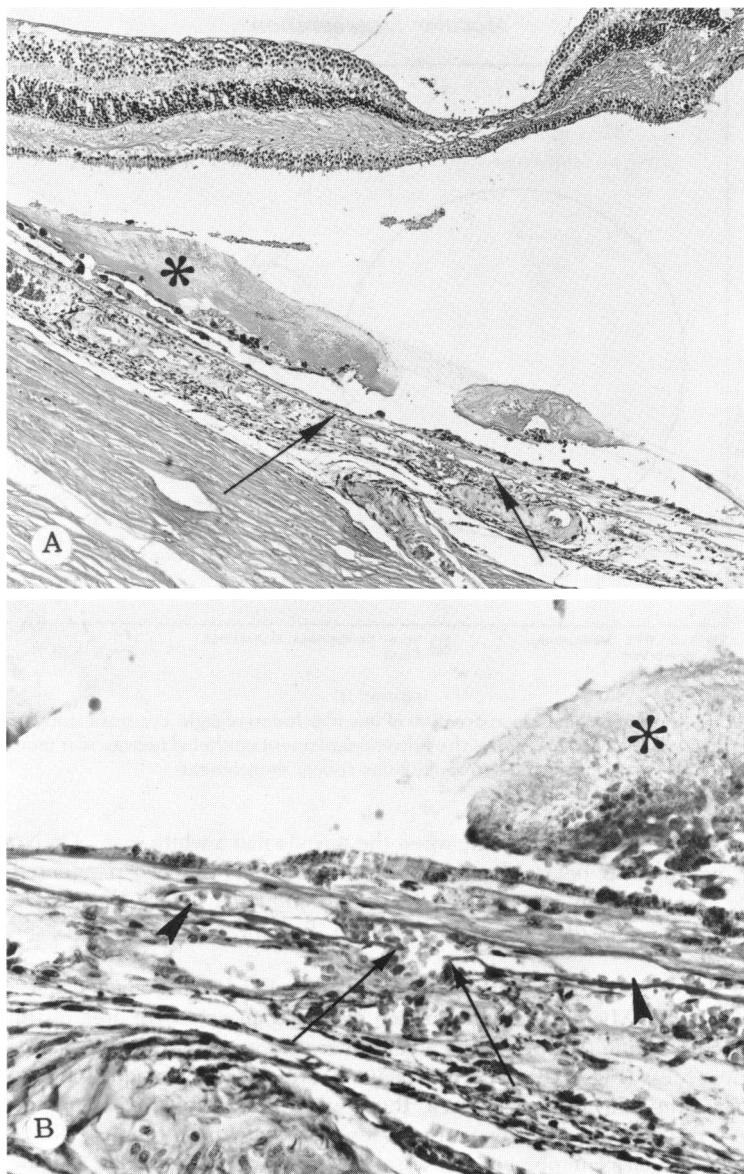


FIGURE 32

Case 17. A: Section through the foveola of the left eye showing an extensive subretinal pigment epithelial neovascular membrane (arrows) and a serosanguinous detachment of the macula (asterisk). Thinning of the outer nuclear layer is evident (Periodic-acid Schiff, $\times 60$). B: Higher power showing the single break in Bruch's membrane with traversing choroidal vessel (arrows), subretinal pigment epithelial vascularization (arrowheads) and serosanguinous subretinal material (asterisks) (Periodic-acid Schiff, $\times 240$).

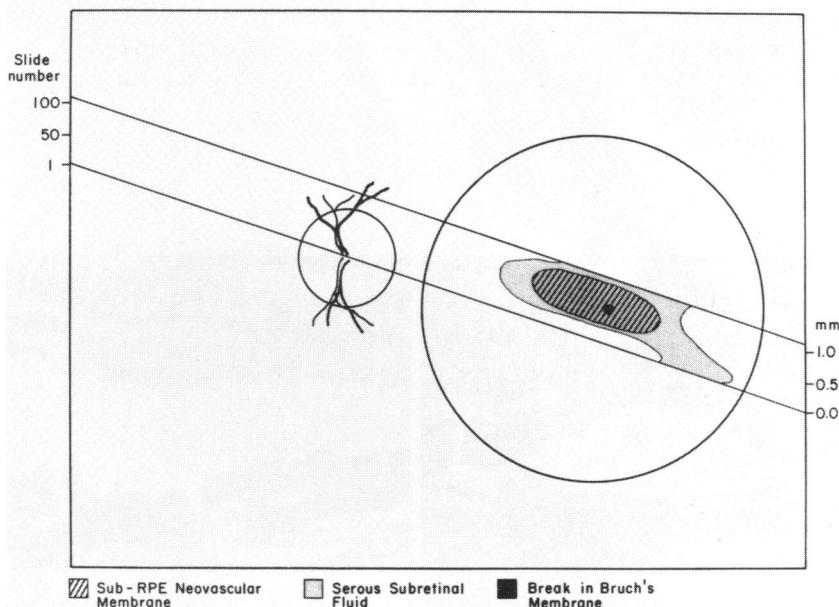


FIGURE 33

Case 17. Two-dimensional reconstruction of the macular lesion of the left eye showing the size and location of the single break in Bruch's membrane, subretinal pigment epithelial neovascularization and serosanguinous retinal detachment.

DISCIFORM SCAR

The development of fibrous disciform scars in the macular area in senile macular degeneration most often, but not exclusively, occurs as the result of the serous and hemorrhagic sequelae of sub-RPE neovascularization. Fibrous tissue, along with choroidal neovascularization, develops between the split layers of Bruch's membrane. A similar process may develop internal to the separated inner layer of Bruch's membrane. The presence of hemosiderin within the disciform plaque suggests that fibrous organization of a hemorrhage plays a role in the evolution of the disciform lesion. Retinal pigment epithelium also contributes to the disciform lesion. Laminated areas of basement membrane are observed in some disciform lesions and suggest successive waves of RPE hyperplasia. Frank hyperplasia of retinal pigment epithelium is a conspicuous feature of many disciform lesions.

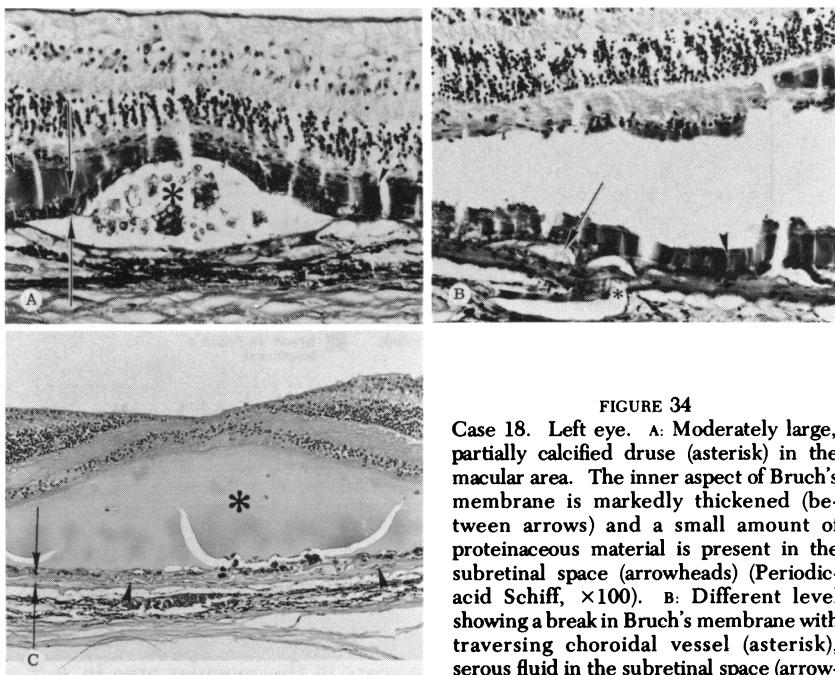


FIGURE 34

Case 18. Left eye. A: Moderately large, partially calcified druse (asterisk) in the macular area. The inner aspect of Bruch's membrane is markedly thickened (between arrows) and a small amount of proteinaceous material is present in the subretinal space (arrowheads) (Periodic-acid Schiff, $\times 100$). B: Different level showing a break in Bruch's membrane with traversing choroidal vessel (asterisk), serous fluid in the subretinal space (arrowhead) and subretinal pigment epithelial head. C: A dome-shaped serous detachment (asterisk). The inner aspect of Bruch's membrane is thickened (between arrows) and a few fine blood vessels (arrowheads) are located between the two layers of Bruch's membrane. The retinal pigment epithelium is intact, but shows some clumping and irregular pigmentation (Hematoxylin and eosin, $\times 85$). neovascularization (arrow) (Hematoxylin and eosin, $\times 105$). Detachment was present in the foveal area (asterisk). The inner aspect of Bruch's membrane is thickened (between arrows) and a few fine blood vessels (arrowheads) are located between the two layers of Bruch's membrane. The retinal pigment epithelium is intact, but shows some clumping and irregular pigmentation (Hematoxylin and eosin, $\times 85$).

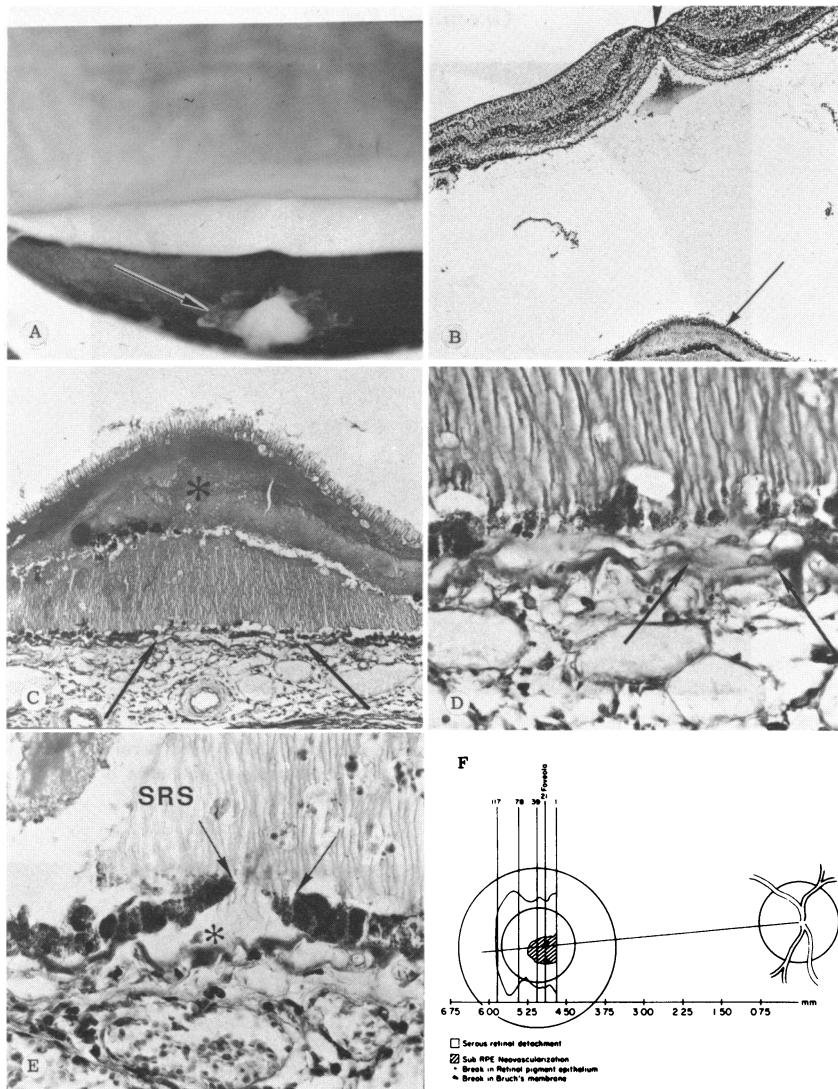


FIGURE 35

Case 19. Right eye. A: Temporal cap showing appearance of a macular lesion (arrow) that was grossly interpreted as a disciform scar. The retina is artifactitiously detached. B: Lower power showing mound-shaped area of serous detachment in the foveal area (foveola — arrowhead) (Van de Grift $\times 20$). C: Area of serous material (asterisk) beneath fovea. A thin, delicate vascular membrane (arrows) is located between the retinal pigment epithelium and Bruch's membrane (Periodic-acid Schiff $\times 80$). D: Area of a small break in Bruch's membrane (between arrows). E: Small area of serous detachment of the retinal pigment epithelium (asterisk) and a break in the RPE (arrows), through which proteinaceous material is in continuity with that in the subretinal space (SRS) (Van de Grift $\times 290$). F: Two-dimensional reconstruction of macular lesion showing the relative size and location of the break in Bruch's membrane, subretinal pigment epithelial neovascularization and serous detachment of the fovea.

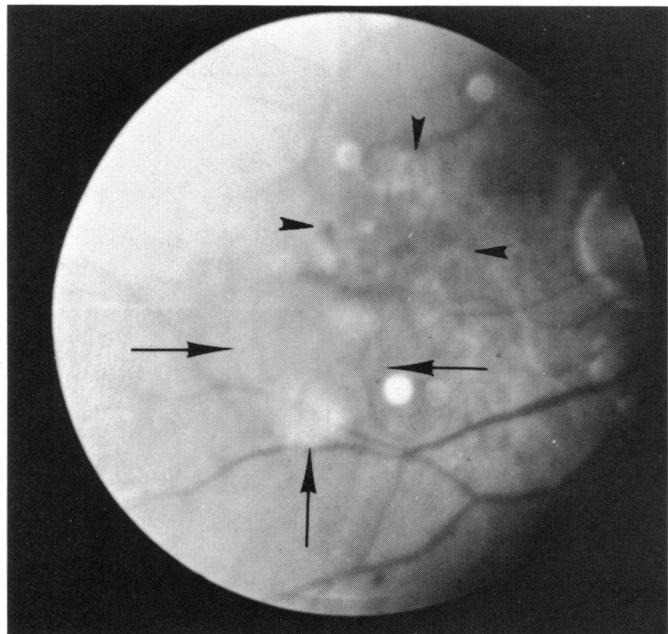


FIGURE 36

Case 20. Ophthalmoscopic appearance in July, 1973 with serous detachment of the retinal pigment epithelium (arrows) and area of mottling of pigment (arrowheads).

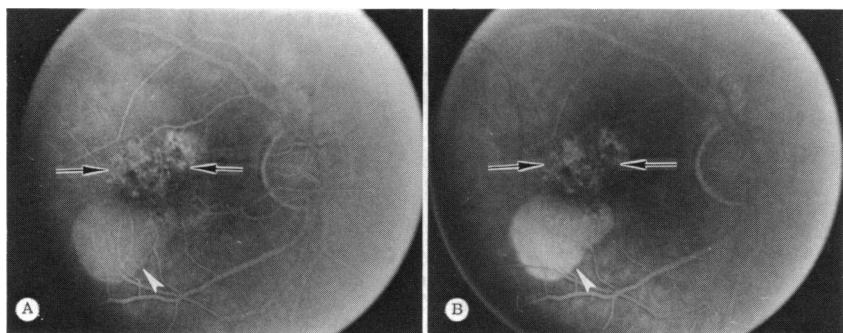


FIGURE 37

Case 20. Fluorescein angiography taken one month prior to death. A: At 38 seconds there is a large area of lacy fluorescence of neovascularization (arrows). It is interspersed with several areas of fluorescein blockage presumably due to retinal pigment epithelial hypertrophy. A large serous detachment of the retinal pigment epithelium (arrowhead) is present. B: At 5½ minutes fluorescence of the neovascularization (arrows) persists and intensifies in the retinal pigment epithelial detachment (arrowhead).

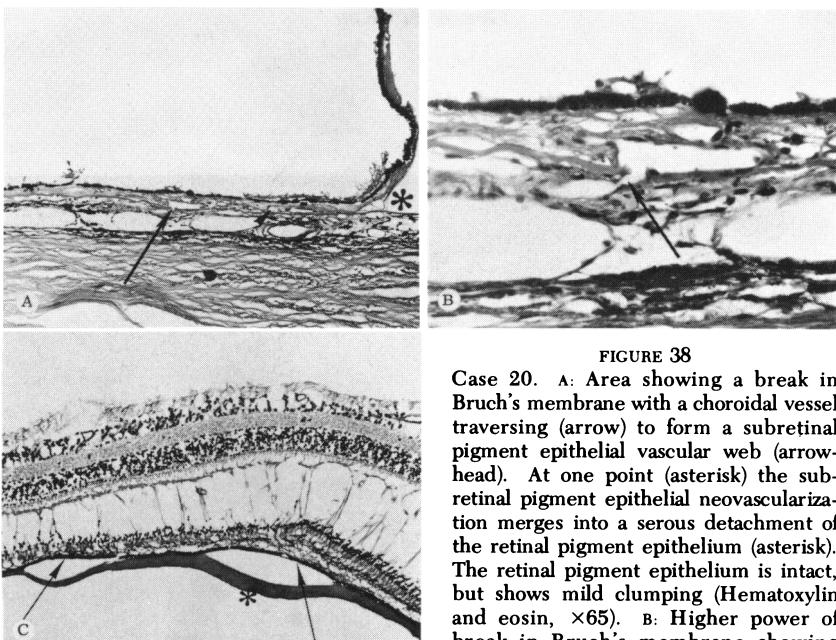


FIGURE 38

Case 20. A: Area showing a break in Bruch's membrane with a choroidal vessel traversing (arrow) to form a subretinal pigment epithelial vascular web (arrowhead). At one point (asterisk) the subretinal pigment epithelial neovascularization merges into a serous detachment of the retinal pigment epithelium (asterisk). The retinal pigment epithelium is intact, but shows mild clumping (Hematoxylin and eosin, $\times 65$). B: Higher power of break in Bruch's membrane showing choroidal vessel going through the break (arrow) (Hematoxylin and eosin, $\times 270$). C: Inferior area of flat serous detachment (asterisk) of retinal pigment epithelium (arrows) and cystic degeneration in the outer plexiform layer of retina (Hematoxylin and eosin, $\times 65$).

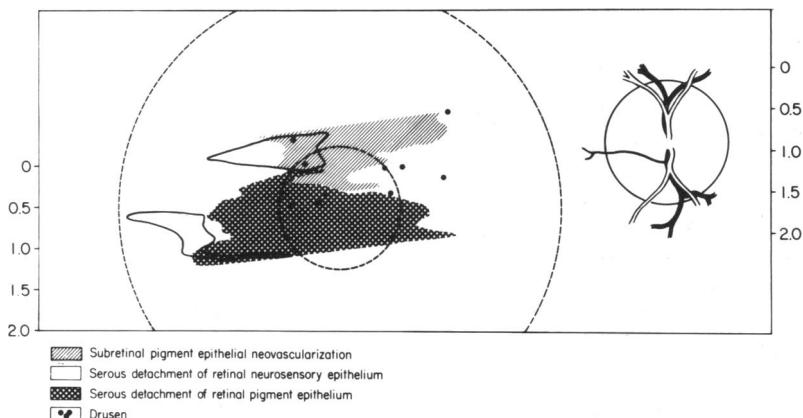


FIGURE 39

Case 20. Two-dimensional reconstruction map of the macular area from the study of serial sections. It shows the distribution of drusen, the size, shape, and location of the subretinal pigment epithelial neovascularization, and its relationship to the serous detachment of the retinal pigment epithelium and retina.

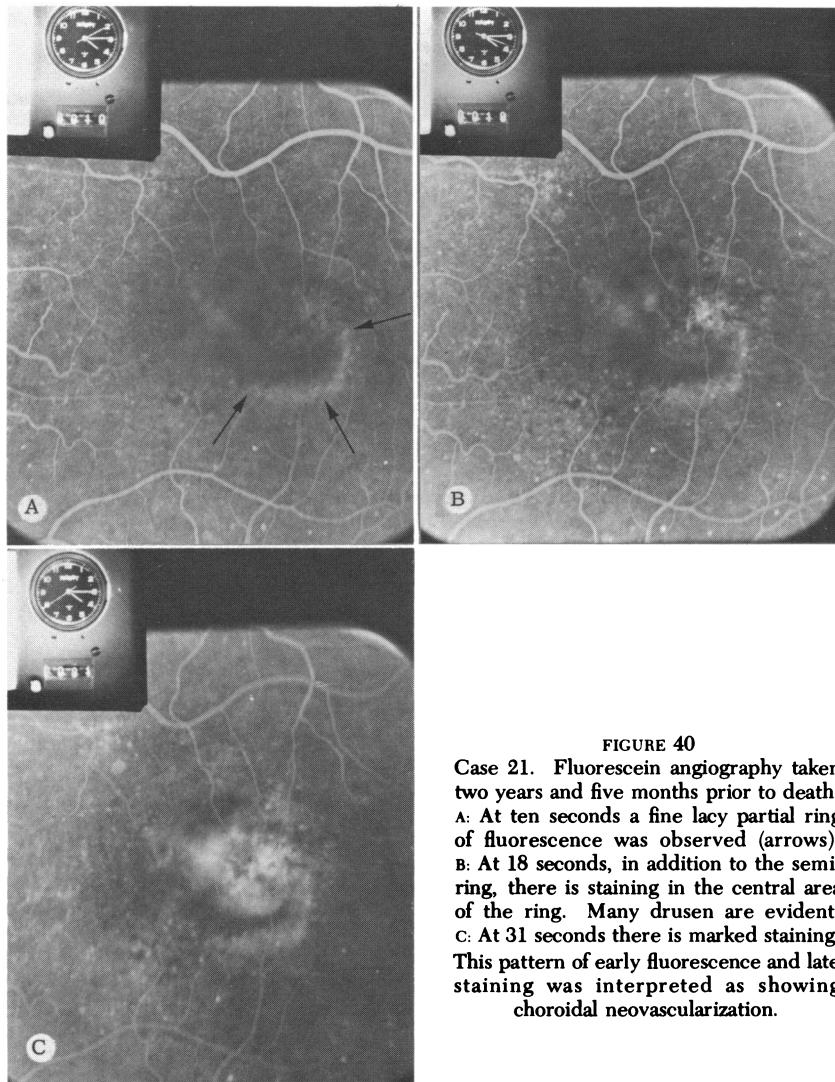


FIGURE 40
Case 21. Fluorescein angiography taken two years and five months prior to death.
A: At ten seconds a fine lacy partial ring of fluorescence was observed (arrows).
B: At 18 seconds, in addition to the semi-ring, there is staining in the central area of the ring. Many drusen are evident.
C: At 31 seconds there is marked staining. This pattern of early fluorescence and late staining was interpreted as showing choroidal neovascularization.

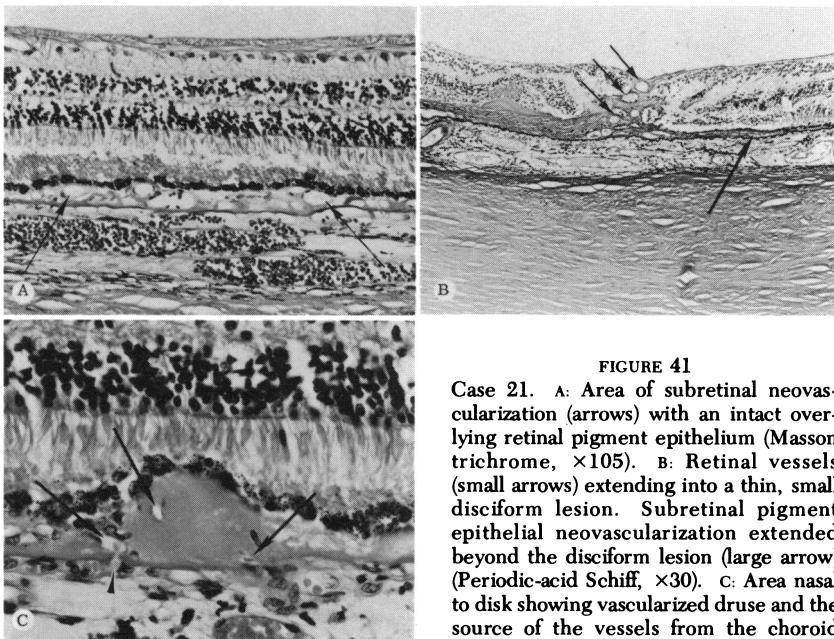


FIGURE 41

Case 21. A: Area of subretinal neovascularization (arrows) with an intact overlying retinal pigment epithelium (Masson trichrome, $\times 105$). B: Retinal vessels (small arrows) extending into a thin, small disciform lesion. Subretinal pigment epithelial neovascularization extended beyond the disciform lesion (large arrow) (Periodic-acid Schiff, $\times 30$). C: Area nasal to disk showing vascularized druse and the source of the vessels from the choroid through a very small break in Bruch's membrane (arrowhead) (Hematoxylin and eosin, $\times 250$).

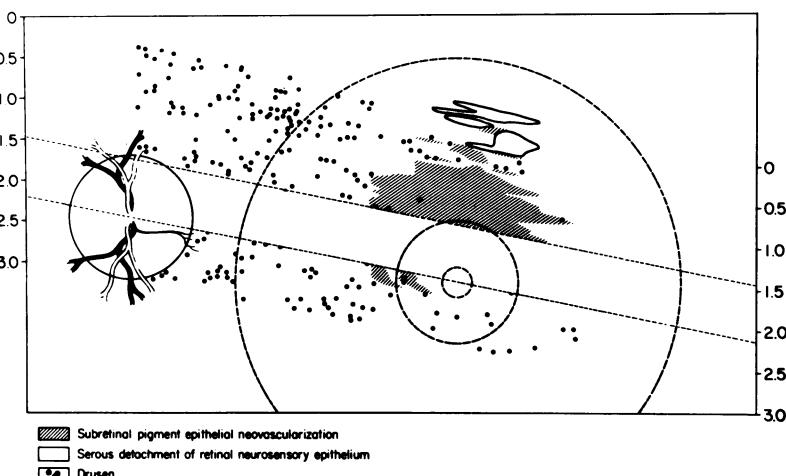


FIGURE 42

Case 21. Extensive two-dimensional reconstruction from the study of serial sections by Dr Mary Louise Small. It depicts actual number of drusen, the location, size, and shape of the subretinal pigment epithelial neovascularization, and disciform lesion, and associated small serous detachments of the retina.

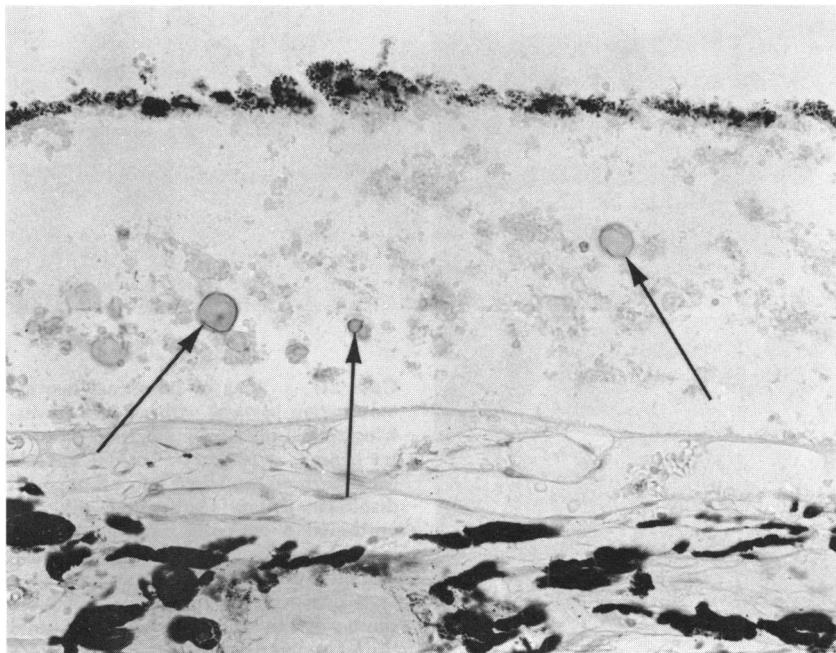


FIGURE 43

Case 22. Relatively small subretinal pigment epithelial disciform lesion showing globules of hemosiderin (arrows) (Prussian blue, $\times 240$).

CASE 22

Both eyes of this 90-year-old black woman disclosed drusen and old disciform lesions located beneath the retinal pigment epithelium. Globules of iron (Fig. 43) suggest that hemorrhage had initiated the disciform lesion.

CASE 23

Both eyes of this 77-year-old white man had drusen with areolar atrophy in the left eye and a disciform lesion in the right eye (Fig. 44). The fibrous tissue is located between the two layers of Bruch's membrane and between the inner layer of Bruch's membrane and the retina. Hyperplastic retinal pigment epithelium is entrapped in that portion of the disciform lesion between the inner layer of Bruch's membrane and the retina. Retinal pigment epithelium is absent over the lesion and there is marked reduction in the photoreceptor cell layer.

CASE 24

A 90-year-old white woman had drusen and a disciform lesion in both eyes. The lesion in the left eye was particularly large and demonstrates fibrous tissue

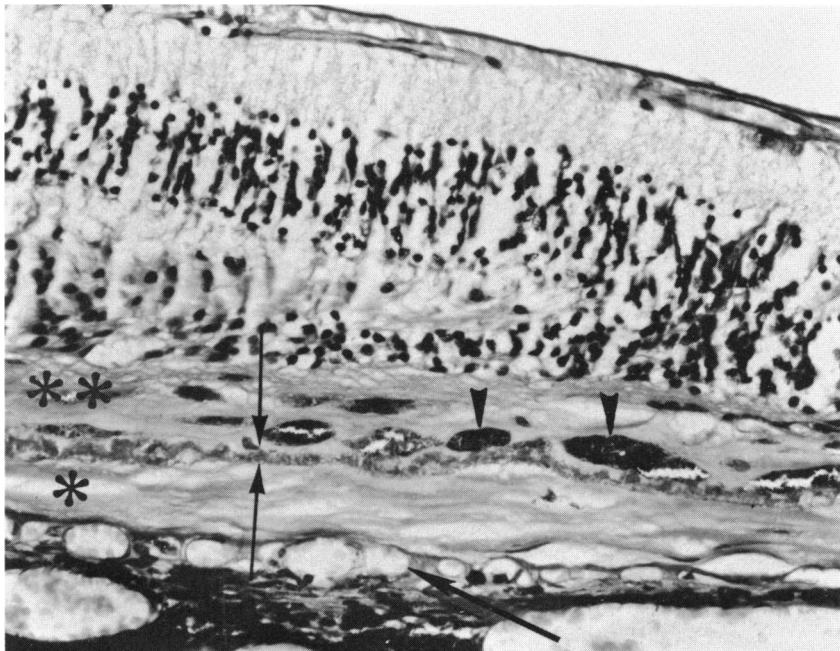


FIGURE 44

Case 23. Disciform lesion located between the two split layers of Bruch's membrane (one asterisk) and between the inner layer of Bruch's membrane and the retina (two asterisks). The thickened and separated inner portion of Bruch's membrane is marked between two small arrows. Entrapped retinal pigment epithelium is present within that portion of the disciform lesion between the inner layer of Bruch's membrane and the retina (arrowheads). Retinal pigment epithelium is lost over the lesion and there is partial atrophy of the outer nuclear layer of the retina. The choriocapillaris is intact (large arrow) (Periodic-acid Schiff, $\times 260$).

between the two layers of Bruch's membrane and between the inner layer of Bruch's and the retina (Fig. 45).

CASE 25

Both eyes of this 79-year-old white man disclosed a disciform lesion. The patient had several ophthalmologic examinations during his last 10 years of life. In 1966 he was described as having drusen in the macula of both eyes. The picture evolved to "extensive macular degeneration." In the right eye the lesion was quite large and displayed bone formation centrally (Fig. 46A). A prominent lymphocytic infiltration was present in the choroid in one area subjacent to the disciform lesion (Fig. 46B). The left eye had a relatively flat disciform lesion (Fig. 47A). Study of serial sections through most of this lesion of the left eye disclosed two small breaks in Bruch's membrane. Most of the disciform lesion was located between

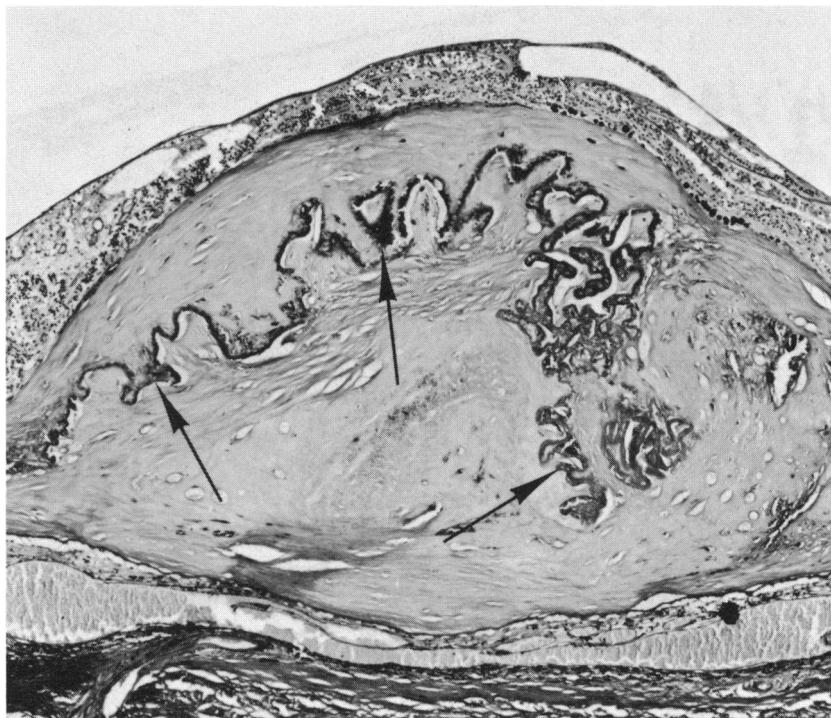


FIGURE 45

Case 24. Very large disciform lesion, the larger portion of which is located between the two layers of Bruch's membrane and smaller portion between the inner layer of Bruch's membrane and the thin, effaced and degenerated retina. The inner layer of Bruch's membrane is markedly thickened and redundant (arrows) (Periodic-acid Schiff, $\times 60$).

the two layers of Bruch's membrane, while a smaller portion was located between the inner layer of Bruch's membrane and the retina. Of interest was the finding of branching dendritic melanocytes (Fig. 47B) in the smaller disciform lesion located between the two layers of Bruch's membrane in the left eye. These melanocytes apparently migrated into this area through a break in Bruch's membrane.

CASE 26

Both eyes of this 89-year-old white woman has drusen. In addition, a small fibrous nodule was present in a large central area of areolar atrophy in the left eye (Fig. 48A). No choroidal neovascularization was present in the serial sections through this small disciform lesion. Drusen were present outside the areolar area (Fig. 48B).

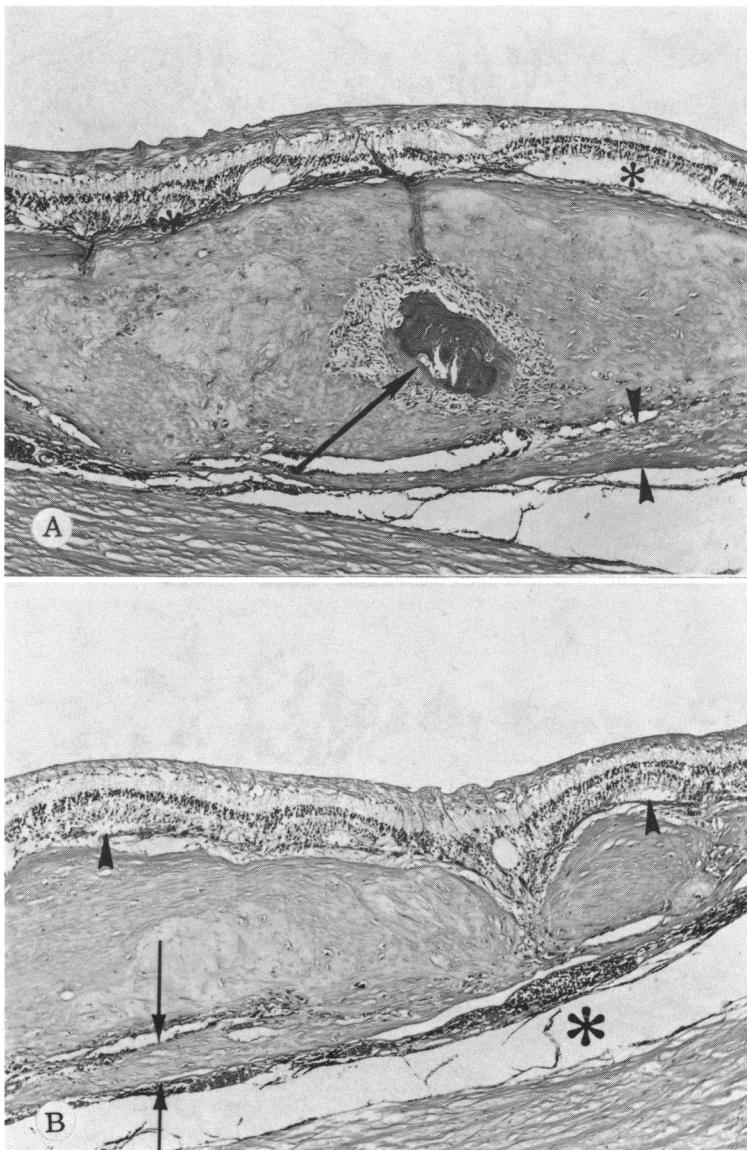


FIGURE 46

Case 25. Right eye. A: Large disciform lesion with a central area of bone formation (arrow). Only a small portion of the disciform lesion is located between the two split layers of Bruch's membrane (between arrowheads) and the remainder is between the inner layer of Bruch's membrane and the retina. Amazingly, the photoreceptor cell layer is relatively intact over much of the lesion (asterisks) (Hematoxylin and eosin, $\times 65$). B: Different level of disciform lesion showing intra-Bruch's-membrane component (between arrows). A prominent aggregate of lymphocytes is present in the subjacent choroid (asterisk). The outer nuclear layer is intact in some areas over the lesion (arrowheads) (Periodic-acid Schiff, $\times 60$).

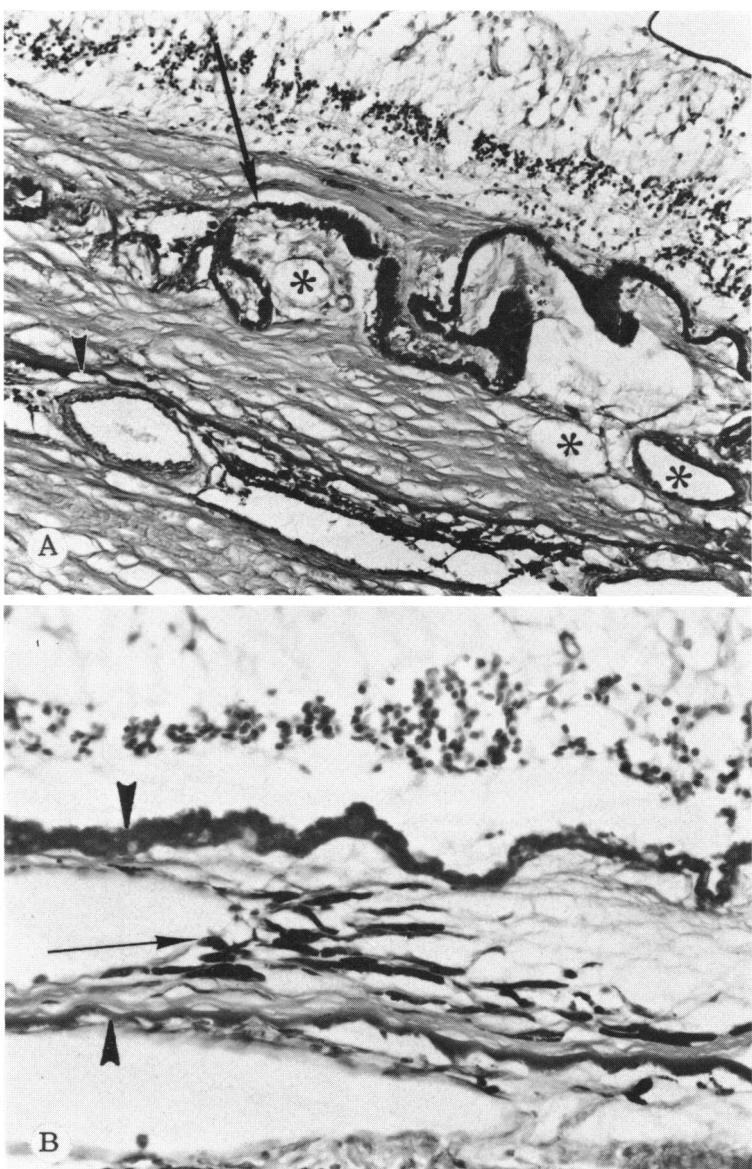


FIGURE 47

Case 25. Left eye. A: Disciform lesion located between the thickened and separated inner (arrow) and outer (arrowheads) layers of Bruch's membrane. A small portion is located between the inner layer of Bruch's membrane and the retina. The retinal pigment epithelium and photoreceptor cell layer are absent. Choroidal neovascularization is present in the intra-Bruch's-membrane portion of the disciform lesion (asterisks) (Periodic-acid Schiff, $\times 145$). B: Branching dendritic melanocytes (arrow) presumably from the choroid and located in the disciform lesion between the two layers of Bruch's membrane (arrowheads).

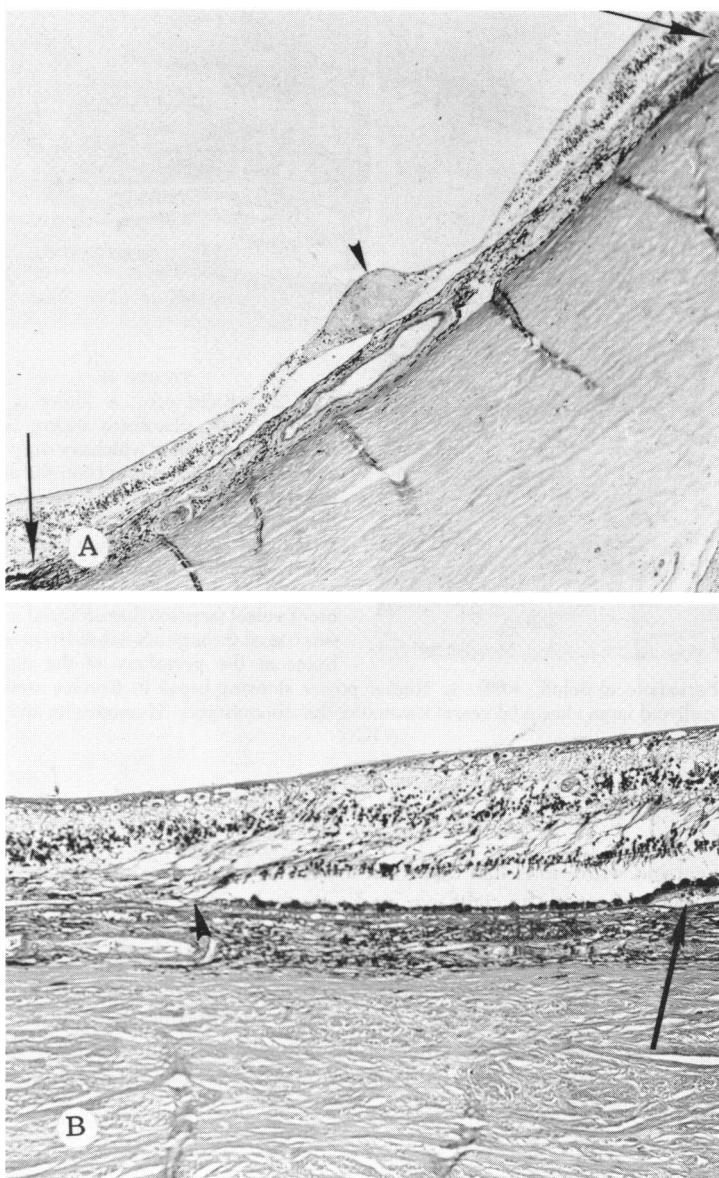


FIGURE 48

Case 26. A: Small disciform nodule (arrowhead) in a central area of areolar atrophy (between arrows). There was no choroidal neovascularization in this fibrous nodule (Periodic-acid Schiff, $\times 210$). B: Peripheral area of areolar atrophy (arrowhead) and drusen (arrow) (Hematoxylin and eosin, $\times 100$).

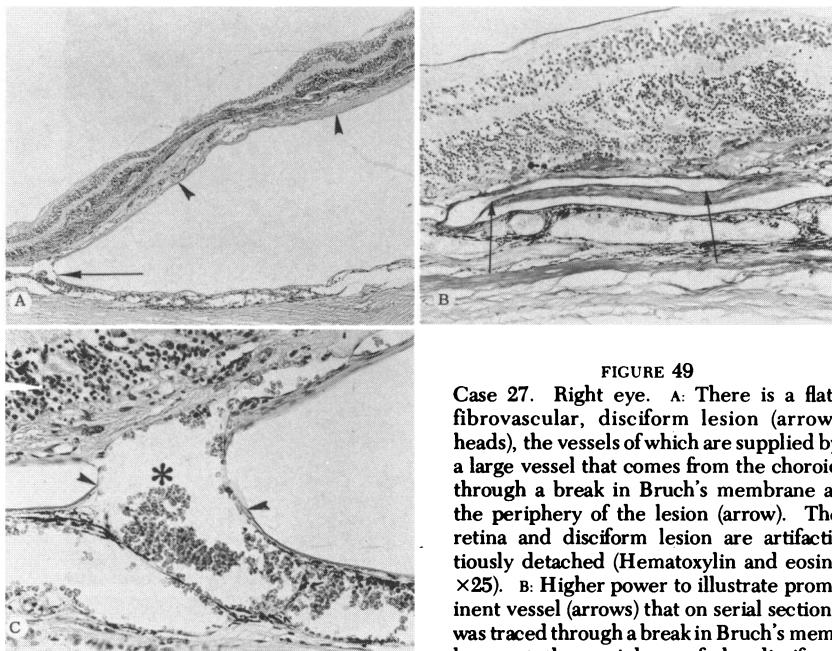


FIGURE 49

Case 27. Right eye. A: There is a flat, fibrovascular, disciform lesion (arrowheads), the vessels of which are supplied by a large vessel that comes from the choroid through a break in Bruch's membrane at the periphery of the lesion (arrow). The retina and disciform lesion are artificially detached (Hematoxylin and eosin, $\times 25$). B: Higher power to illustrate prominent vessel (arrows) that on serial sections was traced through a break in Bruch's membrane at the periphery of the disciform

lesion (Periodic-acid Schiff, $\times 65$). C: Higher power showing break in Bruch's membrane (arrowhead) and large choroidal vessel traversing the discontinuity (Hematoxylin and eosin, $\times 125$).

CASE 27

An 80-year-old white man had disciform lesions in both eyes. A thin, relatively flat scar was present in the right eye, and a single break in Bruch's membrane at the periphery of the lesion was the only site of choroidal neovascularization (Figs. 49A, B, and C). In the left eye, the disciform lesion included an area of hyperplasia of the retinal pigment epithelium (Fig. 50A) and retinal arterialization (Fig. 50B). At one area of the disciform lesion, the fibrous tissue was located between the two layers of Bruch's membrane, internal to the inner layer of Bruch's membrane, and was continuous with a preretinal fibrous plaque through a break in the internal limiting membrane (Fig. 50C).

CASE 28

Both eyes of this 79-year-old white man disclosed drusen and diffuse thickening of Bruch's membrane. The right eye had a small disciform lesion with nodular periodic-acid-Schiff-positive basement-membrane-like material (Fig. 51), subretinal pigment epithelial neovascularization, and areolar atrophy. Drusen, diffuse thickening of the inner aspect of Bruch's membrane (Fig. 52A), areolar

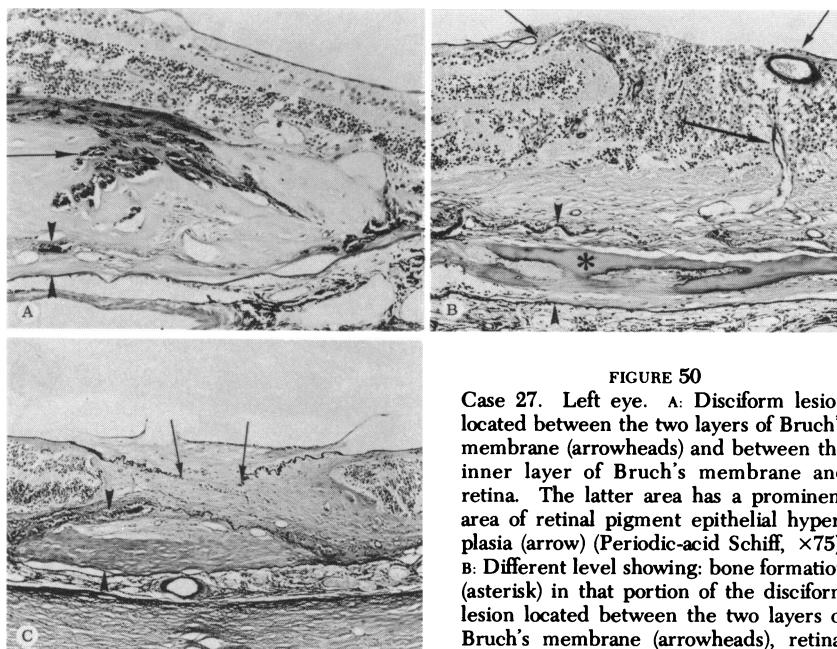


FIGURE 50
Case 27. Left eye. A: Disciform lesion located between the two layers of Bruch's membrane (arrowheads) and between the inner layer of Bruch's membrane and retina. The latter area has a prominent area of retinal pigment epithelial hyperplasia (arrow) (Periodic-acid Schiff, $\times 75$). B: Different level showing: bone formation (asterisk) in that portion of the disciform lesion located between the two layers of Bruch's membrane (arrowheads), retinal vascular supply to the subretinal disciform

lesion (large arrow) and a discontinuity in the internal limiting membrane of the retina (small arrows) (Periodic-acid Schiff, $\times 55$). C: A third level showing disciform lesion between the two layers of Bruch's membrane (arrowheads), internal to the inner layer of Bruch's membrane and extending through a break in the internal limiting membrane (arrows) to be continuous with a fibrous nodule on the inner surface of the retina (Periodic-acid Schiff, $\times 30$).

atrophy, and subretinal pigment epithelial neovascularization were present in the left eye (Fig. 52B). Electron microscopic examination of tissue from the area centralis of the right eye taken out of paraffin disclosed marked thickening of both collagenous zones of Bruch's membrane by vesicles and electron-dense material. Internal to the inner collagenous zone was the deposition of a very thick layer of fibrillar-granular material containing large clumps of wide-spaced collagen (Fig. 53). Splitting had occurred within this thickened area between retinal pigment epithelium and degenerated inner collagenous zone of Bruch's membrane.

CASE 29

A 76-year-old white man (E.P. 42851) was examined by Dr A. E. Maumenee who noted drusen in both eyes and a small serous detachment of the retina in the macular area of the left eye (Fig. 54). Fluorescein angiography was not very clear because of cataractous changes. There was late pooling of fluorescein, suggestive of serous



FIGURE 51

Case 28. Right eye. There is a small disciform lesion composed of nodular and laminar periodic-acid-Schiff-positive material (arrows) which is presumably basement membrane derived from hyperplastic retinal pigment epithelium (Periodic-acid Schiff, $\times 240$).

detachment of the retinal pigment epithelium in the left eye. Both eyes were obtained postmortem 6 years later. Section of the left eye disclosed a relatively flat disciform lesion located between the two layers of the split Bruch's membrane (Fig. 55A). A single break in Bruch's membrane, through which a large choroidal vessel extended into the disciform lesion, was present (Fig. 55B). A small area of hemorrhagic detachment of the retinal pigment epithelium was present (Fig. 55C). Drusen, some of which were calcified, were observed (Fig. 55C). In addition, subretinal and intraretinal hemorrhage were observed (Figs. 55A and B). Two-dimensional reconstruction of the lesion from study of serial sections disclosed the relationships and extent of the break in Bruch's membrane, disciform lesion, subretinal pigment epithelial neovascularization, areolar RPE atrophy, sub-RPE and subretinal and intraretinal hemorrhage (Fig. 56). Sections of the right eye disclosed extensive sub-RPE neovascularization (Fig. 57A) from a single break in Bruch's membrane with traversing choroidal vessels (Fig. 57B).

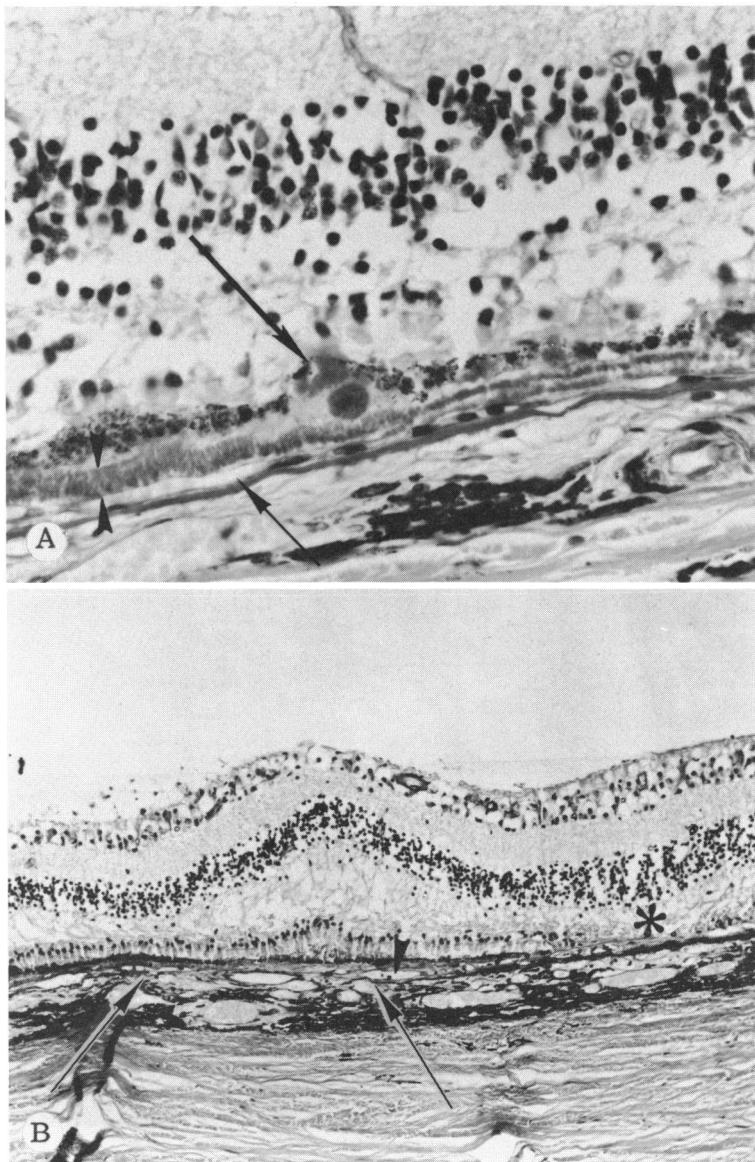


FIGURE 52

Case 28. Left eye. A: There is diffuse thickening of the inner aspect of Bruch's membrane (between arrowheads), drusen (large arrow) and intra-Bruch's-membrane neovascularization (small arrow). The retinal pigment epithelium is still present, but markedly attenuated. Prominent degeneration of the photoreceptor cell layer has occurred (Periodic-acid Schiff, $\times 450$). B: Another area showing a break in Bruch's membrane (between arrows), sub-retinal pigment epithelial neovascularization (arrowhead) and areolar atrophy (asterisk) (Periodic-acid Schiff, $\times 120$).

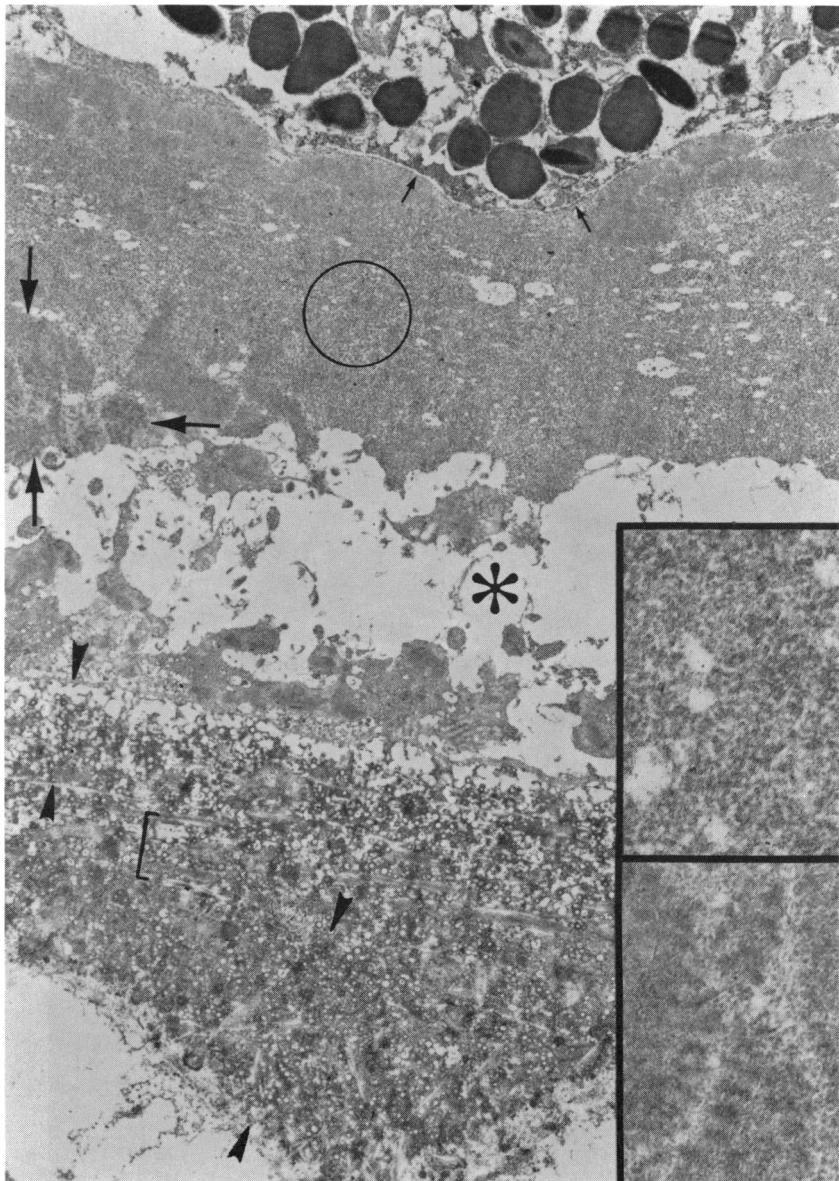
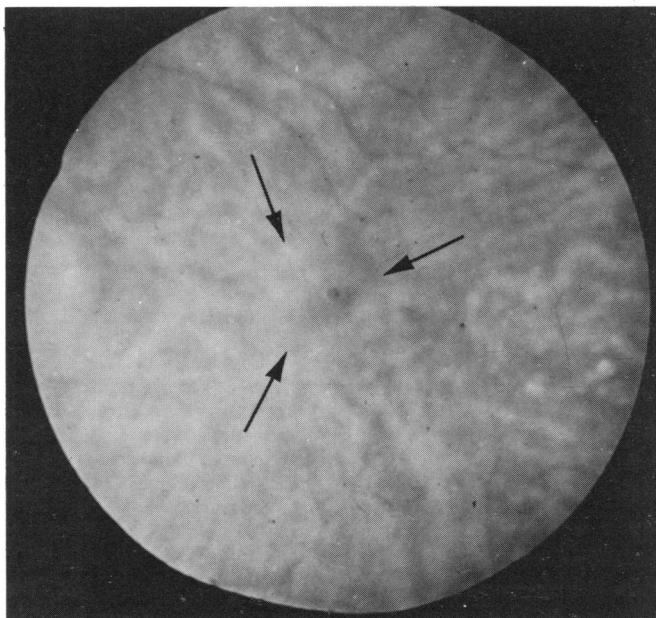


FIGURE 53

Case 28. Macular area of right eye taken out of paraffin and processed for electron microscopy. The basement membrane of the retinal pigment epithelium is normal (smaller arrows). The elastic layer of Bruch's membrane (bracket) and the outer, and what appears to be inner, collagenous layers are thickened by small vesicles and electron-dense material (between arrowheads). There is deposition of abundant fine fibrillar-granular material (circle and lower inset) and large aggregates of wide-spaced collagen (larger arrows and upper inset). Splitting (asterisk) has occurred in this thick new layer between the retinal pigment epithelium and the degenerated inner collagenous zone of Bruch's membrane ($\times 7460$, upper inset $\times 45200$, lower inset $\times 45200$).

**FIGURE 54**

Case 29. Ophthalmoscopic appearance of left eye 6 years prior to death. Several drusen are present, and a small area of serous retinal detachment was noted (arrows).

CASE 30

Sections of both eyes of this 88-year-old Asian man disclosed drusen. In addition, a disciform lesion was present between two layers of Bruch's membrane, and between the inner layer of Bruch's membrane and retina in the left eye, (Fig. 58A). Peripheral to the disciform lesion there was extension of intra-Bruch's-membrane neovascularization, and areolar pigment epithelial atrophy (Fig. 58B). The right eye exhibited intra-Bruch's-membrane neovascularization, areolar RPE atrophy, and serous detachment of the retina (Fig. 59).

CASE 31

Both eyes of this 82-year-old white woman disclosed a very thin disciform lesion in the macular area. Prominent hyperplasia and migration of the retinal pigment epithelium were noted in the right eye (Fig. 60A). This hyperplastic RPE was located primarily around retinal vessels (Fig. 60B), which in study of serial sections could be traced to anastomose with vessels in the disciform lesion, and in turn, with choroidal vessels. Within the area of the disciform lesion and subretinal pigment epithelial neovascularization, two breaks in Bruch's membrane were identified (Figs. 60C and D). Choroidal vessels could be traced, through one

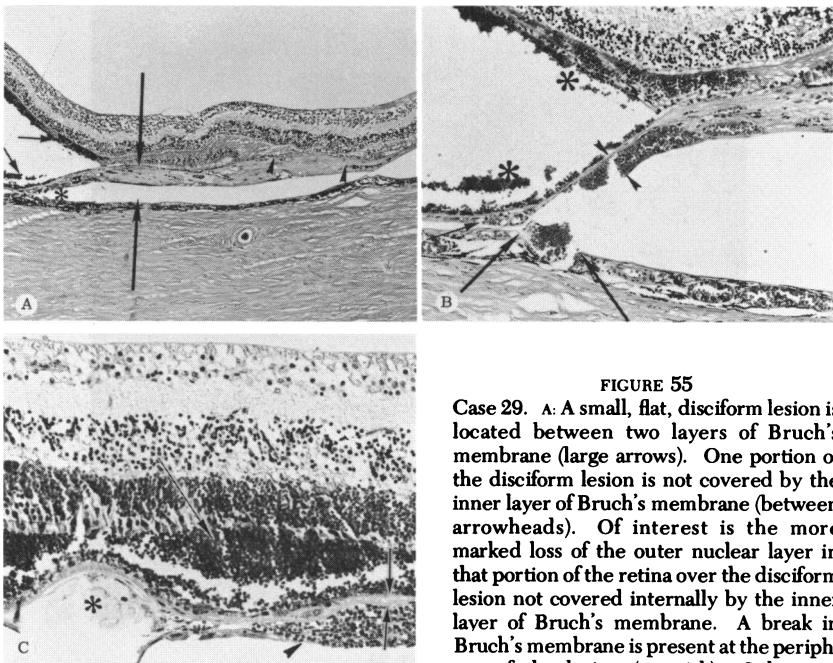


FIGURE 55

Case 29. A: A small, flat, disciform lesion is located between two layers of Bruch's membrane (large arrows). One portion of the disciform lesion is not covered by the inner layer of Bruch's membrane (between arrowheads). Of interest is the more marked loss of the outer nuclear layer in that portion of the retina over the disciform lesion not covered internally by the inner layer of Bruch's membrane. A break in Bruch's membrane is present at the periphery of the lesion (asterisk). Subretinal

hemorrhage is present peripheral to the disciform lesion (small arrows). The retina and disciform lesion are artifactitiously detached. B: Higher power of area of break in Bruch's membrane (between larger arrows) at a different level. The outer wall of the choroidal blood vessel (arrowheads) extending through the break in Bruch's membrane and into the disciform lesion is artifactitiously disrupted. Blood (asterisks) is present in the subretinal space and within the retina. Subretinal pigment epithelial neovascularization has extended peripherally for a short distance (small arrow) (Hematoxylin and eosin, $\times 160$). C: Temporal to the disciform lesion, there are calcified drusen (asterisks), subretinal hemorrhage (large arrow), and subretinal pigment epithelial (intra-Bruch's-membrane) hemorrhage (arrowhead). The inner aspect of Bruch's membrane is markedly thickened (between smaller arrows) (Van de Grift, $\times 255$).

of these breaks, into the disciform lesion and then to anastomose with retinal vessels. Both eyes displayed prominent thickening of the inner aspect of Bruch's membrane (Fig. 60E). The left eye also showed a thin disciform lesion with a prominent vascular contribution from the retina (Fig. 61A), RPE atrophy, and localized areas of RPE hyperplasia. A single small break in Bruch's membrane with a traversing choroidal vessel was identified (Fig. 61B).

CASE 32

This patient has been followed ophthalmologically for 47 years. The first signs of early senile macular degeneration were noted in 1953 by Dr Alan C. Woods, who noted "a malty appearance and a few drusen spots and occasionally a little

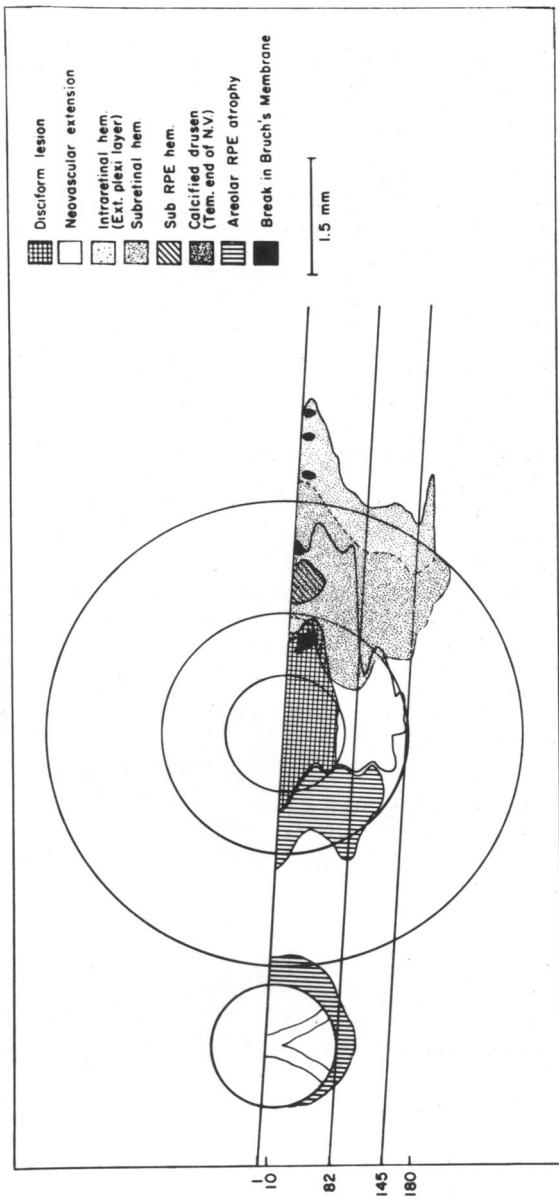


FIGURE 56
Case 29. Two-dimensional reconstruction map from study of serial sections of the left eye showing the location, size and interrelationships of the break in Bruch's membrane, disciform lesion, choroidal neovascularization, subretinal and subretinal pigment epithelial hemorrhage, arcolar atrophy, and calcified drusen.

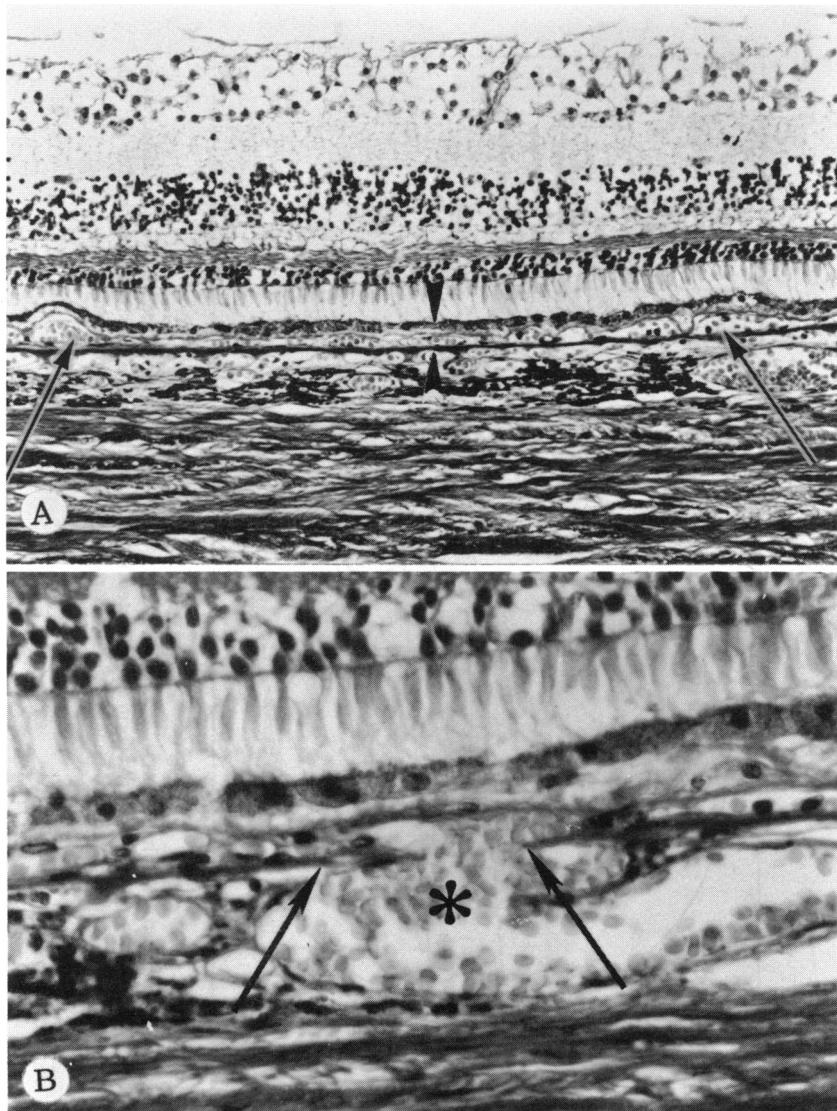


FIGURE 57

Case 29. Right eye. A: Sections through the macular area showing extensive subretinal pigment epithelial neovascularization (arrows). Arrowheads mark the retinal pigment epithelium and Bruch's membrane. The retinal pigment epithelium and photoreceptor cell layer are normal over the neovascular membrane. B: Single break in Bruch's membrane (between arrows) through which choroidal vessels (asterisk) were the only source of blood vessels found in the extensive neovascular membrane. The overlying retinal pigment epithelium and photoreceptor cell layer are normal (Van de Grift, $\times 500$).

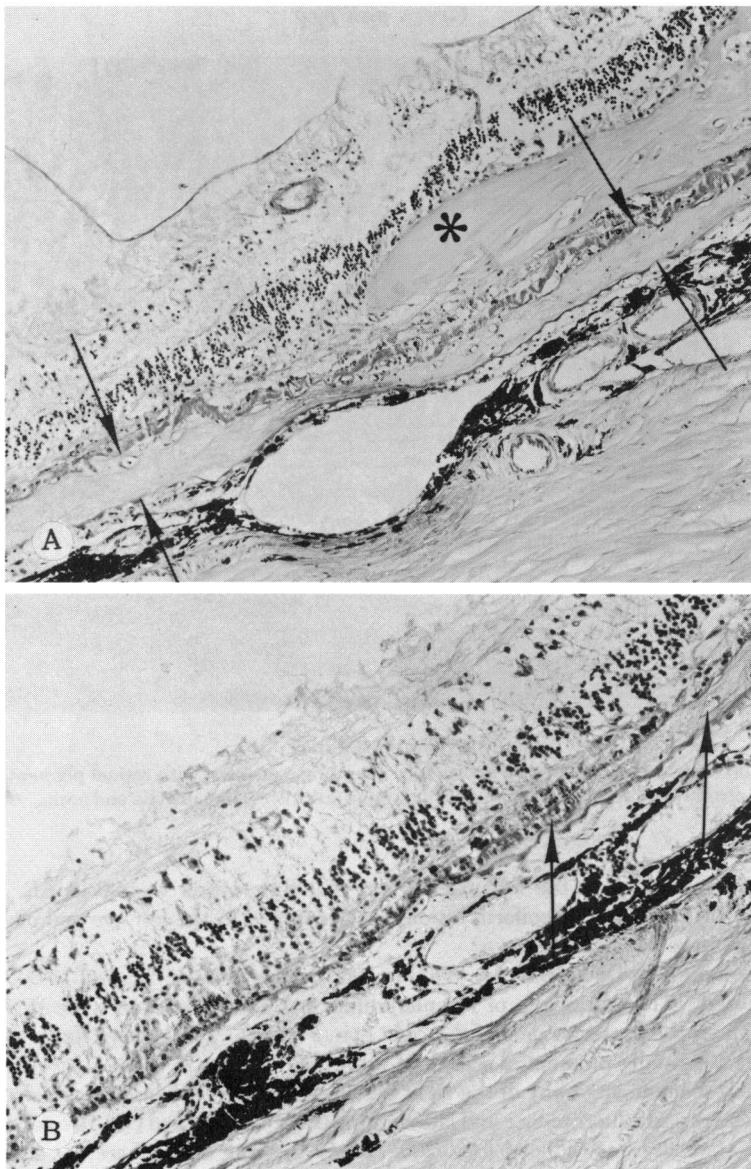


FIGURE 58

Case 30. Left eye. A. There is a moderate-sized disciform lesion between the two layers of Bruch's membrane (between arrows) and between the inner layer of Bruch's membrane and the retina (asterisk). Retinal pigment epithelial and outer nuclear layer atrophy have occurred over the lesion (Periodic-acid Schiff, $\times 110$). B: Peripheral to the disciform lesion, there is intra-Bruch's-membrane neovascularization (arrows). In addition, areolar atrophy is present in both areas with and without the neovascular membrane. There is marked atrophy of the photoreceptor cell layer (Periodic-acid Schiff, $\times 180$).



FIGURE 59

Case. 30. Right eye. There is a neovascular membrane (arrows) with retinal pigment epithelial atrophy and serous detachment of the retina (asterisk) (Hematoxylin and eosin, $\times 240$).

fine pigmentation" in the left macula. At that time vision was 20/15 RE, and 20/40 LE. By 1961, a disciform lesion had developed in the left eye and drusen were observed in the right eye.

When seen by Dr Stewart M. Wolff in 1963, vision of 20/15 RE and 10/200 LE was noted. There was loss of macular reflex and several drusen were present throughout the posterior pole of the right eye (Fig. 62). The left eye had a large, elevated, partially pigmented scar, and subretinal exudate.

Fluorescein angiography of the right eye in April, 1968 disclosed many drusen and areas of early fluorescence and late staining (Figs. 63A, B, and C). The patient's vision gradually was reduced to 20/200. By 1972, large areas of areolar atrophy were observed. The patient had taken Lipotriad for over 15 years. He died in 1974 and both eyes were obtained postmortem.

Microscopic examination of stepped-serial sections (every 0.1 mm) for 5 mm of the posterior pole region of the right eye disclosed diffuse thickening of the inner aspect of Bruch's membrane. In some areas there was loss of retinal pigment epithelium and the photoreceptor cell layer (Fig. 64). Numerous drusen (some of which were large and calcified) were observed. In some areas a very thin

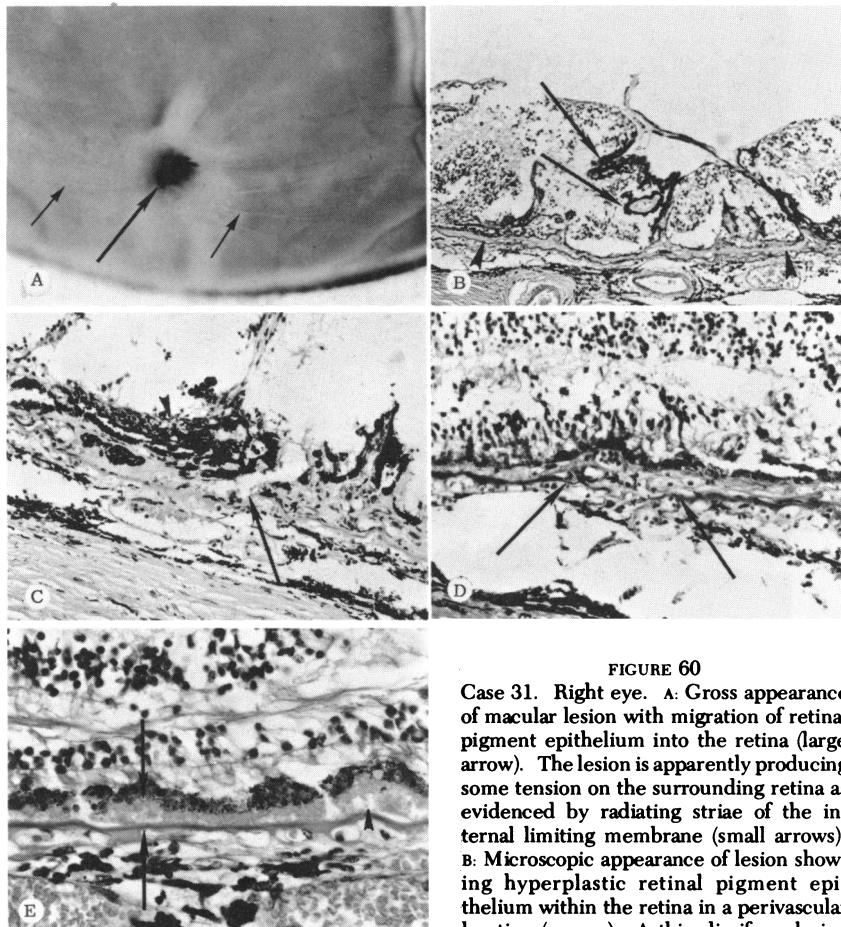


FIGURE 60
Case 31. Right eye. A: Gross appearance of macular lesion with migration of retinal pigment epithelium into the retina (large arrow). The lesion is apparently producing some tension on the surrounding retina as evidenced by radiating striae of the internal limiting membrane (small arrows). B: Microscopic appearance of lesion showing hyperplastic retinal pigment epithelium within the retina in a perivascular location (arrows). A thin disciform lesion is present between two layers of Bruch's membrane (arrowheads). Several retinal vessels extend down to the disciform lesion. C: Break in Bruch's membrane (arrow) through which a choroidal vessel traversed and could be traced in serial section to anastomose with a retinal vessel. A nodule of hyperplastic retinal pigment epithelium is present (arrowhead) (Hematoxylin and eosin, $\times 100$). D: The subretinal pigment epithelial neovascularization extends beyond the central area and there was an additional break in Bruch's membrane (between arrows) through which a choroidal vessel extended into the subretinal space (Masson trichrome, $\times 145$). E: Outside the neovascular area the inner aspect of Bruch's membrane is markedly thickened (between arrows) and the overlying retinal pigment epithelium and outer nuclear layer are intact. Occasional thicker drusen-like nodules are present (arrowhead).

is present between two layers of Bruch's membrane (arrowheads). Several retinal vessels extend down to the disciform lesion. C: Break in Bruch's membrane (arrow) through which a choroidal vessel traversed and could be traced in serial section to anastomose with a retinal vessel. A nodule of hyperplastic retinal pigment epithelium is present (arrowhead) (Hematoxylin and eosin, $\times 100$). D: The subretinal pigment epithelial neovascularization extends beyond the central area and there was an additional break in Bruch's membrane (between arrows) through which a choroidal vessel extended into the subretinal space (Masson trichrome, $\times 145$). E: Outside the neovascular area the inner aspect of Bruch's membrane is markedly thickened (between arrows) and the overlying retinal pigment epithelium and outer nuclear layer are intact. Occasional thicker drusen-like nodules are present (arrowhead).

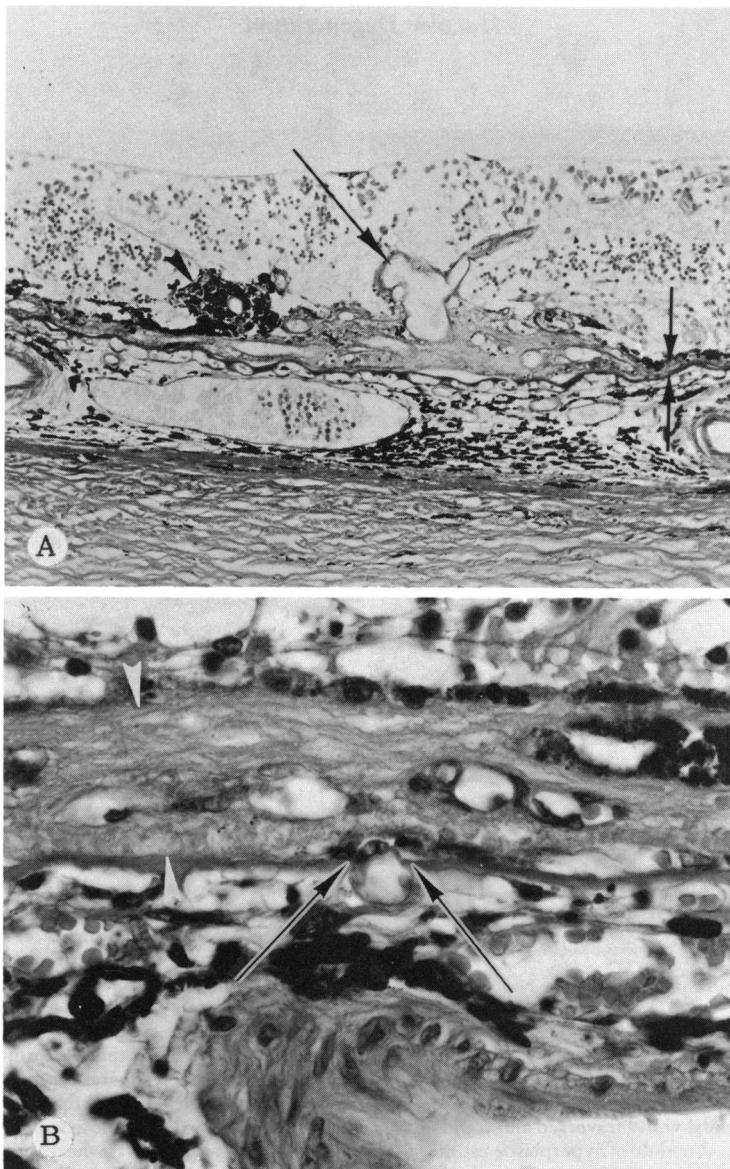


FIGURE 61

Case 31. Left eye. A: There is a flat disciform lesion with prominent retinal vascular contribution (large arrow), nodules of hyperplastic retinal pigment epithelium (arrowhead) and marked thickening of the inner aspect of Bruch's membrane (small arrows) (Hematoxylin and eosin, $\times 475$). B: Area of disciform lesion located between Bruch's membrane and partially atrophic retinal pigment epithelium (arrowheads). A small break in Bruch's membrane (arrows) with a choroidal vessel traversing is present (Hematoxylin and eosin, $\times 600$).

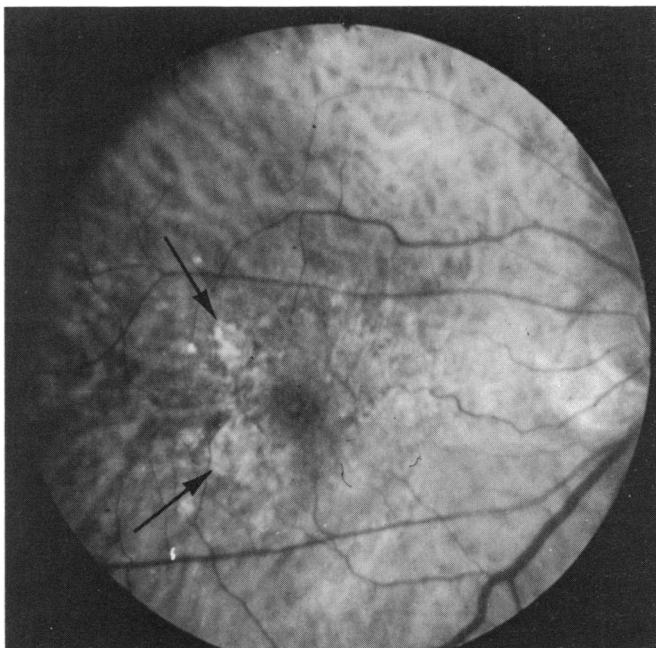


FIGURE 62

Case 32. Right eye. Fundus photograph taken in 1968 showing areas of atrophy and drusen, some of which appear to be calcified. Two larger, and several smaller areas of areolar atrophy (arrows) show late staining with fluorescein (see Fig. 63C).

fibrous tissue, containing occasional spindle-shaped, fibroblast-appearing cells were observed between the outer and thickened inner layers of Bruch's membrane. No breaks in Bruch's membrane were observed, and no blood vessels were seen in the thin fibrous tissue layer between the two layers of Bruch's membrane. Electron microscopic examination of tissue from the superior portion of the parafoveal area (Fig. 65) discloses thickening of Bruch's membrane with the accumulation of vesicles and electron-dense material. Widely-spaced collagen is present in the outer collagenous zone of Bruch's membrane. A new layer of collagen with fibrils having a cross diameter of 265 Å and periodicity of 260 Å is located between the outer and the thickened inner portion of Bruch's membrane. In addition, occasional elongated cells without basement membrane are present in this zone. The retinal pigment epithelium is absent in this area. A thick layer composed primarily of widely-spaced collagen and some granular material is located between the retina and the fibrous connective tissue zone.

In the left eye, a large disciform lesion was noted (Figs. 66A and B). In some areas laminated basement-membrane-like material was observed (Fig. 66C).

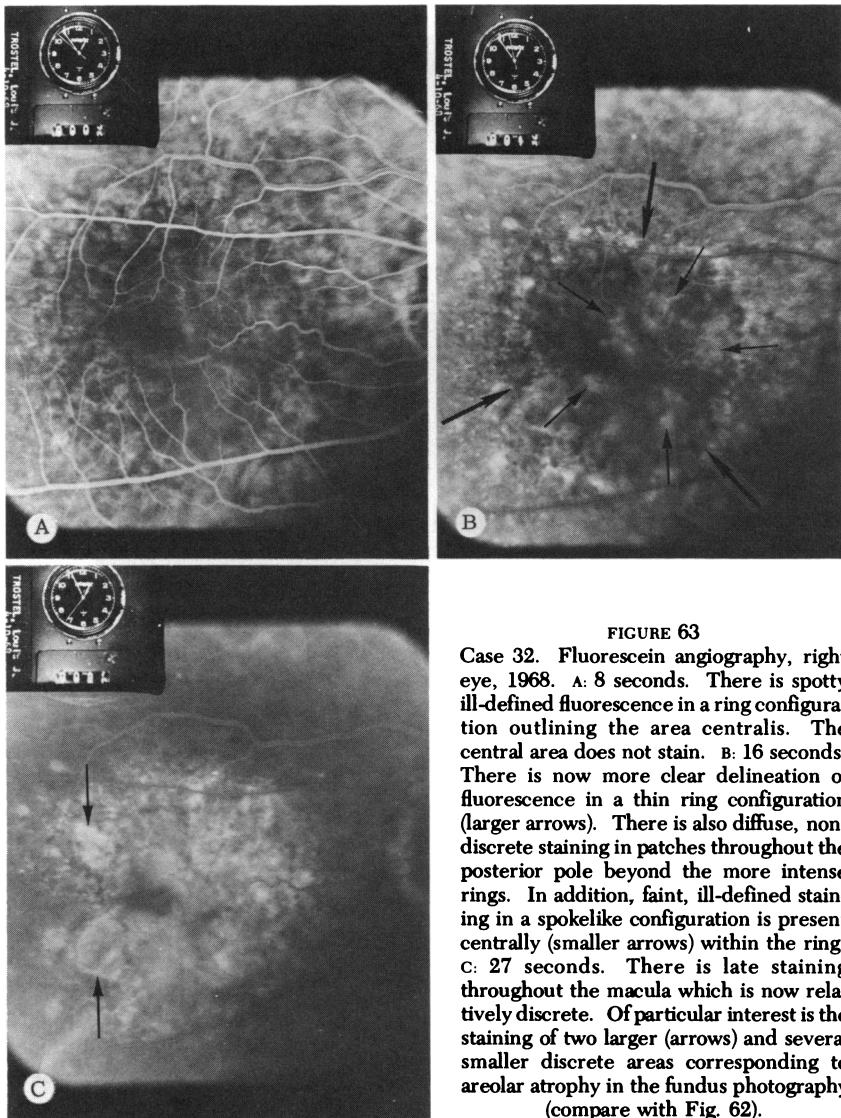


FIGURE 63
Case 32. Fluorescein angiography, right eye, 1968. A: 8 seconds. There is spotty ill-defined fluorescence in a ring configuration outlining the area centralis. The central area does not stain. B: 16 seconds. There is now more clear delineation of fluorescence in a thin ring configuration (larger arrows). There is also diffuse, non-discrete staining in patches throughout the posterior pole beyond the more intense rings. In addition, faint, ill-defined staining in a spokelike configuration is present centrally (smaller arrows) within the ring. C: 27 seconds. There is late staining throughout the macula which is now relatively discrete. Of particular interest is the staining of two larger (arrows) and several smaller discrete areas corresponding to areolar atrophy in the fundus photography (compare with Fig. 62).

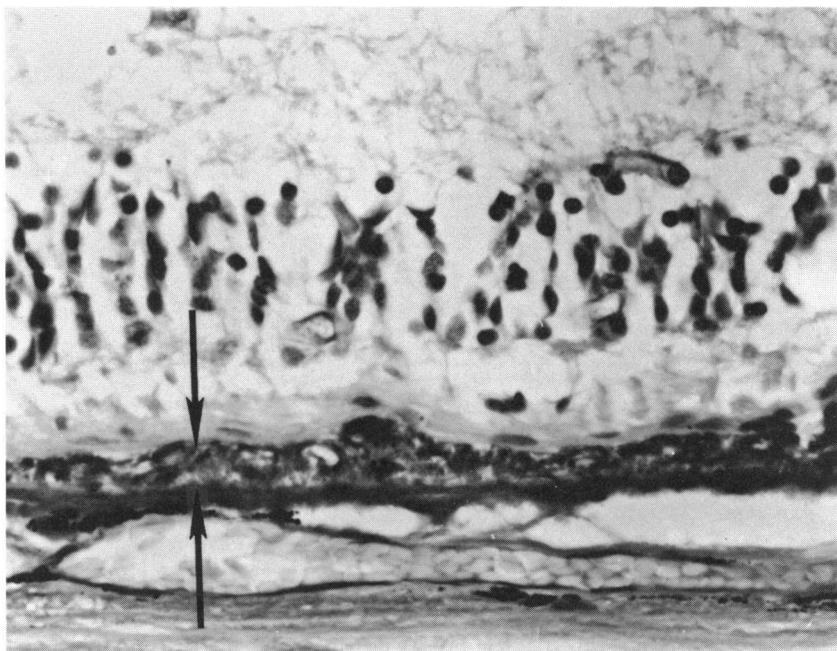


FIGURE 64

Case 32. Typical appearance of the pattern of changes in the right eye including: marked thickening of the inner aspect of Bruch's membrane (between arrows), loss of retinal pigment epithelium and the photoreceptor cell layer (Periodic-acid Schiff, $\times 750$).

Two-dimensional reconstruction from study of serial sections of the left eye depicts two breaks in Bruch's membrane and the relationships of the sub-RPE and subretinal components of the disciform lesion (Fig. 67).

DRUSEN, DISCIFORM WITH SECONDARY SEROUS OR HEMORRHAGIC DETACHMENT OF RETINAL PIGMENT EPITHELIUM AND/OR RETINA

CASE 33

This 102-year-old white woman had bilateral macular degeneration with disciform lesions in the macula and periphery of both eyes. The macular disciform lesions were located both between two layers of Bruch's membrane, and between the inner layer of Bruch's membrane and the retina. In addition, marked exudation was present in and under the retina (Fig. 68A). Similar disciform lesions were located in the periphery (Figs. 68B and C). One of these had marked subretinal exudation and cystic degeneration of the retina (Fig. 68C) and a third displayed marked exudation with numerous lipid and cholesterol deposits (Coats' response) (Fig. 68D).

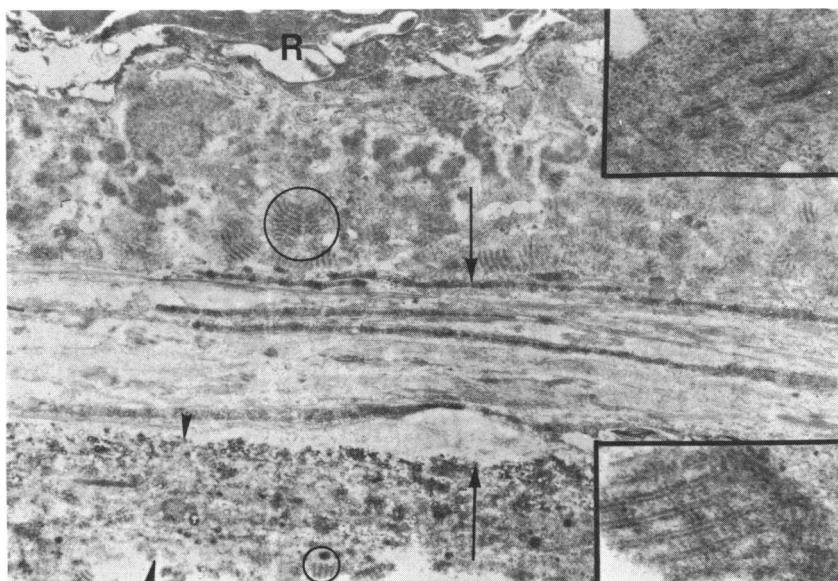


FIGURE 65

Case 32. Ultrastructural appearance of Bruch's membrane in posterior pole of right eye. The elastic and two collagenous zones of Bruch's membrane (between arrowheads) are thickened by the accumulation of vesicles and electron-dense material. Prominent aggregates of widely-spaced collagen are present in the outer collagenous zone (smaller circle and lower inset). The retinal pigment epithelium is absent and the retina (R) rests against the thickened and detached inner layer of Bruch's membrane which is primarily composed of large aggregates of widely-spaced collagen (larger circle and upper inset) and granular material. A thin layer (between arrows) of collagen with a cross diameter of 265 Å and periodicity of 260 Å is present between the outer and detached, thickened inner layer of Bruch's membrane ($\times 7665$, upper inset $\times 32180$, lower inset $\times 33970$).

CASE 34

A 62-year-old man with drusen in both eyes was considered to have a melanoma in the macular area of the right eye, and enucleation was performed in 1955. Microscopic examination disclosed a small disciform lesion that was detached along retinal pigment epithelium (Fig. 69A). Of particular interest was the detachment of drusen (Fig. 69B) along with the RPE and disciform lesion. In addition, an area of retinal pigment epithelial "window" defect was noted near the RPE detachment (Fig. 69C). The RPE was intact in this area but was flattened, with fewer nuclei than normal and had partial loss of pigment granules.

CASE 35

The right eye of this 46-year-old woman was enucleated because of the suspicion of malignant melanoma. Microscopic examination disclosed diffuse and marked

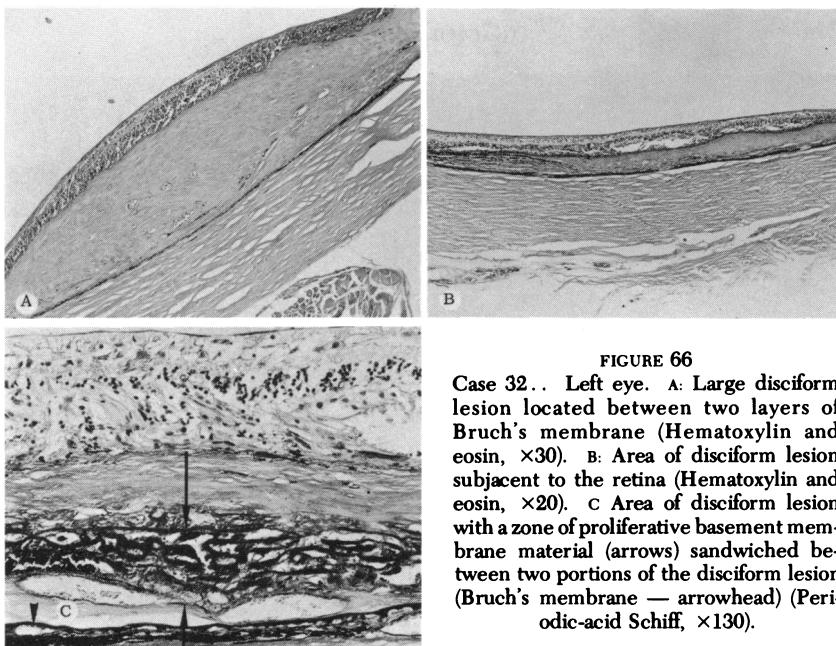


FIGURE 66

Case 32.. Left eye. A: Large disciform lesion located between two layers of Bruch's membrane (Hematoxylin and eosin, $\times 30$). B: Area of disciform lesion subjacent to the retina (Hematoxylin and eosin, $\times 20$). C: Area of disciform lesion with a zone of proliferative basement membrane material (arrows) sandwiched between two portions of the disciform lesion (Bruch's membrane — arrowhead) (Periodic-acid Schiff, $\times 130$).

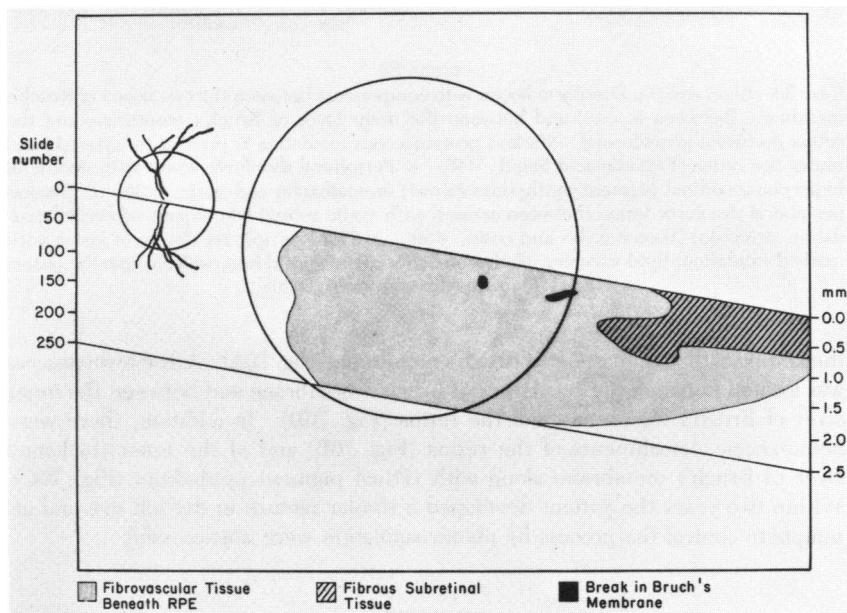


FIGURE 67

Case 32. Two-dimensional reconstruction of lesion of the left eye showing the size and location of two breaks in Bruch's membrane, and the large disciform lesion.

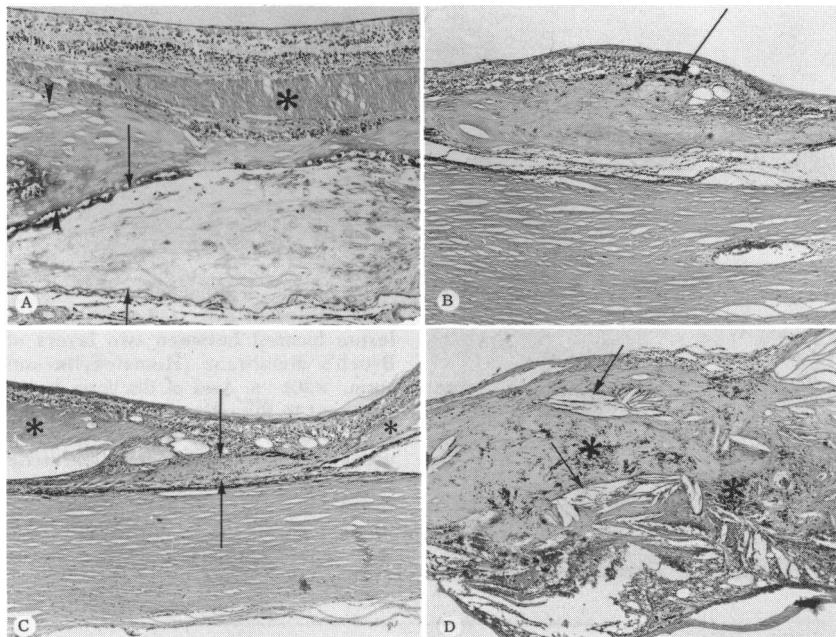


FIGURE 68

Case 33. Right eye. A: Disciform lesion with components between the two layers of Bruch's membrane (between arrows) and between the inner layer of Bruch's membrane and the retina (between arrowheads). Marked proteinaceous exudation is present in (asterisk) and under the retina (Periodic-acid Schiff, $\times 40$). B: Peripheral disciform lesion with nodule of hyperplastic retinal pigment epithelium (arrow) (hematoxylin and eosin, $\times 30$). C: Second peripheral disciform lesion (between arrows) with cystic retinal edema and subretinal exudation (asterisks) (Hematoxylin and eosin, $\times 30$). D: Third peripheral disciform lesion with marked exudation, lipid vacuoles, cholesterol slits (arrows), and hemosiderin staining (asterisks) (Hematoxylin and eosin, $\times 30$).

thickening of the inner aspect of Bruch's membrane (Fig. 70A). A disciform process was located between the two layers of Bruch's membrane and between the inner layer of Bruch's membrane and the retina (Fig. 70B). In addition, there were hemorrhagic detachments of the retina (Fig. 70B) and of the inner thickened layer of Bruch's membrane along with retinal pigment epithelium (Fig. 70C). Within two years the patient developed a similar picture in the left eye and attempts to control the process by photocoagulation were unsuccessful.

DISCUSSION

Senescent changes in the retinal pigment epithelium and Bruch's membrane occur in many persons over age 40, as shown histopathologically

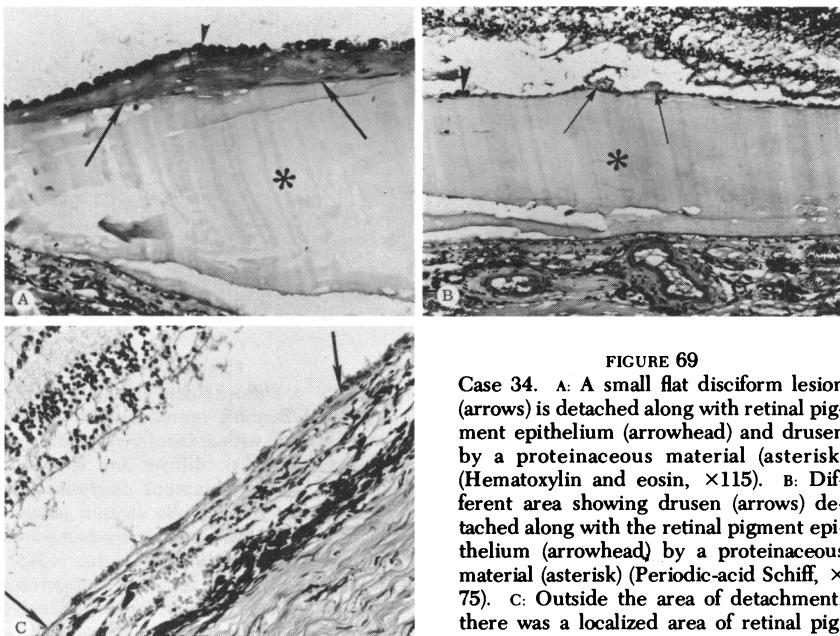


FIGURE 69

Case 34. A: A small flat disciform lesion (arrows) is detached along with retinal pigment epithelium (arrowhead) and drusen by a proteinaceous material (asterisk) (Hematoxylin and eosin, $\times 115$). B: Different area showing drusen (arrows) detached along with the retinal pigment epithelium (arrowhead) by a proteinaceous material (asterisk) (Periodic-acid Schiff, $\times 75$). C: Outside the area of detachment, there was a localized area of retinal pigment epithelial window defect (arrows).

Here the epithelium is intact, but has fewer and larger nuclei than normal and has lost most or all of its pigment granules (Hematoxylin and eosin, $\times 120$).

by Hogan.¹³ Initially, the changes are ultrastructural, detected by electron microscopy as accumulation of lipofuscin and other material in the cytoplasm of retinal pigment epithelial cells and in Bruch's membrane. This deposition may be diffuse, causing thickening of Bruch's membrane, or may be in localized masses, forming drusen.¹³ Histochemically, at least some of the material in drusen appears to be derived from the retinal pigment epithelium.¹⁴

Other ultrastructural changes in Bruch's membrane include deposition of calcium and other substances, alteration of the collagen fibers, and disruption of the elastic layer.¹⁵ By light microscopy, these changes appear as increased staining with Schiff's periodic-acid (PAS) technique, basophilia, thickening, and fragmentation of Bruch's membrane. Although insufficiency of the choriocapillaris might be involved, histopathologic studies have not demonstrated consistent alterations of the choriocapillaris beneath Bruch's membrane and drusen.^{16,17} Primary degeneration or metabolic disturbance of the retinal pigment epithelium would seem to be at least partially responsible for the formation of drusen.

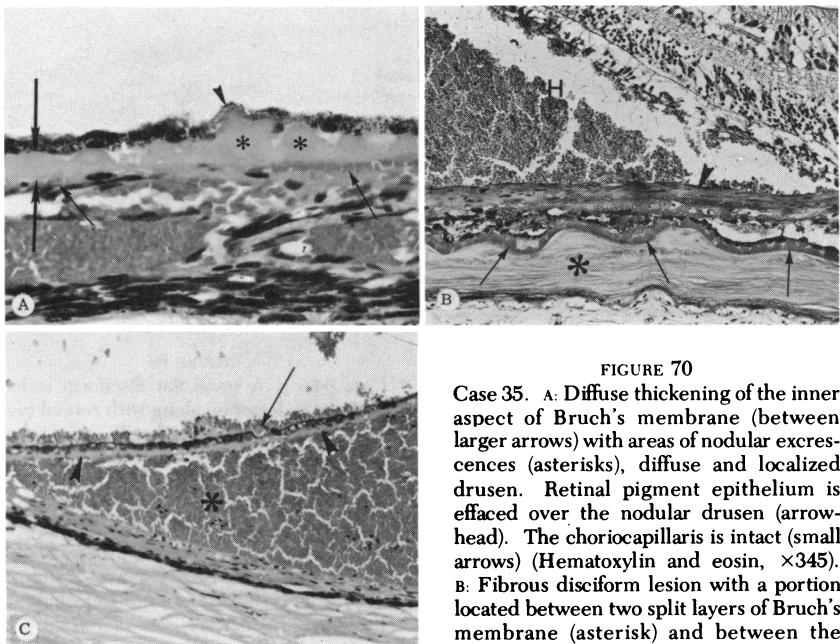


FIGURE 70

Case 35. A: Diffuse thickening of the inner aspect of Bruch's membrane (between larger arrows) with areas of nodular excrescences (asterisks), diffuse and localized drusen. Retinal pigment epithelium is effaced over the nodular drusen (arrowhead). The choriocapillaris is intact (small arrows) (Hematoxylin and eosin, $\times 345$). B: Fibrous disciform lesion with a portion located between two split layers of Bruch's membrane (asterisk) and between the inner layer of Bruch's membrane and retina (arrowhead). Hemorrhage (H) is present beneath the retina. There are diffuse nodular drusen (arrows) throughout the separated inner portion of Bruch's membrane (Verhoeff van Gieson, $\times 130$). C: Hemorrhagic detachment (asterisk) of the thickened inner portion of Bruch's membrane (arrowheads), drusen (arrow), and retinal pigment epithelium (Hematoxylin and eosin, $\times 105$).

One result of the processes associated with drusen is loss of the retinal pigment epithelium, leading to areolar atrophy (Figs. 2-6, 19E, 21, 64). When this occurs, the drusen may disappear.⁵ In areolar atrophy, the photoreceptors are lost too, probably because they are metabolically dependent upon the retinal pigment epithelium.

In the cases studied in this review, the underlying choriocapillaris in areolar atrophy was often sclerosed with thickening of the intercapillary septae. In some instances, endothelium of the choriocapillaris was lacking (Fig. 6B). The loss of retinal pigment epithelium and photoreceptors cannot be explained simply on a vascular basis, however, for this picture is distinct from the type of atrophy caused by choroidal insufficiency. In diseases presumably due to insufficiency of the choriocapillaris, such as peripheral pavingstone degeneration,¹⁸ and healed Elschnig spots, the outer portion of the inner nuclear layer of the retina is usually affected, since it is supplied by the choriocapillaris. The inner nuclear layer is

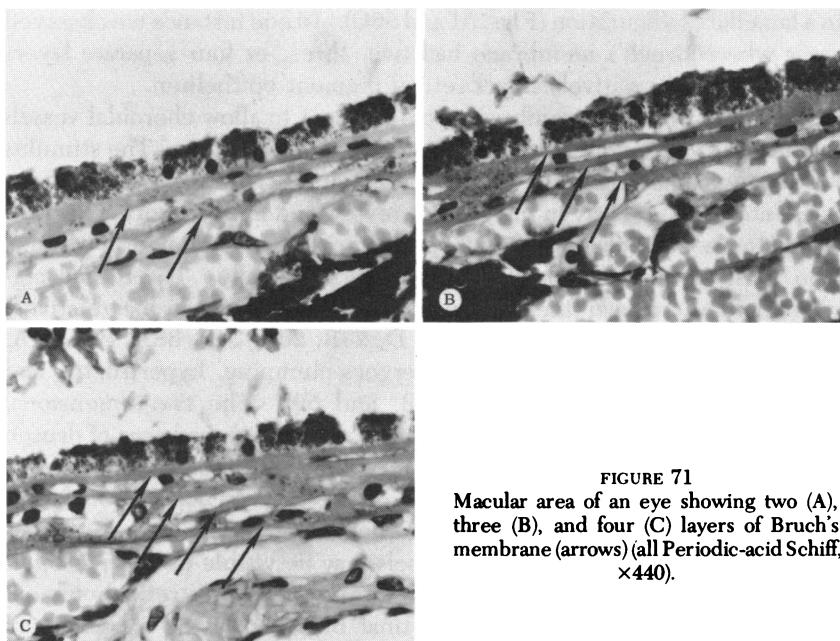


FIGURE 71
Macular area of an eye showing two (A), three (B), and four (C) layers of Bruch's membrane (arrows) (all Periodic-acid Schiff, $\times 440$).

spared in areolar atrophy in senile macular degeneration (Figs. 2A, 3B, 4B, and C, 5A and B, 19D and E, 20, 21, 23A, 48, and 58B).

Most eyes with senile macular degeneration have a diffuse thickening of the inner aspect of Bruch's membrane (basal linear deposit, Sarks¹⁹) in addition to more typical drusen (Figs. 4C, 7B, 8, 13B, 14, 21, 47A and B, 52A, 53, 60E, 64, 65, 70A and C and 71). It appears that this change is frequently the predisposing factor to the splitting of Bruch's membrane and secondary serous and/or hemorrhagic detachment of the retinal pigment epithelium and choroidal neovascularization. The cause of this thickening is obscure, but the material consists of elaboration of reticulum of parallel membranous profiles, vesicles, and widely-spaced collagen embedded within material that is presumably basement-membrane substance (Figs. 14, 53, and 65). Occasional aggregates of widely-spaced collagen are encountered. This thickening apparently weakens Bruch's membrane and allows splitting to occur. Then, serous detachment of the thickened inner portion of Bruch's membrane, drusen, and RPE may occur. Areolar atrophy may follow the resolution of these serous detachments.¹⁰

In some instances, presumably successive detachment or proliferation of retinal pigment epithelium leads to replication of basement membrane

in a lamellar configuration (Figs. 51 and 66C). In one instance we observed areas where Bruch's membrane had two, three, or four separate layers (Fig. 71) with a relatively intact retinal pigment epithelium.

Splitting of Bruch's membrane would appear to allow choroidal vessels to enter the space beneath the retinal pigment epithelium. The stimulus for this vascular ingrowth remains unknown. This complication was encountered frequently in the present review and in the report of Sarks.²⁰ She found neovascularization in 20 percent of 150 eyes of elderly patients who were examined clinically and histopathologically. The retinal pigment epithelium over these neovascular membranes may be relatively intact (Figs. 15, 17A and B, 19C and D, 23B, 20A, 34B, 38A, 40A, 41A, 57A and B, and 60D), but often undergoes clumping, hypertrophy, and atrophy^{19,20} (Figs. 20, 21C, 32, 58B, and 59). The two-dimensional reconstruction map in Fig. 18 illustrates a relatively broad area of drusen formation and pigmentary disturbance surrounding an underlying neovascular membrane. In this autopsy eye, the neovascular network was supplied through multiple breaks in Bruch's membrane.

Ophthalmoscopically, the new vessels may be visible through atrophic retinal pigment epithelium, or obscured by hypertrophic retinal pigment epithelium or fibrous tissue. Subretinal blood and lipid exudates are associated signs that suggest the presence of neovascularization. The membrane may be identified angiographically as a fine network of vessels that fill early, along with the choroid (Figs. 37, 40).

These neovascular membranes tend to leak and bleed, causing serous or hemorrhagic detachment of the retinal pigment epithelium (actually intra-Bruch's membrane) (Figs. 38, 55, 69A and B, 70B and C). The hematoma may resorb,²¹ dissect under the retina, or, rarely, even break into the vitreous cavity. The hemorrhage stimulates proliferation of fibrous tissue between the two layers of Bruch's membrane and may stimulate proliferation of retinal pigment epithelium and fibrous tissue beneath the retina⁴ (Figs. 43-47, 49-51, 55, 56, 58A, 61B, 66, 68, 70B). A clinical example of progression from subretinal-pigment-epithelial neovascularization to disciform fibrovascular scar is illustrated in Figs. 40, 41, and 42.

The retina overlying the disciform scar undergoes cystic degeneration and loss of its photoreceptor cell layer. Central vision is lost. Disciform lesions can become extensive. Secondary changes may occur in the scar, such as bone formation (Figs. 46A and 50B), and retinal arteriolization with retinochoroidal vascular anastomosis (Figs. 41B, 50B, 60B and C, and 61A).²² A nonspecific inflammatory response may be observed in the choroid (Figs. 5B and 46B).²³

Profuse serous exudation from vessels within the disciform lesion may give massive accumulations of intra- and subretinal serous exudate (Figs. 68A and C) which may be rich in lipid (Fig. 68D). The resultant fundus picture has been called "senile Coats' disease," "Coats'-like response," or "exudative senile maculopathy."²⁴

We often found examples of areolar atrophy and neovascularization occurring together in the same individual (22 of 63 cases with neovascularization in which both eyes were studied. In addition, these two processes were sometimes found in the same eye, as illustrated in Figs. 19D, 20, 21C, 52B, 56, 58B, and 59. In one patient, both eyes had breaks in Bruch's membrane. The right eye had choroidal neovascularization adjacent to areolar atrophy and the left eye had the breaks within the area of atrophy and no neovascularization (Figs. 22-25).

SUMMARY

The histopathologic features of 176 eyes from 115 patients with senile macular degeneration have been studied. The results support the view that older persons with drusen are predisposed to the development of serous detachments, areolar retinal pigment epithelial atrophy, and sub-retinal pigment epithelial neovascularization. Direct clinicopathologic correlation was accomplished in 11 cases. Serial sections through the macular lesions were prepared and studied in 45 eyes. Five eyes were studied with stepped-serial sections through the macula at 0.1 mm intervals. Two-dimensional map reconstruction of the macular lesion of eight eyes was performed. Electron microscopic study of Bruch's membrane was performed in five eyes.

A flow chart illustrating the interrelationships of the various morphologic forms of senile macular degeneration is proposed.

REFERENCES

1. Gifford SR, Cushman B: Certain retinopathies due to changes in the lamina vitrea. *Arch Ophthalmol* 23:60-75, 1940.
2. Elwyn H: *Diseases of the Retina*, ed 2. New York, Blakiston Co, 1953, p 261.
3. Maumenee AE: Serous and hemorrhagic disciform detachment of the macula. *Trans Pac Coast Otoophthalmol Soc* 40:139-160, 1959.
4. Gass JDM: Pathogenesis of disciform detachment of the neuroepithelium. III. Senile disciform macular degeneration. *Am J Ophthalmol* 63:617-644, 1967.
5. Gass JDM: Drusen and disciform macular detachment and degeneration. *Arch Ophthalmol* 90:206-217, 1973.
6. Teeters VW, Bird AC: The development of neovascularization of senile disciform macular degeneration. *Am J Ophthalmol* 76:1-18, 1973.
7. Gragoudas ES, Chandra SR, Friedman E, et al: Disciform degeneration of the macula. II. Pathogenesis. *Arch Ophthalmol* 94:755-757, 1976.

8. Pearce WG: Doyne's honeycomb retinal degeneration: Clinical and genetic features. *Br J Ophthalmol* 52:73-78, 1968.
9. Deutman AF, Jansen LMAA: Dominantly inherited drusen of Bruch's membrane. *Br J Ophthalmol* 54:373-382, 1970.
10. Gass JDM: *Stereoscopic Atlas of Macular Diseases: A Funduscopic and Angiographic Presentation*, St. Louis, Mosby, 1970, p 32.
11. Frank RN, Green WR, Pollack IP: Senile macular degeneration: Clinicopathologic correlations of a case in the predisciform stage. *Am J Ophthalmol* 75:587-594, 1973.
12. Small ML, Green WR, Alpar JJ et al: Senile macular degeneration: A clinicopathologic correlation of two cases with neovascularization beneath the retinal pigment epithelium. *Arch Ophthalmol* 94:601-607, 1976.
13. Hogan MJ: Honored guest presentation: Role of the retinal pigment epithelium in macular disease. *Trans Am Acad Ophthalmol Otolaryngol* 76:64-80, 1972.
14. Farkas TG, Sylvester V, Archer D, Altona M: The histochemistry of drusen. *Am J Ophthalmol* 71:1206-1215, 1971.
15. Hogan MJ, Alvarado JA, Weddell JE: *Histology of the Human Eye*, Philadelphia, Saunders, 1971, p 330.
16. Hogan MJ: Bruch's membrane and disease of the macula: Role of elastic tissue and collagen. *Trans Ophthalmol Soc UK* 87:113-161, 1967.
17. Spencer WH: Symposium: Macular diseases: Pathogenesis: Light microscopy. *Trans Am Acad Ophthalmol Otolaryngol* 69:662-667, 1965.
18. Okun E: Gross and microscopic pathology in autopsy eyes. II. Peripheral chorioretinal atrophy. *Am J Ophthalmol* 50:574-583, 1960.
19. Sarks SH: Aging and degeneration in the macular region: A clinicopathological study. *Br J Ophthalmol* 75:587-594, 1973.
20. Sarks SH: New vessel formation beneath the retinal pigment epithelium in senile eyes. *Br J Ophthalmol* 60:324-341, 1976.
21. Reese AB, Jones IS: Hematomas under the retinal pigment epithelium. *Trans Am Ophthalmol Soc* 59:43-79, 1961.
22. Green WR, Gass JDM: Senile disciform degeneration of the macula: Retinal arterialization of the fibrous plaque demonstrated clinically and histopathologically. *Arch Ophthalmol* 86:487-494, 1971.
23. Verhoeff FH, Grossman HP: Pathogenesis of disciform degeneration of the macula. *Arch Ophthalmol* 18:561-585, 1937.
24. Schatz H, Patz A: Exudative senile maculopathy: I. Results of argon laser treatment. *Arch Ophthalmol* 90:183-196, 1973.

DISCUSSION

DR ROBERT C. WATZKE. Traditionally, senile macular degeneration has been divided into a dry or degenerative type characterized by alteration of the pigment epithelium, atrophy of the photoreceptors, and even hole formation; and a disciform type characterized by exudation and hemorrhage from a fibrovascular membrane. Drs Green and Key however hypothesize that such a distinction is artificial and that both processes are part of a broad spectrum of aging and degeneration.

These aging and degenerative changes consist of [Slide]:

- 1) Choroidal alterations consisting of hyalinization of intercapillary tissue, atrophy, and thinning of the choroid leading to prominence of choroidal vessels and a tigroid fundus.
- 2) Bruch's membrane changes consisting of thickening, hyalinization, calcification, and breaks.

3) The invasion of new fibrovascular tissue both within Bruch's membrane and internal to it.

4) Atrophy of the pigment epithelium.

5) Serous and hemorrhagic detachment of the pigment epithelium.

Two other entities have also been mentioned as significant in the development of senile macular degeneration. These are drusen formation and a so-called basal laminar deposit.

In this fine study Drs Green and Key have found a high degree of association of drusen with disciform degeneration. Their pathologic study corroborates the clinical studies of Gass and Gragoudas and others who found a high association of drusen in the fellow eyes of patients with disciform degeneration.

If we are going to use drusen as a clinical sign of the predisciform state we should try to agree on a concept of exactly what drusen are and what is their clinical definition.

In my experience drusen appear to fall into three classifications: The first [Slide] type are drusen which are familiar to all of us. They are discrete, small, round, globular, golden colored masses usually no larger than the diameter of a tertiary arteriole. They correspond to the globular hyalin excrescences of Bruch's membrane so well demonstrated in many eyes.

The second clinical type of drusen which we see are different in appearance [Slide]. These are larger, amorphous, yellow deposits, irregular in shape and of varying size with a soft appearance to them, situated deep to the retina. They are often confluent and they certainly have a tendency to change in shape and even to disappear later [Slide]. They are often associated with detachments of the pigment epithelium, but they appear both angiographically and morphologically to be different.

The exact histologic appearance of this type of drusen has not been settled. Bonnet calls these "colloid bodies" and feels that they are possibly lipid in nature and hence are usually not recognized on the usual type of formalin fixed tissue. Sarks believes that they correspond to what she calls "granular drusen" and I show a slide of this type of drusen material kindly loaned to me by Dr Sarks [Slide]. There is an accumulation of granular material at the base of the pigment epithelium. These often contain foci of calcification and their contents are frequently lost during fixation for histologic study.

A third type of drusen are glittering, hard deposits usually surrounded by an aureola of atrophic pigment epithelium [Slide]. Here are such drusen and a section through them [Slide] showing them to be basophilic, probably calcified, material surrounded by atrophic pigment epithelium.

Sarks has mentioned also a very significant deposit which she terms a basal laminar deposit or basal linear deposit. This is a granular material taking a Mallory stain at the base of the pigment epithelial cells. It correlates very well with the stage of disciform degeneration and the vision of the patient. By electron microscopy this material consists mainly of degenerative or newly formed collagen material. It probably comes from degenerative pigment epithelium.

She states that it is not clinically visible, which is unfortunate since it might be an excellent indicator of the stage of degeneration of the macula.

I would appreciate Dr Green's comments particularly on the term drusen and in what context he uses his both clinically and histologically. Does he believe that it is possible clinically to differentiate between the different histologic varieties of drusen? What is the nature of these amorphous colloid bodies or "giant drusen"? Has he found Sarks' basal laminar deposit to be uniformly present in the eyes which he studied and does he feel it is also commonly associated with disciform degeneration?

It has been a pleasure to read and discuss this fine paper. I look forward to the published work, for his brief oral presentation has only sampled the information learned from such a detailed study of so many eyes with this disease.

PROFESSOR JULES FRANÇOIS. I agree completely with Doctor Green. Thirty years ago I insisted that atrophic senile macular degeneration and the disciform type are two evolutive stages of the same disease. Genetics, which is much more important than one can think, gives you another proof. Senile macular dystrophy is inherited as an autosomal dominant trait. If you have a family with two affected generations, you can find the various forms in the same family.

PROFESSOR M. LUNTZ. Dr Harrington, I want to thank you for the opportunity to participate in the discussion. In Johannesburg we have the opportunity of examining large numbers of black patients. One point of major interest is that in our black patients we see many with advanced forms of retinal pigment epithelial degeneration and with drusen, but we have not yet seen one patient with the wet form of senile macular degeneration.

As far as our white patients are concerned, they show the same disease patterns as described by Dr Green in his excellent presentation.

Last year, a Fellow who was working with me from the Moorfields Eye Hospital and one of my residents examined the maculas of 1000 black patients over the age of 50. They found patients with senile forms of retinal pigment degeneration and drusen but in not one patient were they able to demonstrate the wet form of senile macular degeneration, so-called disciform degeneration, although many of these patients as I mentioned had colloid at the macula, drusen of the macula, and retinal epithelial degenerative diseases. Our pathologists have examined and are in the process of examining a large number of globes on black patients at random and once again have not yet found one case with the wet type of senile macular degeneration. I noticed that Dr Green had some black patients in his series and I wonder if he has any comments to make on this point.

Thank you very much.

DR J. DONALD M. GASS. I would like to make several comments. First, I congratulate Dr Green and Dr Key on giving us some additional clinicopathologic correlative information. It confirms what Sarks and others have shown, that patients with this disease develop new vessels that grow from the choroid through

Bruch's membrane and that initially these are small and non-detectable, not only with the slit-lamp, but with fluorescein angiography. Our inability to detect these small neovascular membranes creates a problem when we proceed with photo-coagulation. These undetected membranes may be the cause of bleeding occurring during or soon after the application of photocoagulation to one edge of these membranes.

Second, I want to agree with what Dr François said. We refer to this disease as senile macular degeneration and the implication is that it's merely an aging phenomenon that would happen to all of us if we lived long enough. I think, however, that there is good evidence that we are dealing primarily with an autosomal dominant dystrophic disease that has many clinical manifestations. Most people go through life without losing significant vision in both eyes. It is interesting that despite the fact that we have good histopathologic information about this disease, we still do not know the primary locus of this disease. Is it the pigment epithelium, is it Bruch's membrane, or is it the choriocapillaris?

Thank you.

DR WILLIAM RICHARD GREEN: I wish to thank all the discussants for their comments, especially Dr Watzke for his kind remarks.

Dr Watzke raised the question of the definition of drusen. I think that perhaps we all can agree on the typical druse as being a relatively small yellowish-white lesion which lights up early with fluorescein and stains late with no leakage. The extent to which these lesions are seen ophthalmoscopically, without fluorescein, depends on thinning of the overlying retinal pigment epithelium. Drusen may become calcified and presumably have a more glistening appearance. This has not been confirmed by a direct clinicopathologic study.

Drusen do become larger and have the same ophthalmoscopic and fluorescein angiographic appearance as small serous detachments of the retinal pigment epithelium. We reported the clinicopathologic findings of one patient who had been followed for many years by several ophthalmologists. This patient was thought to have early senile macular degeneration with prominent drusen in the macula of both eyes (*Am J Ophthal* 75:587-594, 1973). Two-dimensional reconstruction of the macular areas of both eyes from the study of serial sections disclosed some typical drusen, and several small serous detachments of the retinal pigment epithelium in the areas corresponding to the lesions observed clinically.

The cut-off point between a large druse and a small serous retinal pigment epithelial detachment is not clear. I suspect that most of us rely on the size of the lesion.

We often see a diffuse thickening of the inner aspect of Bruch's membrane. One of the principal constituents of this thickened material is clumps of widely-spaced collagen. We have shown several examples of this and it has also been described by Sarks as basal laminar deposits. This diffuse type of drusen (if that is an appropriate designation) is not always evident clinically. In some cases, however, it is detected by a diffuse mottling of the retinal pigment epithelium and with fluorescein there is a diffuse lighting up and staining in these areas. We have conducted clinicopathologic studies on several cases of this type. Small, nubby,

drusen-like excrescences are often superimposed on the diffusely thickened area.

The diffusely thickened inner aspect of Bruch's membrane is apparently weakened, for there is usually separation within this layer with subsequent serous retinal pigment epithelial (or, should we say, intra-Bruch's membrane) detachment.

Professor François has reminded us that senile macular degeneration is possibly an hereditary disease. The evidence for this is certainly suggestive, but as yet it is not substantial. We had only limited data concerning the genetic aspects of the disease in the patients studied in our group of patients.

Dr Gass has astutely indicated concern regarding the initial changes in senile macular degeneration. We have to say that we obviously do not know. We did carefully study the choriocapillaris, particularly in the areolar atrophy form, in an effort to determine whether vascular sclerosis and ischemia play a role. Evaluation of the choriocapillaris in routine sections may be quite difficult, but we concluded that there was no consistent pattern of choriocapillaris loss. Also, the pattern of retinal atrophy is not one of outer ischemic atrophy with loss of all outer layers up to and including a portion of the inner nuclear layer. We often found the inner nuclear layer and a portion of the outer plexiform layer remaining intact.

On the basis of the morphologic changes, we would postulate that the initial abnormality is at the level of the retinal pigment epithelium and that this tissue is responsible for the production of drusen and the diffuse thickening of the inner aspect of Bruch's membrane with the deposition of abnormal substances including widely-spaced collagen. Whether or not there is some abnormality in the biochemical interplay between the retinal pigment epithelium and photoreceptor cells is not known.

Professor Luntz's comments concerning the occurrence of this disease in black patients in Johannesburg are interesting. As we noted, we did have eyes from black patients, but we were impressed that 85% of our patients were white, yet over 50% of the autopsies performed during the period of collection of our cases were blacks.

Dr Key and I appreciate the opportunity to present the results of our study and again would like to thank the discussants.