Selected Papers on Progress in Recent Ophthalmology

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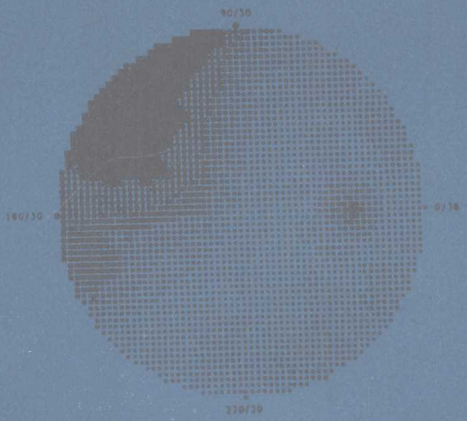

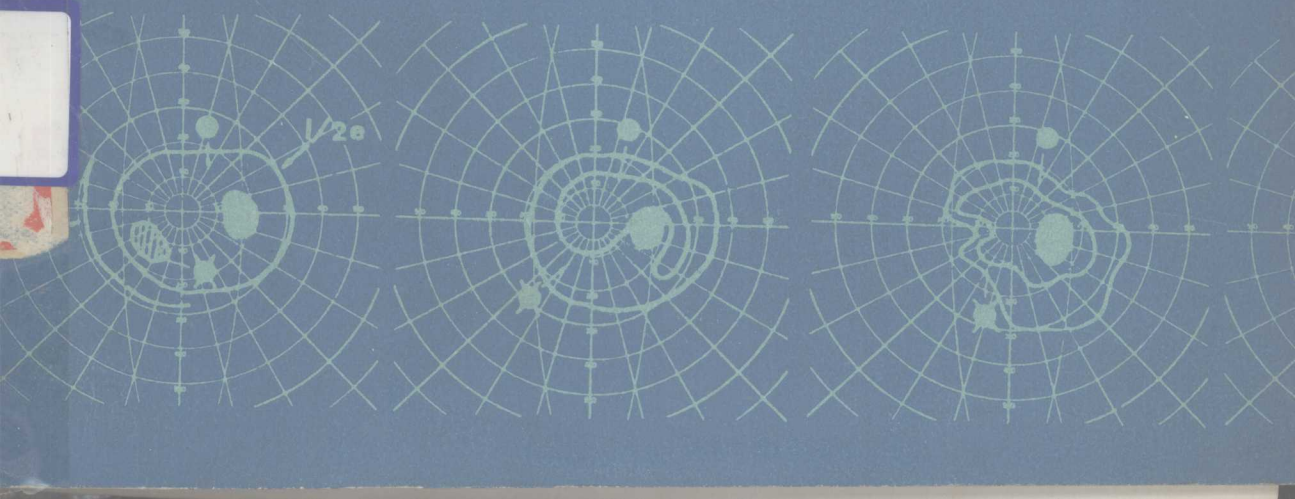

Selected Papers on Progress in Recent Ophthalmology

II

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SENILE MACULAR DEGENERATION: A HISTOPATHOLOGIC STUDY*

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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, subretinal 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-

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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 Degneration	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 Gass[4] 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

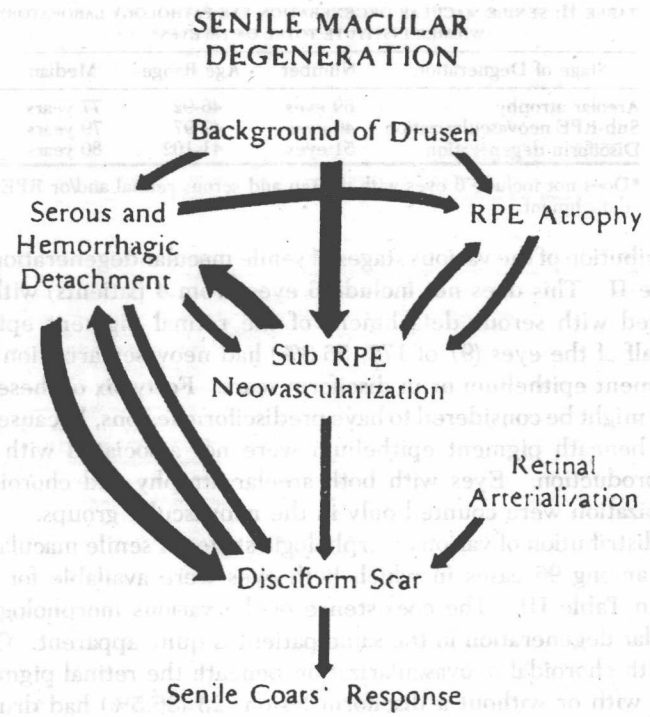

FIGURE 1

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.

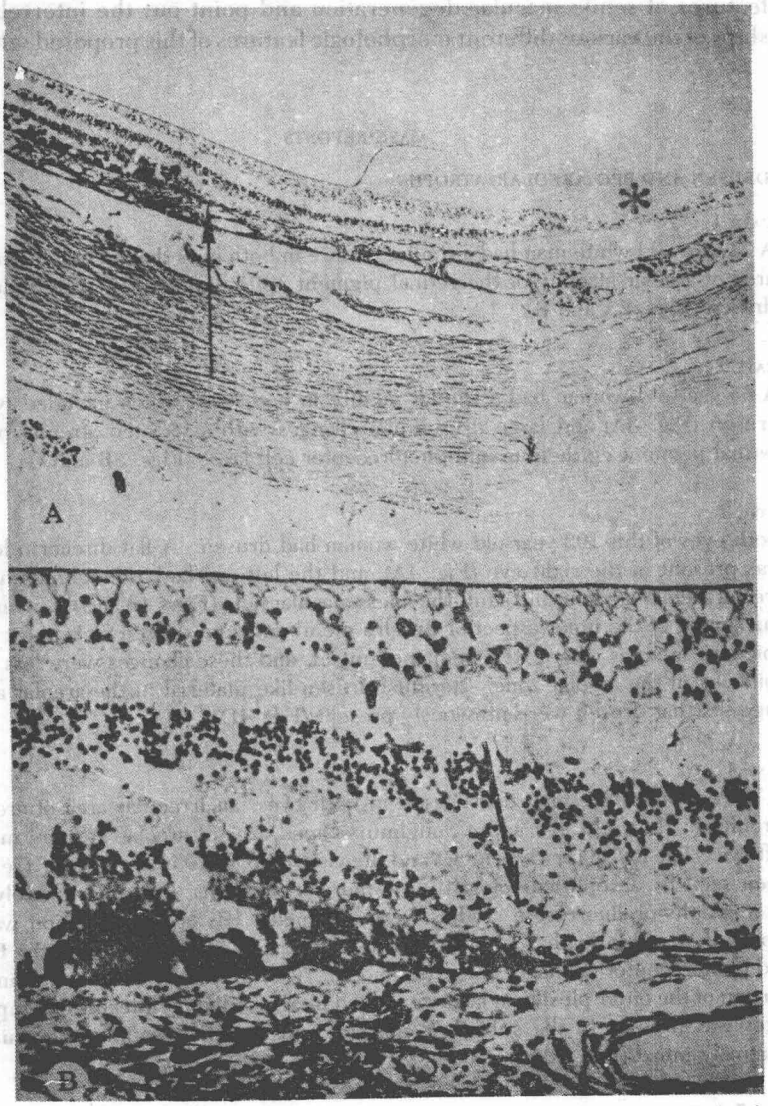

FIGURE 2

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, ×40). B. Higher power of abrupt junction (arrow) between areolar and drusen areas (Periodic-acid Schiff, ×240).

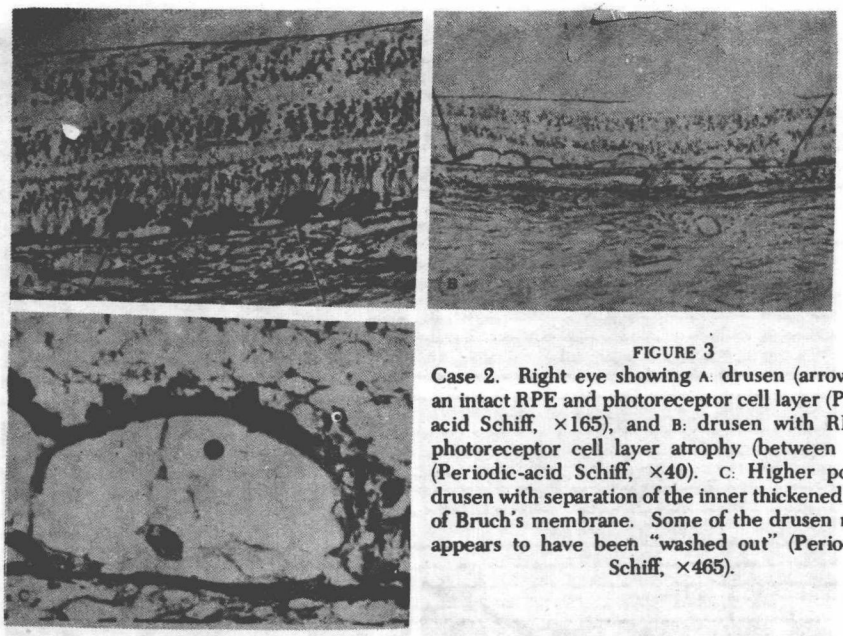

FIGURE 3

Case 2. Right eye showing A: drusen (arrows) with an intact RPE and photoreceptor cell layer (Periodic-acid Schiff, ×165), and B: drusen with RPE and photoreceptor cell layer atrophy (between arrows) (Periodic-acid Schiff, ×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, ×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

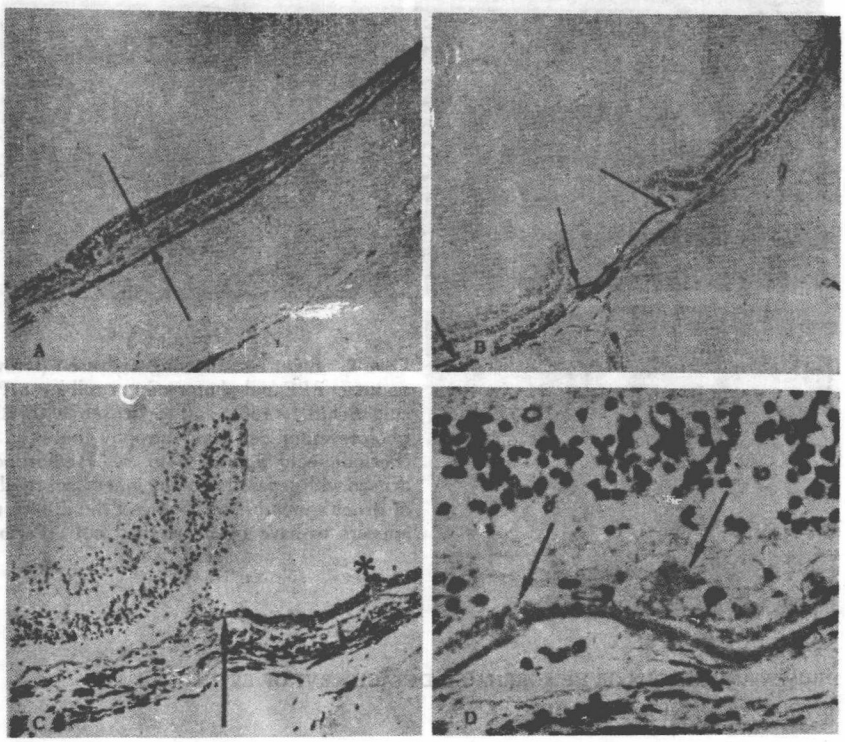

FIGURE 4

Case 3. A: Flat disciform lesion (between arrows) of the right eye (Hematoxylin and eosin, ×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, ×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, ×100). D: Areolar area showing residual drusen-like material (arrows) (Periodic-acid Schiff, ×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).

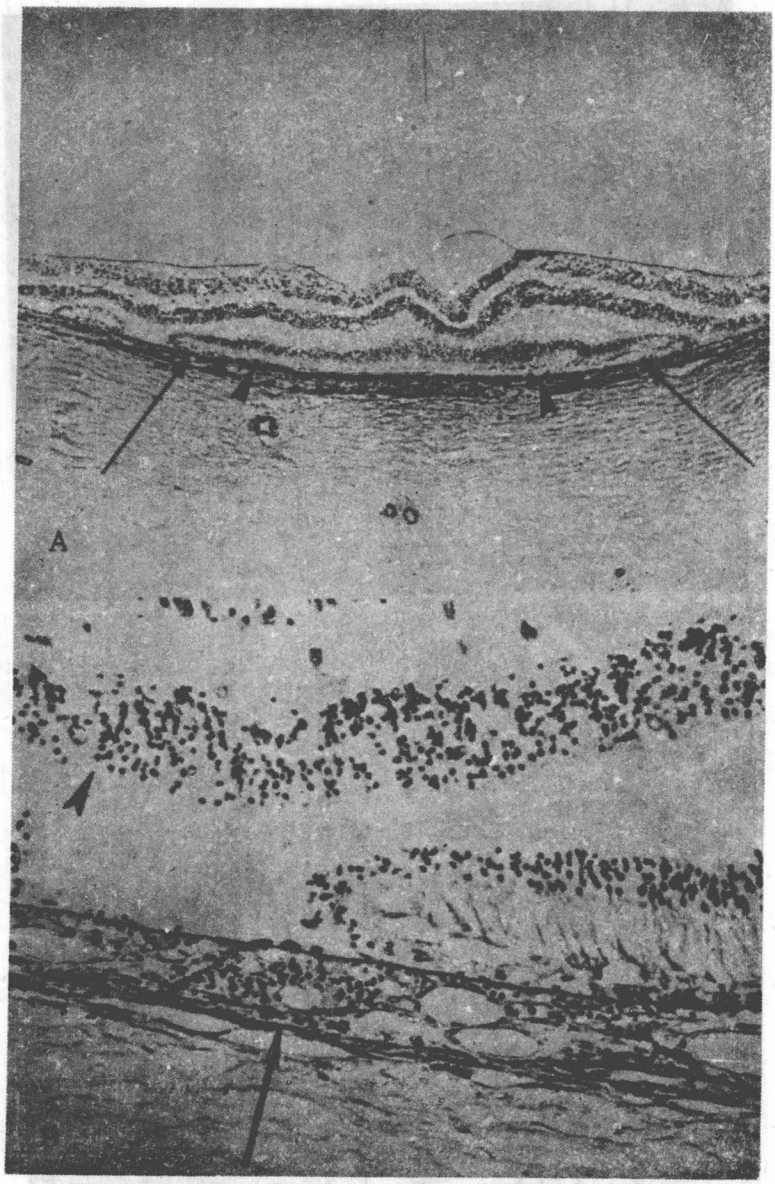

FIGURE 5

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, ×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, ×240).

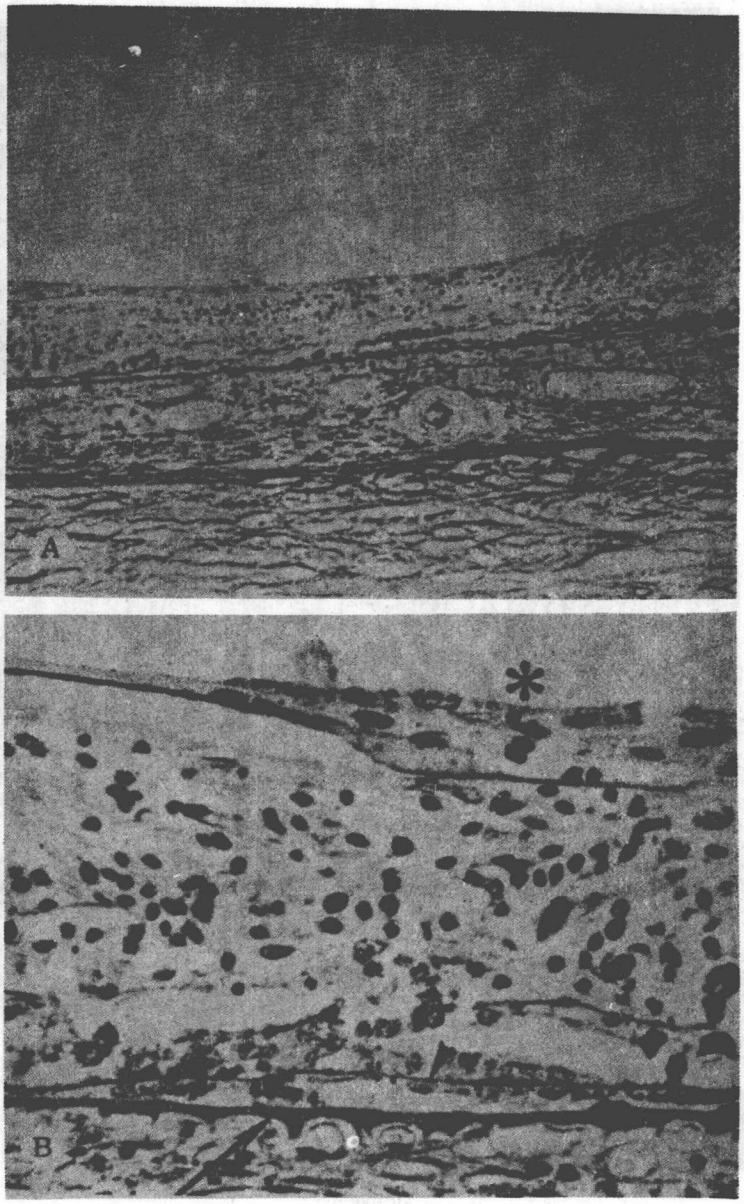

FIGURE 6

Case 5. A: Central area of areolar atrophy (Periodic-acid Schiff, ×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, ×500).

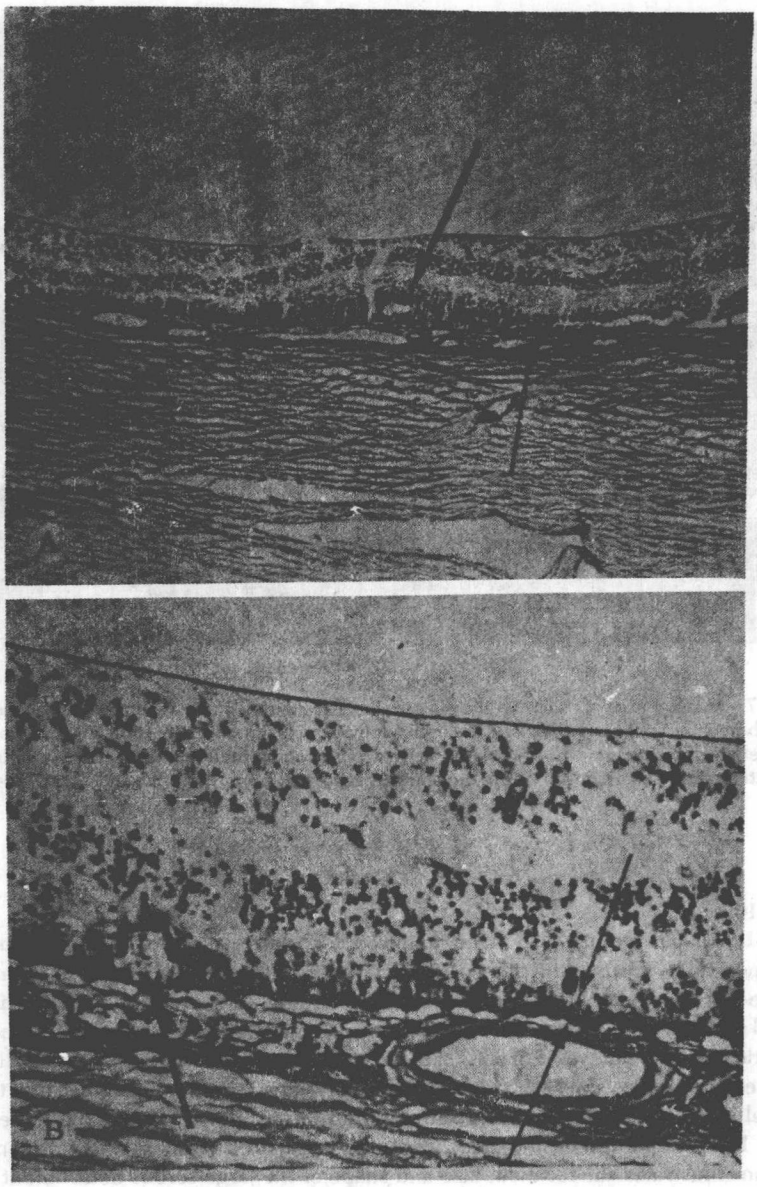

FIGURE 7

Case 6. A: Small serous detachment of retina (large arrow) associated with drusen (small arrows) (Periodic-acid Schiff, ×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, ×210).

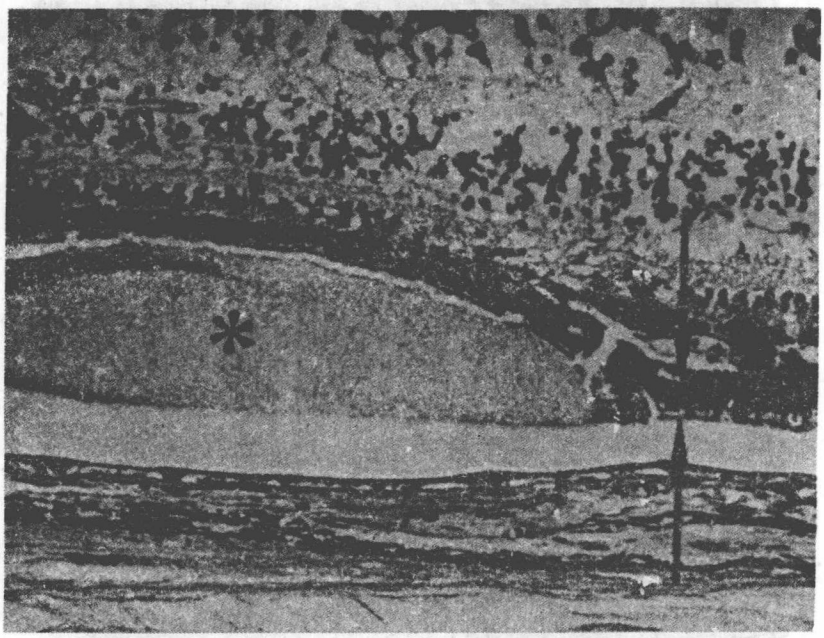

FIGURE 8

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, ×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

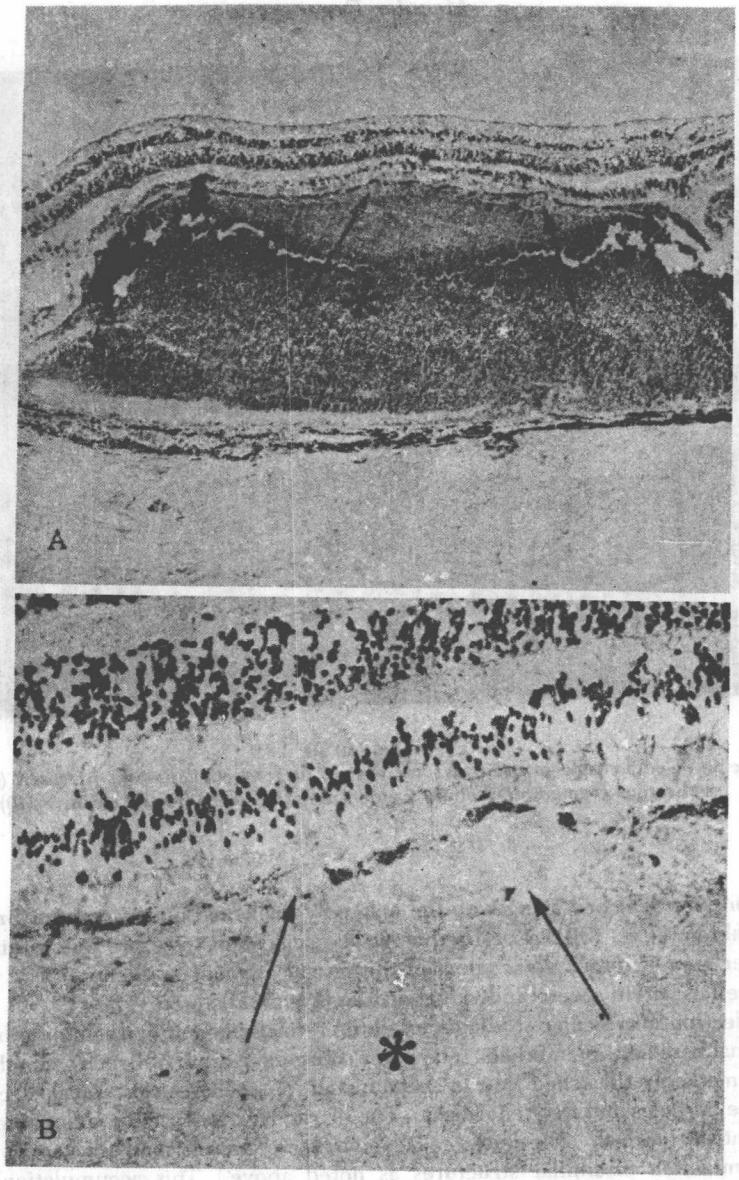

FIGURE 9

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, ×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, ×240).

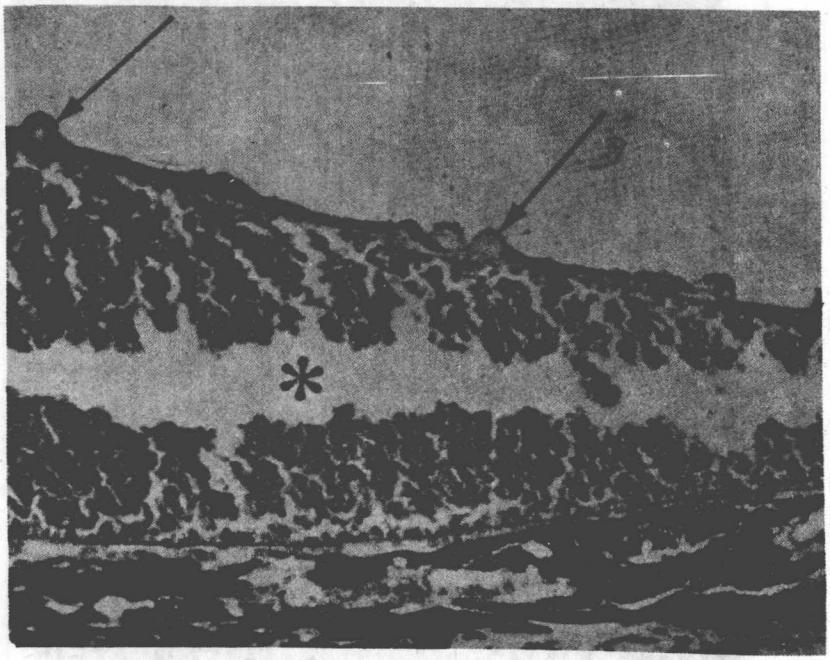

FIGURE 10
Case 9. Hemorrhagic intra-Bruch's membrane detachment (asterisk). Drusen (arrows) and retinal pigment epithelium are detached (Hematoxylin and eosin, ×240).

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 electon-dense material, but no disks of the outer segments (Fig. 14).