



Histopathology of age-related macular degeneration

W. Richard Green

Departments of Ophthalmology and Pathology, Johns Hopkins Medical Institutions, Baltimore, MD

Age-related macular degeneration is a diffuse condition involving the retinal pigment epithelium, the photoreceptor cell layer, and perhaps the choriocapillaris. The early morphologic change is the development of basal deposits of two distinct types. This phase is not ophthalmoscopically detectable but psychophysical testing may demonstrate reduced function. The process becomes detectable with the occurrence of secondary changes in the pigment epithelium, soft drusen formation, and choroidal neovascularization. A reparative response results in disciform scars. The various morphologic forms of age-related macular degeneration are interrelated.

Histopathologic and clinicopathologic correlative studies have delineated most of the morphologic features of age-related macular degeneration (AMD) [1-6] and the interrelationship of the various morphologic forms [5]. Figure 1 is a flow diagram that shows the interrelationships of the various morphologic features of AMD [6]. The entire area centralis may be involved but the most marked changes often occur in the central area inclusive of the parafoveal area.

The earliest morphologic feature of AMD is the development of basal deposits external to the RPE, originally termed "diffuse drusen" [5]. It now seems clear that two distinct types of deposits occur, basal laminar (BLamD) and basal linear (BLinD) [1]. This terminology was put forward in an attempt to reduce the confusion generated by previous conflicting terms. BLamD is composed of granular material with wide-spaced collagen located between the plasma membrane and the basal lamina of the RPE [1] (Figure 2). BLinD is composed of material with coated and non-coated vesicles and some membranous profiles that is located external to the basal lamina of the RPE, that is, in the inner collagenous zone of Bruch's membrane (Figure 3). This early stage of AMD may not be evident by ophthalmoscopic examination but can be inferred by reduced retinal function and, in some cases, by a very faint, late fluorescein staining.

The presence of basal deposit becomes ophthalmoscopically evident by secondary changes in the RPE, and by the development of soft drusen, choroidal neovascularization and disciform scarring.

The RPE changes, often described as "pigment modeling," consist of RPE attenuation with depigmentation, hypertrophy, hyperplasia and atrophy [1,7] (Figure 4). Accumulation of pigmented cells in the subretinal space contributes to the appearance of clumping.

The second major feature is the development of soft (large) drusen [1,7]. These are usually larger than nodular drusen and have a less discrete margin. Several types of soft drusen have been observed and include localized detachment of BLamD

with or without BLinD [1]. Localized accumulation of basal linear material is emerging as the most frequent form of soft drusen [7] (Figure 5).

A third major feature is the development of choroidal neovascularization (CNV), which begins in the choroid and extends into a plane between BLamD along with RPE and the remainder of Bruch's membrane [1] (Figure 6). Only rarely do the vessels extend through the RPE and into the subretinal space. In the early stages of AMD, these vessels are capillary-like [8] (Figure 7) and with time evolve into arteries and veins [1,5] (Figure 8). The number of points of origin of choroidal CNV varies from 1 to 12. Study of serial sections throughout the macular area of 63 eyes with CNV disclosed an average of 2.2 sources per eye (Unpublished data, WR Green, July 1998). CNV may in turn lead to serous and/or hemorrhagic detachment of the RPE and/or retina, pigment modeling, exudation and RPE tears. CNV may be promoted by cellular breakdown of Bruch's membrane (Figure 9) [9]. This early phase of CNV is observed in a small percentage of eyes. Most eyes with CNV are clinically occult as defined by fluorescein angiographic features: fluorescein leakage of undetermined origin [10] (Figure 10) and fibrovascular RPE detachment [11] (Figure 11). Findings of CNV by indocyanine green angiography include late, plaque-like staining (Figure 12) and a "hot spot" [12,13] (Figure 13).

The fourth major feature is the development of disciform scarring. In a study of a large series of disciform scars, Green and Enger [1] found that the scar was non-vascularized in 25%, vascularized in 75%, and had a variable histologic pattern. The scar was thin, nonvascularized and located between the BLamD and the remainder of Bruch's membrane in 6.5% of eyes (Figure 14) and was a thin fibrovascular sub-RPE with BLamD in 13.2% of eyes (Figure 6). The scar had a single subretinal component in 32.2% of the cases (Figure 15) and two components (subretinal and sub-RPE with BLamD) in 48.1% of cases (Figure 16). In those scars with two components, the subretinal portion was larger in 47.7% of eyes, the sub-RPE with BLamD was larger in 34.2% and the two components were about the same size in 18.1% of the cases. Of the 231 eyes with vascularized lesions, the new vessels were from the choroid only in 223 (96%), from the retina and chor-

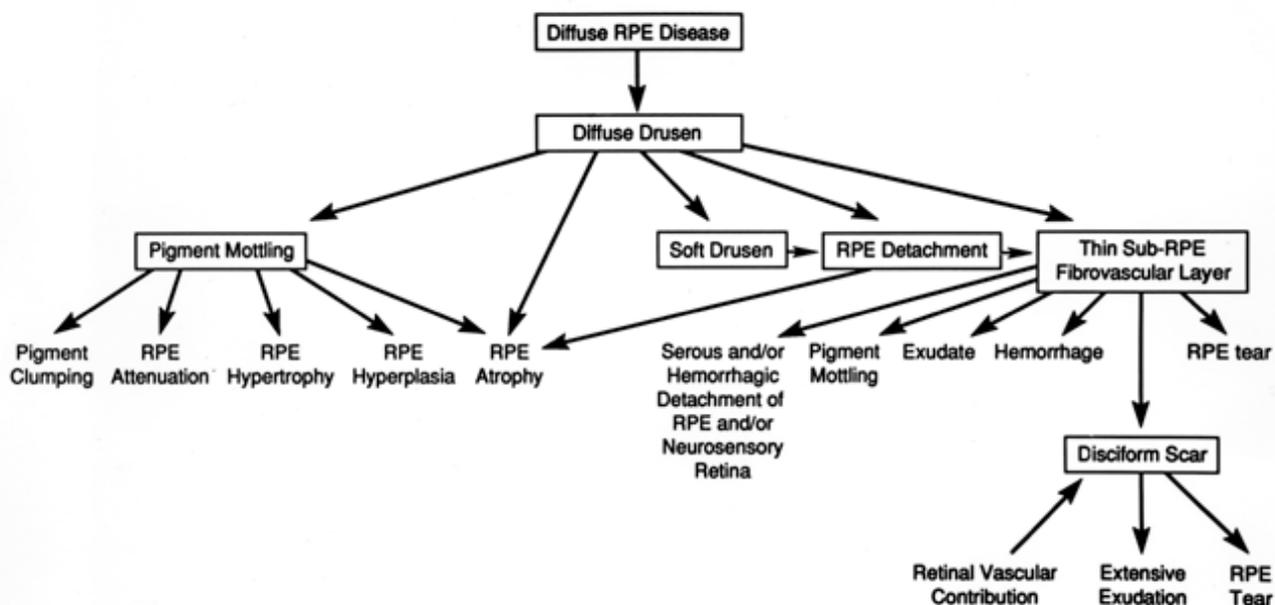


Figure 1. Flow diagram illustrates the relationships of the various morphologic forms of age-related macular degeneration. Age-related macular degeneration is a diffuse process that involves the RPE, photoreceptor cells and perhaps the choroidal vasculature. The first morphologic features is the development of basal deposits. Unfortunately, this phase only becomes evident with the effects on adjacent tissues including: pigment mottling with RPE clumping, attenuation, hypertrophy, hyperplasia, and atrophy; soft drusen; RPE detachment; and choroidal neovascularization. Choroidal neovascularization may then lead to serous and/or hemorrhagic detachment of the RPE and/or the neurosensory retina, pigment mottling, exudation, hemorrhage, and RPE tears. These features lead to a reparative process—a disciform scar that usually has subretinal and sub-RPE components. Disciform scars may have vascular contributions from the retina, marked exudation, and contribute to RPE tears. Figure 1 reprinted with permission, from: Green WR. Age-related macular degeneration. In: Franklin RM, editor. Retina and vitreous: proceedings of the Symposium on Retina and Vitreous, New Orleans, LA, USA, March 12-15, 1992. New York: Kugler; 1993. p. 7-13.

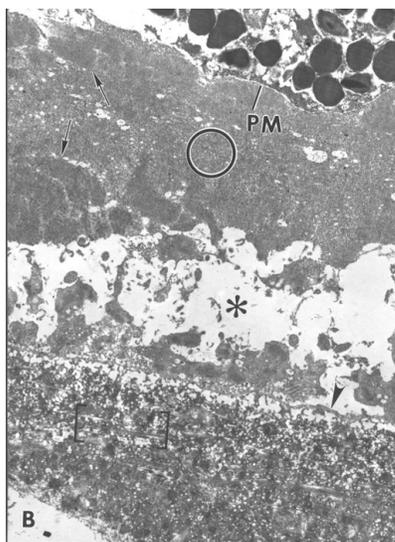
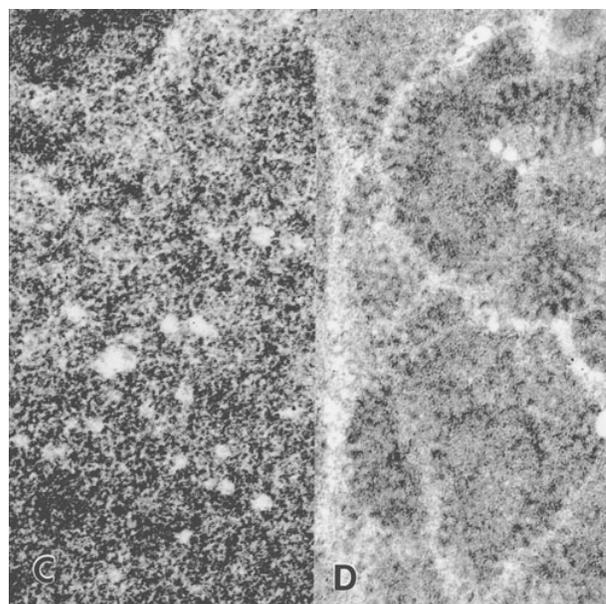
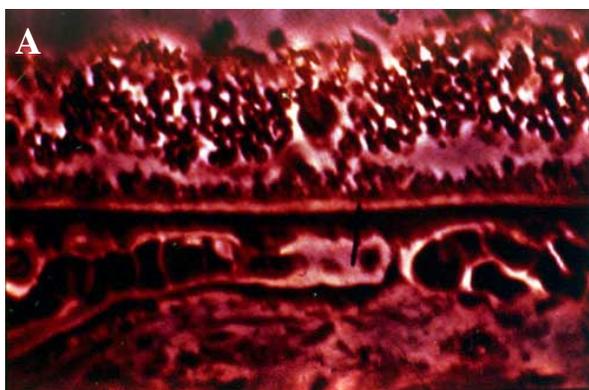


Figure 2. Basal lamina deposit. **A.** Phase contrast appearance of BlamD with serrated inner margin. (x9,900). **B.** Thick layer of basal lamina deposit is located between the plasma (PM) and basal lamina (arrowhead) of the RPE and consists of membrano-granular material (circle) and foci of wide-spaced collagen (arrows). Splitting (asterisk) has occurred in this new, thick layer. Brackets mark the elastic tissue layer of Bruch's membrane. (x50,000). Figure 2B reprinted with permission, from: Green WR, Key SN 3d. Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc* 1977; 75:180-254. **C.** Membrano-granular material (x29,000). **D.** Wide-spaced collagen (x29,000). Figures 2C-D reprinted with permission, from: Green WR, Key SN 3d. Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc* 1977; 75:180-254.

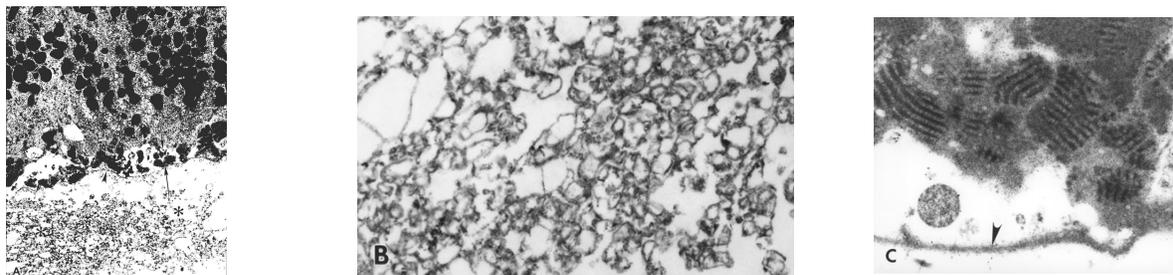


Figure 3. Basal linear deposit. **A**. Ultrastructural appearance of a 6.4 μm -thick basal linear deposit composed of vesicular material (asterisks) located between the retinal pigment epithelial basal lamina (arrowhead) and the remainder of Bruch's membrane. A 2.2 μm -thick layer of wide-spaced collagen (basal laminar deposit, between arrows) is present internal to the retinal pigment epithelial basal lamina (arrowhead). x15,000. Figure 3A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. **B**. Higher power view of vesicular material in basal linear deposit (x40,000). Figure 3B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. **C**. Higher power view of basal laminar deposit with foci of wide-spaced collagen located internal to the RPE basal lamina (arrowhead). (x40,000) Figure 3C reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

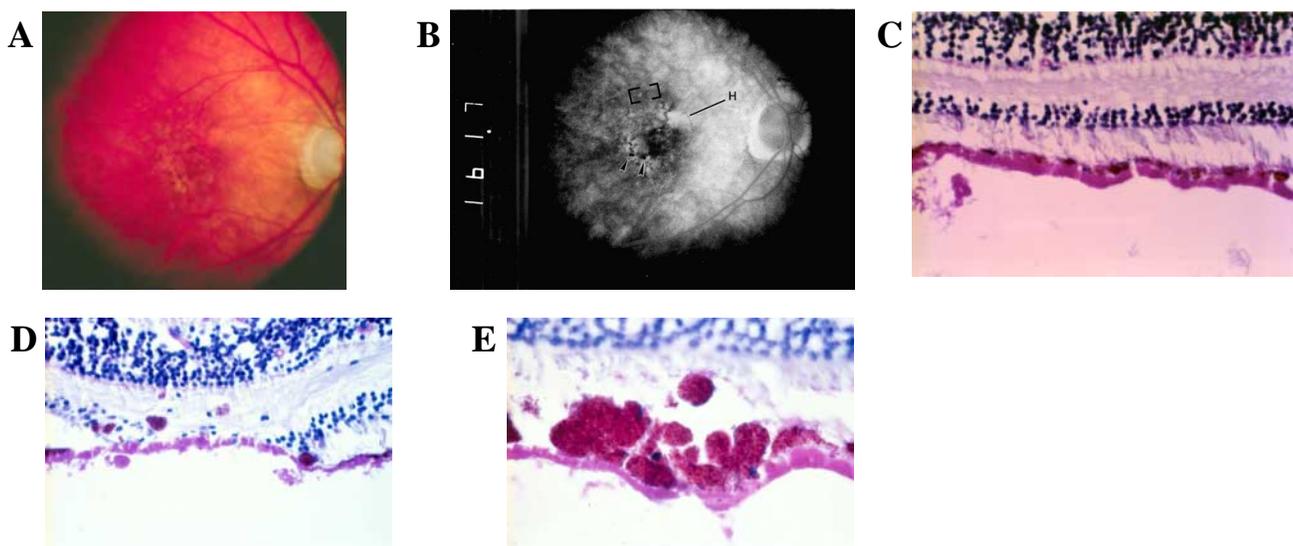


Figure 4. Retinal pigment epithelial changes. **A & B**. Ophthalmoscopic and early-phase angiogram showing some large drusen with slight staining (brackets). Mottled areas of hypopigmentation demonstrate more persistent staining (H), and focal areas of hyperpigmentation show blocked fluorescence (arrowheads). Figure 4A reprinted with permission, from: Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130-42. Figure 4B reprinted with permission, from: Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130-42. Histopathologic study of the area of BlamD has RPE attenuation with partial loss of photoreceptor cells (**C**), an area of RPE and photoreceptor cell atrophy (**D**), and an area with a clump of pigmented cells (**E**). (periodic acid Schiff: **C & D**, x25; **E**, x40) Figure 4C reprinted with permission, from: Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130-42. Figure 4D reprinted with permission, from: Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130-42. Figure 4E reprinted with permission, from: Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. Retina 1994; 14:130-42.

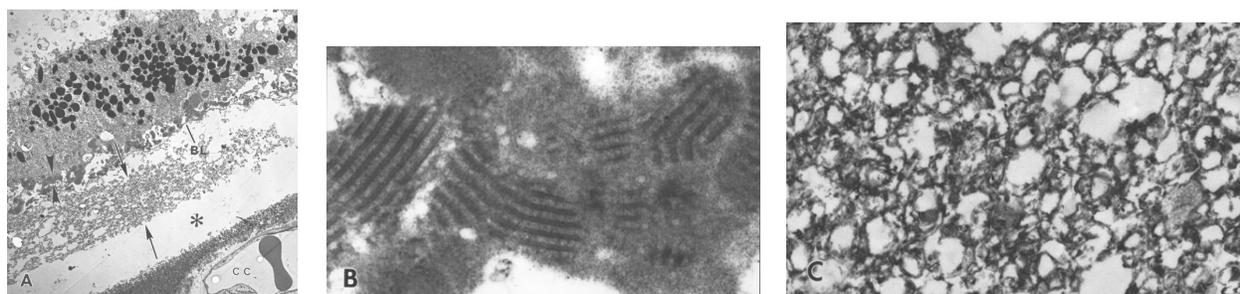


Figure 5. Soft druse from the localized accumulation of basal linear deposit. **A**. Soft drusen from localized basal linear vesicular material (between arrows and **C**) located between the retinal pigment epithelial and the remainder of the Bruch's membrane. A thin layer of basal laminar deposit (between arrowheads and **B**) is present between the intact RPE and the RPE basal lamina (BL). The detachment of the basal linear deposit (asterisk) is probably artifact (cc=choriocapillaries). x2,800. Figure 5A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. **B**. Higher power of basal laminar deposit with wide-spaced collagen that has a periodicity of 100 nm. x40,000. Figure 5B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. **C**. Higher power of basal linear deposit with granular and vesicular material. x19,000. Figure 5C reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.



Figure 6. Early choroidal neovascularization. Examples of thin subretinal pigmented epithelial fibrovascular membranes (asterisks) located between the layer of basal laminar deposit (arrows) and Bruch's membrane. The retinal pigment epithelium is intact, with moderate photoreceptor cell degeneration present (Van de Grift, x40) Figure 6 reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

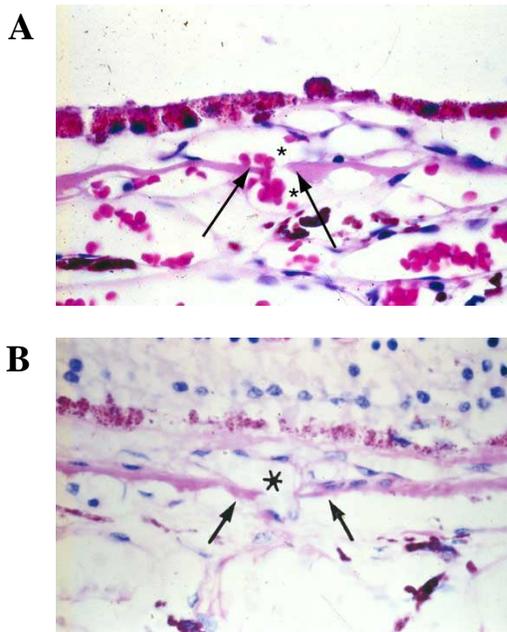


Figure 7. Early choroidal neovascularization. Examples of choroidal neovascularization with capillaries (asterisks) extending through defects in Bruch's membrane (between arrows) and into the plane between RPE and Bruch's membrane (periodic acid-Schiff, x40). Figure 7 (lower) reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

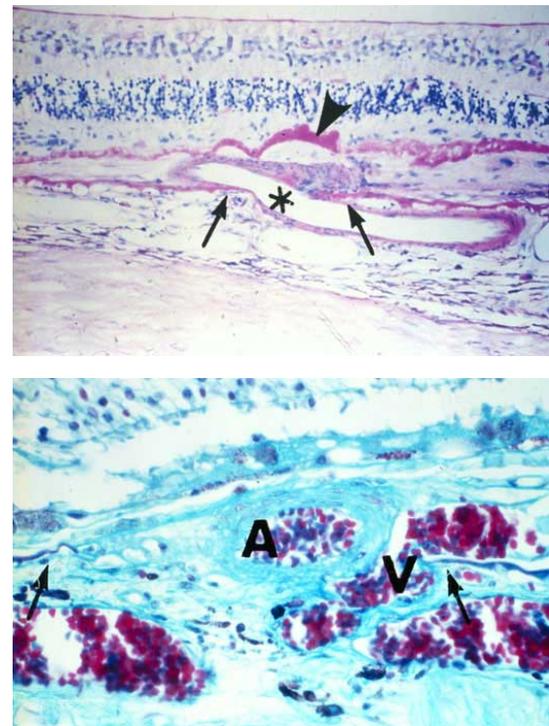


Figure 8. Choroidal neovascularization. **A.** Area where a choroidal artery (asterisk) extends through a defect in Bruch's membrane and into a plane between BlamD (arrowhead) and the remainder of Bruch's membrane. (periodic acid-Schiff, x16) Figure 8A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. **B.** Area where a choroidal artery (A) and vein (V) extends through a defect in Bruch's membrane (between arrows) and into a plane between BlamD with RPE and the remainder of Bruch's membrane. (periodic acid-Schiff, x160) Figure 8B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

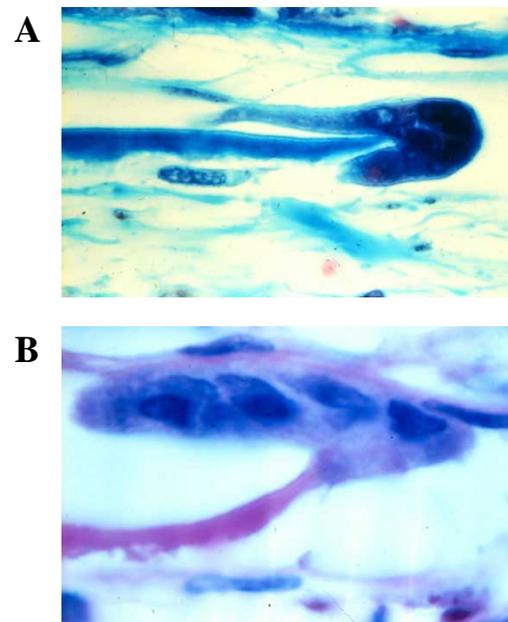


Figure 9. Cellular breakdown of Bruch's membrane. Granulomatous reaction to Bruch's membrane with multinucleated giant cells apparently engulfing a margin of Bruch's membrane. **A.** Van de Grift, x25. Figure 9A reprinted with permission, from: Dastgheib K, Green WR. Granulomatous reaction to Bruch's membrane in age-related macular degeneration. Arch Ophthalmol 1994; 112:813-8. **B.** Periodic acid Schiff, x40.

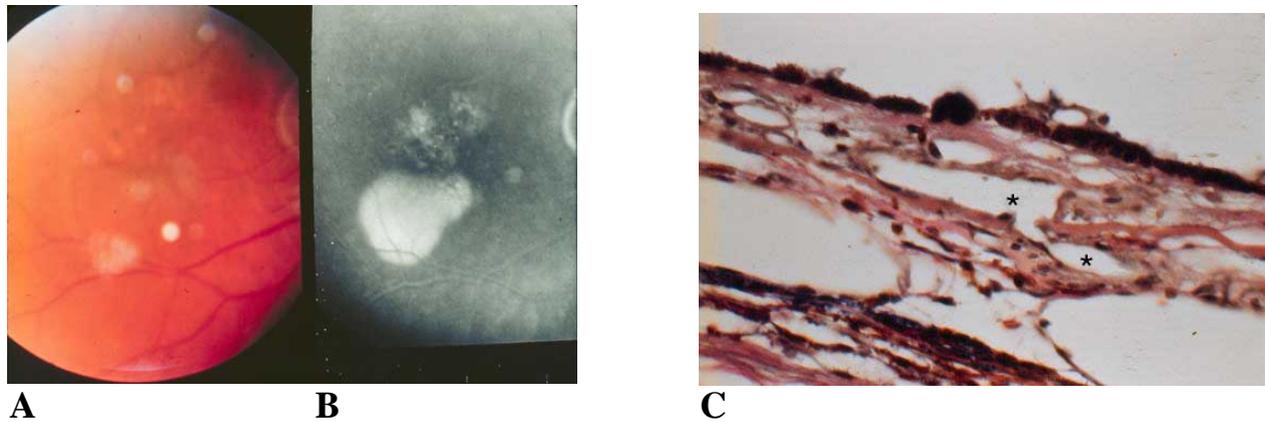


Figure 10. Occult choroidal neovascularization. **A.** Ophthalmoscopic appearance of area of pigment modeling contiguous with an inferior area of RPE detachment. **B.** Fluorescein angiographic appearance of lacy late staining superior and a serous RPE detachment inferiorly. Figures 10A-B reprinted with permission, from: Small ML, Green WR, Alpar JJ, Drewry RE. Senile macular degeneration. A clinicopathologic correlation of two cases with neovascularization beneath the retinal pigment epithelium. *Arch Ophthalmol* 1976; 94:601-7. **C.** Area where a choroidal vessels (asterisks) extends through a defect in Bruch's membrane and into a plane located between Bruch's membrane with RPE and the remainder of Bruch's membrane (Verhoeff van Geisen, x40) Figures 10C reprinted with permission, from: Small ML, Green WR, Alpar JJ, Drewry RE. Senile macular degeneration. A clinicopathologic correlation of two cases with neovascularization beneath the retinal pigment epithelium. *Arch Ophthalmol* 1976; 94:601-7.

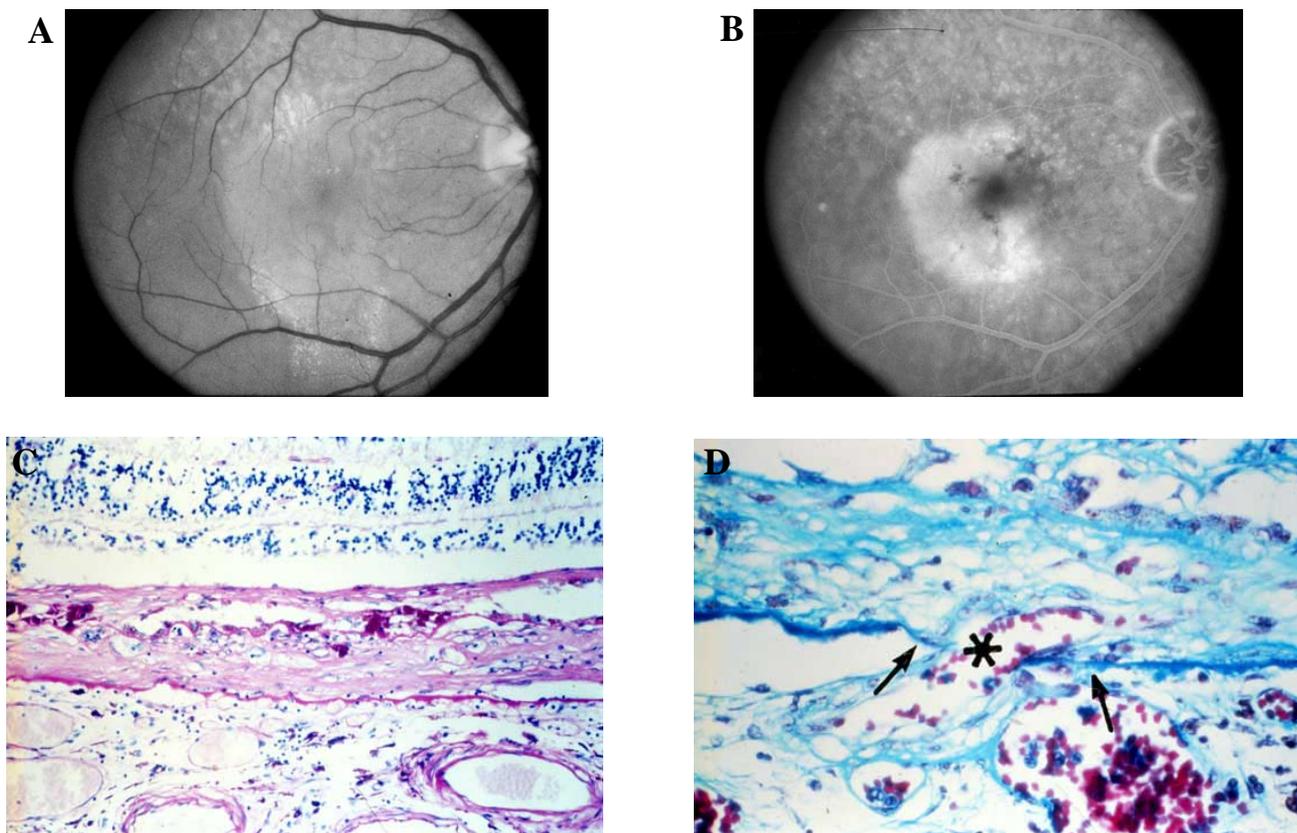


Figure 11. Occult choroidal neovascularization. **A.** Red-free photograph of right macula showing subretinal fluid surrounded by lipid (arrows), overlying apparent choroidal neovascularization. Figures 11A reprinted with permission, from: Bressler SB, Silva JC, Bressler NM, Alexander J, Green WR. Clinicopathologic correlation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 1992; 110:827-32. **B.** Angiogram demonstrates occult choroidal neovascularization with staining of irregularly elevated area of retinal pigment epithelium and poorly demarcated leakage in the late phase in which the exact boundaries of the neovascularization cannot be determined with certainty. Figures 11B reprinted with permission, from: Bressler SB, Silva JC, Bressler NM, Alexander J, Green WR. Clinicopathologic correlation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 1992; 110:827-32. **C.** Area of fluorescein staining corresponds to a 100 µm-thick scar with a 10 µm non-vascularized subretinal and 90 µm vascularized intraBruch's membrane components. Periodic acid Schiff, x25. Figures 11C reprinted with permission, from: Bressler SB, Silva JC, Bressler NM, Alexander J, Green WR. Clinicopathologic correlation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 1992; 110:827-32. **D.** Area shows a single source of neovascularization (asterisk) from the choroid through a defect in Bruch's membrane (between arrows). Periodic acid Schiff, 40. Figures 11D reprinted with permission, from: Bressler SB, Silva JC, Bressler NM, Alexander J, Green WR. Clinicopathologic correlation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 1992; 110:827-32.

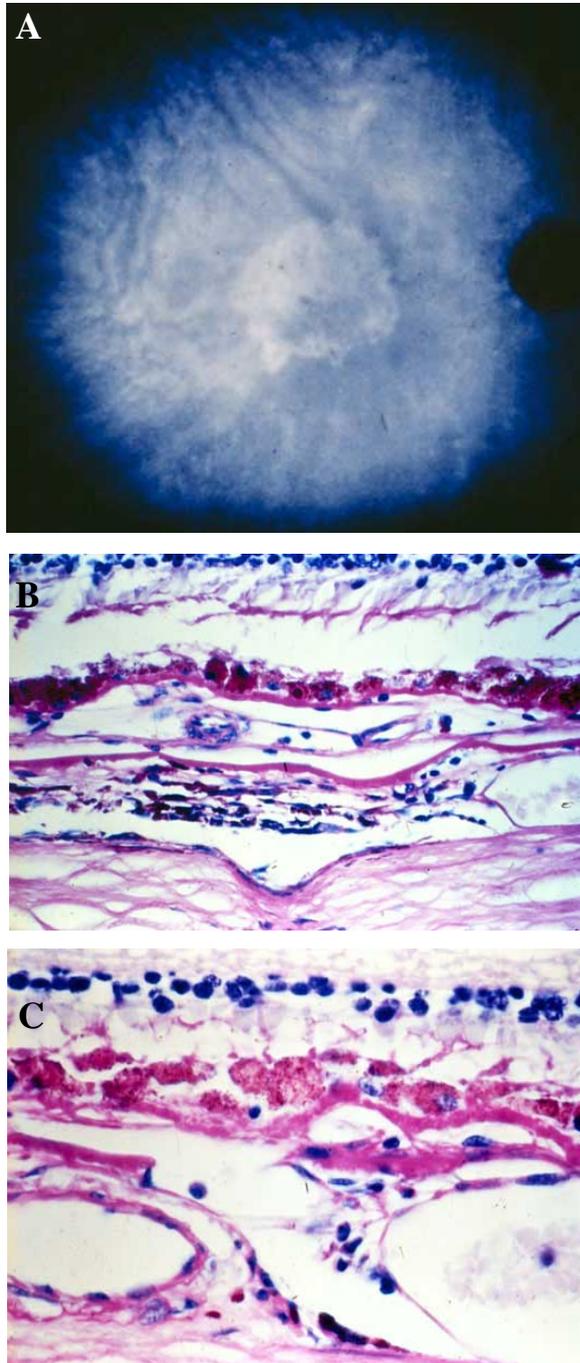


Figure 12. Occult choroidal neovascularization. **A.** Late-phase indocyanine green angiogram demonstrating a well-delineated area of hyperfluorescence consistent with a plaque of CNV. Figures 12A reprinted with permission, from: Chang TS, Freund KB, de la Cruz Z, Yannuzzi LA, Green WR. Clinicopathologic correlation of choroidal neovascularization demonstrated by indocyanine green angiography in a patient with retention of good vision for almost four years. *Retina* 1994; 14:114-24. **B.** Late staining plaque corresponds to an area of CNV located between BlamD with RPE and the remainder of Bruch's membrane. **C.** One of 6 sources of neovascularization from the choroid. Figures 12C reprinted with permission, from: Chang TS, Freund KB, de la Cruz Z, Yannuzzi LA, Green WR. Clinicopathologic correlation of choroidal neovascularization demonstrated by indocyanine green angiography in a patient with retention of good vision for almost four years. *Retina* 1994; 14:114-24.



Figure 13A reprinted with permission, from: Green WR, Kuchle M. Histopathologic studies of choroidal neovascularization. In: Yannuzzi LA, Flower RW, Slakter JS, editors. *Indocyanine green angiography*. St. Louis: Mosby; 1997. p. 151-6.



Figure 13B reprinted with permission, from: Green WR, Kuchle M. Histopathologic studies of choroidal neovascularization. In: Yannuzzi LA, Flower RW, Slakter JS, editors. *Indocyanine green angiography*. St. Louis: Mosby; 1997. p. 151-6.

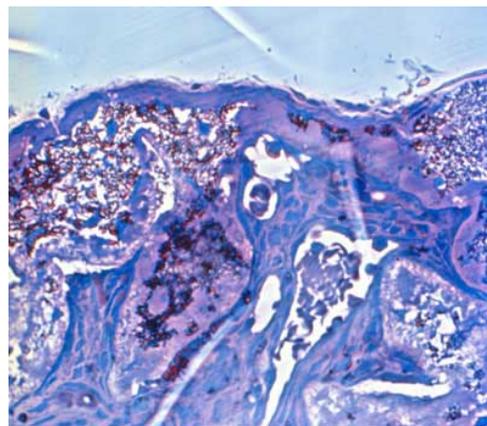


Figure 13C reprinted with permission, from: Green WR, Kuchle M. Histopathologic studies of choroidal neovascularization. In: Yannuzzi LA, Flower RW, Slakter JS, editors. *Indocyanine green angiography*. St. Louis: Mosby; 1997. p. 151-6.

Figure 13. Indocyanine green hot spot. **A.** Preoperative clinical photograph demonstrating subretinal hemorrhage in the macular area. The inferior portion of the extravasated blood has lost its hemoglobin, resulting in the color change. **B.** Late-phase indocyanine green angiogram demonstrating blocked fluorescence from the thicker layers of hemorrhage. A more extensive superior area of hyperfluorescence corresponds to an area of occult CNV. In addition, a linear area of more intense hyperfluorescence just nasal to the blocked fluorescence is consistent with a site of neovascularization ("hot spot"). **C.** Submacular membranectomy specimen with basal laminar deposit (arrows) and numerous blood vessels (asterisks). Paraphenylenediamine, phase contrast, x544.

oid in 6(2.5%) and from the retina only in 2 (0.6%). The mean diameter and thickness of the scars was 3.73 mm and 0.44 mm, respectively [1]. A tear of RPE and BLamD was present in 6.8% of eyes with disciform scars [1-5] (Figure 17). RPE and photoreceptor cell degeneration was progressively greater as the diameter and thickness of the disciform scar increased. Scars of 200 μ m or more in thickness had remaining photoreceptor cells in only about 25% of the surface over the scar.

In two-component disciform scars, the intraBruch's membrane component with blood vessels may extend into the subretinal component through small defects in BLamD and

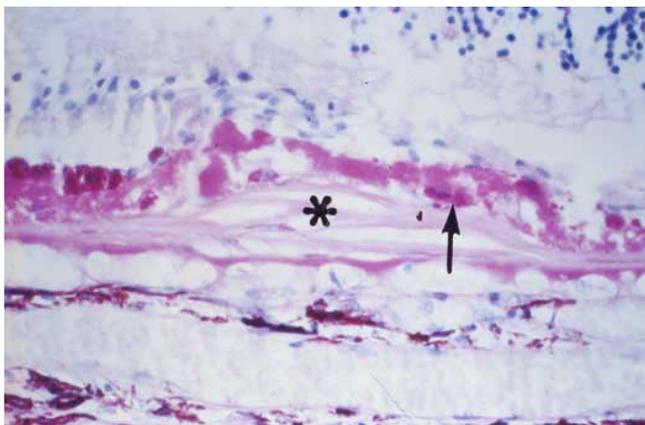


Figure 14. Sub-RPE disciform scar. Example of thin, non-vascularized, subretinal pigment epithelial fibrocellular disciform scars (asterisk) located between basal laminar deposit (arrow) and the remainder of Bruch's membrane. The retinal pigment epithelium and photoreceptor cell layer are atrophic over the scar. Periodic acid-Schiff, x25. Figure 14 reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

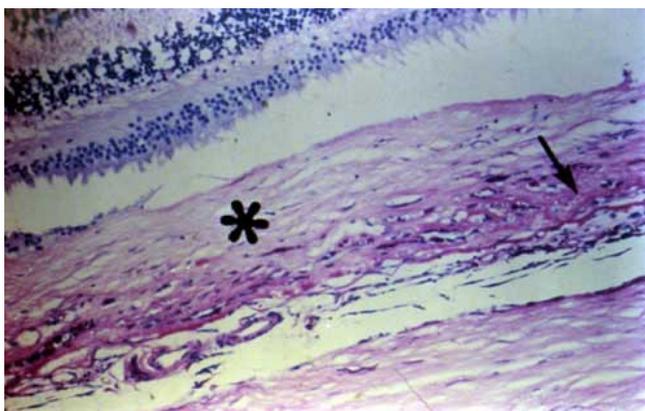


Figure 15. Subretinal disciform scar. Disciform scar with single, subretinal component (asterisk). The scar is located internal to a layer of Bruch's membrane (arrow). Periodic acid-Schiff, x25. Figure 15 reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

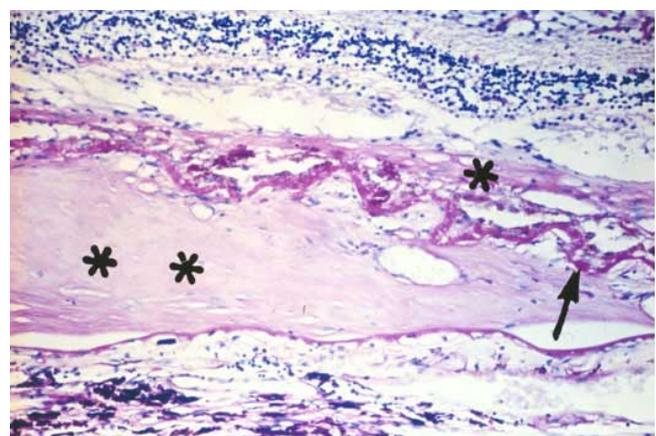


Figure 16. Two-component disciform scar. Two-component disciform scar with the thin subretinal component (asterisk) and thicker intra-Bruch's membrane component (two asterisks) that are separated by a thick layer of Bruch's membrane (arrow) with some residual RPE. Periodic acid-Schiff, x25.

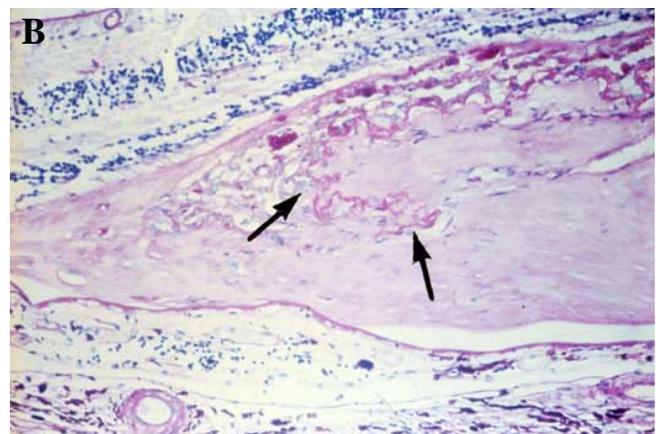
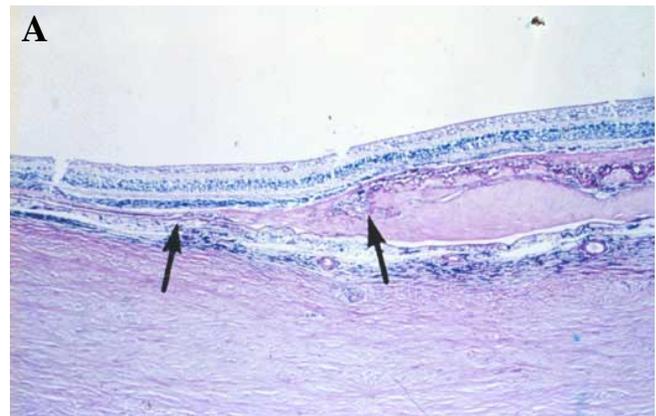


Figure 17. Disciform scar with tear of RPE and Bruch's membrane (BLamD). A. A tear of RPE and Bruch's membrane (BLamD) (between arrows) is present at the nasal margin of a two-component disciform scar. Periodic acid-Schiff, x25. Figure 17A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35. B. Higher power view of the RPE/BLamD tear where the nasal margin of the tear has pulled under temporally (arrows) and the area of the tear is filled in by fibrous tissue. Periodic acid-Schiff, x25. Figure 17B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993; 100:1519-35.

any residual RPE [1,14] (Figure 18). Larger defects in BLamD/RPE (RPE tears) [1,2] is an additional situation in which the two components become continuous [1,2] and blood vessels may extend into the subretinal component from the intraBruch's membrane component. In 8 of 310 (2.6%) of eyes with disciform scars, retinal vessels extended into the disciform scar [1,15] (Figure 19).

Some form of detachment was observed in 79 (10.4%) of 760 eyes with AMD [1]. The detachments were sub-RPE with BLamD in 13 of 79 (16.5%) eyes, serous neurosensory in 35 (44.3%), hemorrhagic neurosensory in 3 (3.8%), serosanguineous RPE in 3 (3.8%) and serosanguineous neurosensory in 7 (8.9%). Massive hemorrhage was present in 6 eyes (7.6%) [1] and was often associated with the use of aspirin or other anti-

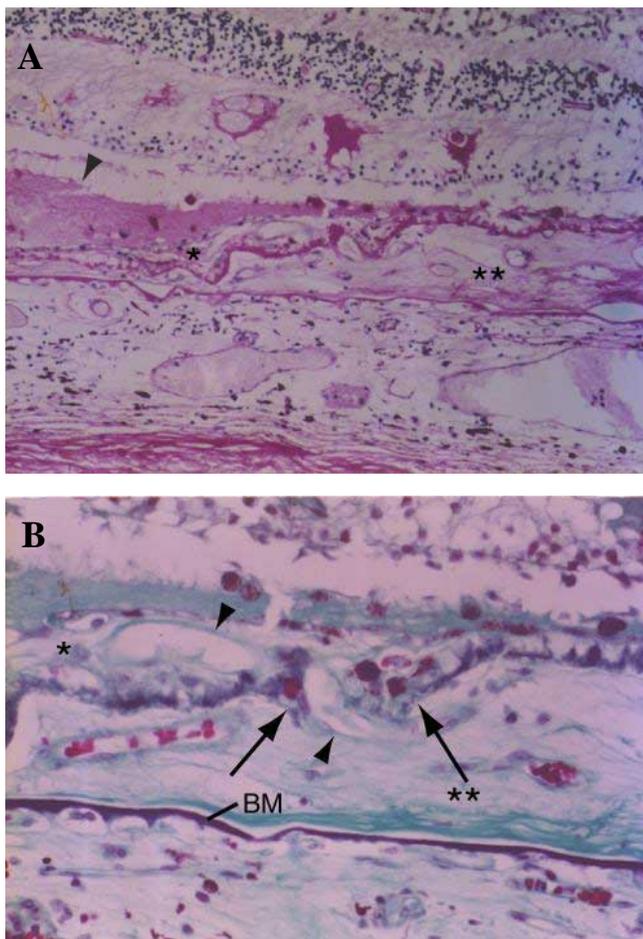


Figure 18. Choroidal neovascularization. **A.** A two-component, 100 µm maximal thickness, disciform scar with a small subretinal component (single asterisk) and a small area of serous detachment of the macula (arrowhead). There is moderate to total loss of the photoreceptor cell layer over the scar, which is most marked over the thicker intra-Bruch's membrane component (double asterisk). (periodic acid-Schiff; x35). Figure 18A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35. **B.** Higher power view of the vascularized intra-Bruch's membrane (BM) component (double asterisk) where the basal laminal deposit has a typical brush-like inner surface and a defect (between arrows) where a capillary (arrowheads) extends from the intra-Bruch's membrane component to the thin subretinal component (Van de Grift; x360). Figure 18B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35.

coagulants [1,16].

RPE atrophy was present in 282 (37.1%) of 760 eyes [1]. Of the 282 eyes, areolar atrophy was associated with disciform scars in 95 (33.7%). Atrophy was unassociated with disciform scars in 187 (24.6%) of 760 eyes. Twenty-one (11.2%) of the 187 eyes with areolar atrophy (2.8% 760 eyes) had no disciform scarring or neovascularization (Figure 20). This form of AMD has been referred to as the "dry form" of AMD. BLamD, BLinD and soft drusen are often present in such eyes.

The various morphologic forms of AMD are a continuum. Points of therapeutic intervention include prevention with micronutrients, antioxidants, and reduced light exposure [17]; antiangiogenesis; destruction of CNV [8,18-23]; antiinflammatory agents; surgical removal of membranes [24-27]; and macular translocation [28]. The morphologic features of AMD give little hope that surgery (submacular membranectomy) will be of much benefit.

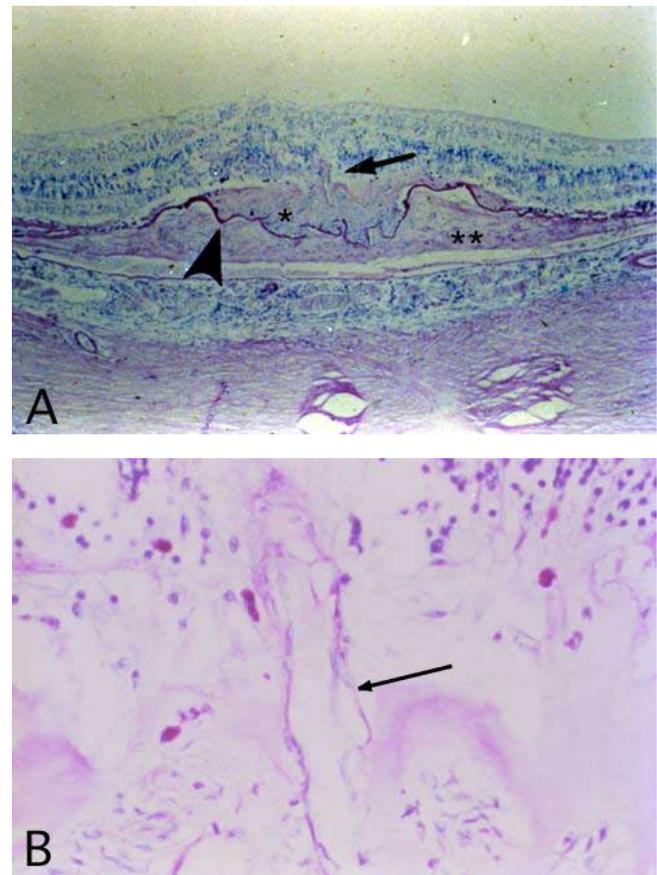


Figure 19. Retinal vascularization of disciform scar. Low (**A**) and higher power view (**B**) of a two-component, 289 µm maximal thickness, disciform scar with marked total atrophy of the photoreceptor cell layer. The subretinal component (single asterisk) is vascularized by a vessel (arrow) from the retina. A 7.1 µm-thick layer of basal laminal deposit (arrowhead) separates the subretinal (single asterisk) and intra-Bruch's membrane (double asterisk) components of the scar. The intra-Bruch's membrane component is vascularized by an artery and vein from the choroid at a different level. Periodic acid-Schiff: **A**, x45; **B**, x155. Figure 19A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35. Figure 19B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35.

ACKNOWLEDGEMENTS

Supported in part by the Independent Order of Odd Fellows, Winston-Salem, NC and the Macula Foundation, New York, NY.

REFERENCES

- Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35.
- Green WR, McDonnell PJ, Yeo JH. Pathologic features of senile macular degeneration. *Ophthalmology* 1985; 92:615-27.
- Green WR. Retina. In: Spencer WH, editor. *Ophthalmic pathology: an atlas and textbook*. 4th ed. Vol 3. Philadelphia: W. B. Saunders; 1996. p. 982-1050.
- Green WR, Schwartz DM. Aspects histopathologiques. In: Coscas G, editor. *Degenerescences maculaires acquises liées à l'âge et neovaisseaux sous-rétiens*. Paris: Masson; 1991. p. 90-119.
- Green WR, Key SN 3d. Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc* 1977; 75:180-254.
- Green WR. Age-related macular degeneration. In: Franklin RM, editor. *Retina and vitreous: proceedings of the Symposium on Retina and Vitreous*, New Orleans, LA, USA, March 12-15, 1992. New York: Kugler; 1993. p. 7-13.
- Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina* 1994; 14:130-42.
- Schneider S, Greven CM, Green WR. Photocoagulation of well-defined choroidal neovascularization in age-related macular degeneration: clinicopathologic correlation. *Retina* 1998; 18:242-50.
- Dastgheib K, Green WR. Granulomatous reaction to Bruch's membrane in age-related macular degeneration. *Arch Ophthalmol* 1994; 112:813-8.
- Small ML, Green WR, Alpar JJ, Drewry RE. Senile macular degeneration. A clinicopathologic correlation of two cases with neovascularization beneath the retinal pigment epithelium. *Arch Ophthalmol* 1976; 94:601-7.
- Bressler SB, Silva JC, Bressler NM, Alexander J, Green WR. Clinicopathologic correlation of occult choroidal neovascularization in age-related macular degeneration. *Arch Ophthalmol* 1992; 110:827-32.
- Chang TS, Freund KB, de la Cruz Z, Yannuzzi LA, Green WR. Clinicopathologic correlation of choroidal neovascularization demonstrated by indocyanine green angiography in a patient

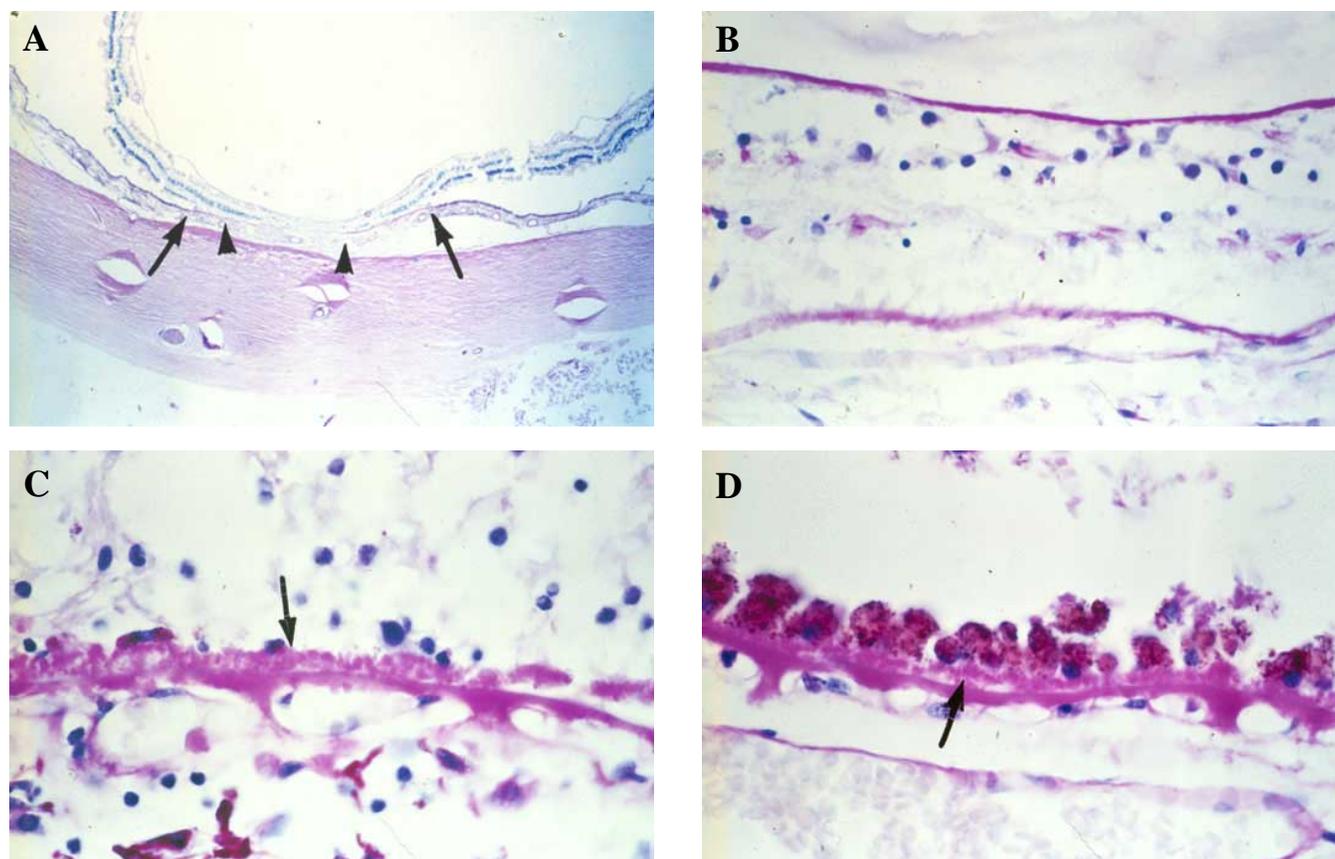


Figure 20. Central areolar retinal pigment epithelial atrophy. **A**. There is total retinal pigment epithelial and photoreceptor cell atrophy in a central 2 mm area (between arrows). Basal laminar deposit has been lost in a 1 mm central area (asterisk and **B**). Basal laminar deposit remains in the peripheral zone of the area of areolar RPE atrophy (between arrowheads and arrows and **C**). Outside the area of RPE areolar atrophy (to either side of arrows and **D**), the RPE and photoreceptors are intact and basal laminar deposit (arrow in **D**) is present (periodic acid-Schiff; **A**, x10; **B**, **C**, and **D**, x40). Figure 20A reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35. Figure 20B reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35. Figure 20C reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35. Figure 20D reprinted with permission, from: Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. *Ophthalmology* 1993; 100:1519-35.

- with retention of good vision for almost four years. *Retina* 1994; 14:114-24.
13. Green WR, Küchle M. Histopathologic studies of choroidal neovascularization. In: Yannuzzi LA, Flower RW, Slakter JS, editors. Indocyanine green angiography. St. Louis: Mosby; 1997. p. 151-6.
 14. Green WR, Harlan Jr JB. Histopathologic features. In: Berger JW, Fine SL, Maguire MG, editors. Age-related macular degeneration. St. Louis: Mosby; 1999. p. 81-154.
 15. Green WR, Gass JD. Senile disciform degeneration of the macula. Retinal arterialization of the fibrous plaque demonstrated clinically and histopathologically. *Arch Ophthalmol* 1971; 86:487-94.
 16. el Baba F, Jarrett WH 2d, Harbin TS Jr, Fine SL, Michels RG, Schachat AP, Green WR. Massive hemorrhage complicating age-related macular degeneration. Clinicopathologic correlation and role of anticoagulants. *Ophthalmology* 1986; 93:1581-92.
 17. Harlan JB, Weidenthal DT, Green WR. Histologic study of a shielded macula. *Retina* 1997; 17:232-8.
 18. Meyer D, Harris WP, Fine SL, Green WR. Clinicopathologic correlation of argon-laser photocoagulation of an idiopathic choroidal neovascular membrane in the macula. *Retina* 1984; 4:107-14.
 19. Guyer DR, Fine SL, Murphy RP, Green WR. Clinicopathologic correlation of krypton and argon laser photocoagulation in a patient with a subfoveal choroidal neovascular membrane. *Retina* 1986; 6:157-63.
 20. Grossniklaus HE, Frank RE, Green WR. Subretinal neovascularization in a pseudophakic eye treated with krypton laser photocoagulation. A clinicopathologic case report. *Arch Ophthalmol* 1988; 106:78-81.
 21. Schwartz D, Green WR. Clinicopathologic correlation of treated choroidal neovascular membranes. In: Gitter KA, Schatz H, Yannuzzi LA, McDonald HR, editors. Laser photocoagulation of retinal disease. San Francisco: Pacific Medical Press; 1988. p. 143-67.
 22. Green WR. Clinicopathologic studies of treated choroidal neovascular membranes. A review and report of two cases. *Retina* 1991; 11:328-56.
 23. Dastgheib K, Bressler SB, Green WR. Clinicopathologic correlation of laser lesion expansion after treatment of choroidal neovascularization. *Retina* 1993; 13:345-52.
 24. Bynoe LA, Chang TS, Funata M, Del Priore LV, Kaplan HJ, Green WR. Histopathologic examination of vascular patterns in subfoveal neovascular membranes. *Ophthalmology* 1994; 101:1112-7.
 25. Hsu JK, Thomas MA, Ibanez H, Green WR. Clinicopathologic studies of an eye after submacular membranectomy for choroidal neovascularization. *Retina* 1995; 15:43-52.
 26. Rosa RH, Thomas MA, Green WR. Clinicopathologic correlation of submacular membranectomy with retention of good vision in a patient with age-related macular degeneration. *Arch Ophthalmol* 1996; 114:480-7.
 27. Grossniklaus HE, Green WR. Histopathologic and ultrastructural findings of surgically excised choroidal neovascularization. Submacular Surgery Trials Research Group. *Arch Ophthalmol* 1998; 116:745-9.
 28. de Juan E Jr, Loewenstein A, Bressler NM, Alexander J. Translocation of the retina for management of subfoveal choroidal neovascularization II: a preliminary report in humans. *Am J Ophthalmol* 1998; 125:635-46.