PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 181, 371–381 (1986)

A Study of Photoreceptor–Retinal Pigment Epithelium Complex: Age-Related Changes in Monkeys (42267)

Y. L. LAI AND M. W. RANA

Bethesda Eye Institute, St. Louis, Missouri 63110, and Department of Anatomy, St. Louis University School of Medicine, St. Louis, Missouri 63104

Abstract. Retinas of 4-, 10-, and 20-year-old monkeys were studied by light microscopy, electron microscopy, and scanning electron microscopy. Sections from the midperipheral region of every retina were selected for comparison. Although no significant differences were found between 4- and 10-year-old retinas, four major changes were found in 20-year-old monkey retinas: (i) increased number of displaced photoreceptor cells (DPC), (ii) increased number of macrophages of different morphology in subretinal space, (iii) increase in pigment granules in retinal pigment epithelium (RPE) cells, and (iv) altered morphology of Muller cells. DPC included both rods and cones. Their location and morphology depended on the stage of their displacement. These cells were usually oval or rounded in shape and were found either among the outer segments of other photoreceptor cells, having stalks extending into the outer nuclear layer, or were located in the subretinal space and had no stalk. A narrow space around the DPC stalks, indicating a change in the intercellular connection between photoreceptor cells and Muller cells, was observed. Furthermore, the Muller cells related to DPC had shortened and markedly reduced microvilli. Two types of macrophages were found in the subretinal space of aged monkey retinas. One type was similar in morphology to RPE cells. Some of these cells were noticed detaching from RPE. Other types of macrophages were nonpigmented. The modifications in RPE were closely related to the changes in the associated neuroretina. The RPE cells in aged retina were devoid of microvilli or had a few thin microvilli. The pleomorphic pigment granules were dispersed throughout the cytoplasm. These cells varied in their size, shape, and surface features. These changes could significantly alter the retinal metabolic equilibrium and may be indicative of age related degenerative processes.

The decline in vision in old age is a well-documented phenomenon (1–5) and is considered to be the core of most age-related eye disorders. A gradual decrease with old age in the number of photoreceptor cells has been observed in rat retinas (6–10). This photoreceptor cell loss was observed in some strains of rats and in all areas of the retina and was influenced to some extent by high ambient light intensities (10, 11). The outward movement of the photoreceptor cells was first identified in the subretinal space of rats (11). This outward movement of the photoreceptor cells into the subretinal space and their subsequent death may be partly responsible for the loss of photoreceptor cells (9).

The same phenomenon was observed in 97% of human retinas examined by Lai *et al.* (10). Significantly more subretinal photoreceptor cells were found in eyes with age-related degenerative disorders, such as senile macular degeneration and senile cataracts, than in normal eyes. The number of subretinal photoreceptor cells was increased in eyes from subjects having diabetes mellitus or systemic infections. There was also a tendency for the total number of subretinal photoreceptor cells to increase with age.

Subretinal photoreceptor cells have also been observed in pigs, cats, dogs, rabbits, guinea pigs, mice, hamsters, whales, and dolphins (12). Weale (5) stated that age-related changes in the neural portion of the visual system, rather than optical changes in light-scattering by the lens, are the primary cause of the defects in visual resolution with age. Any cause of photoreceptor cell loss would undoubtedly result in disruption of the normal anatomic and functional organization of the retina and contribute to the impairment of visual resolution. Interestingly, deficits in the peripheral visual field (4) and in dark adaptation (1) were hypothesized to be a result of aging changes in the various parts of the visual system, specifically, the neuroretina. In this connection, photoreceptor cell loss, expressed as cell death

0037-9727/86 $1.50

in situ, and outward movement and subsequent death of the photoreceptor cells in the subretinal space, undoubtedly contributes to eventual visual impairment in aged retinas. Since both photoreceptor cell death *in situ* and outward movement contribute to photoreceptor cell loss, study of the mechanisms of these phenomena and their contribution of alterations of the structure and function of the retina is important.

The purpose of this study is to analyze (i) the phenomenon of the outward movements of the photoreceptor cells of the monkeys by means of light, transmission, and scanning electron microscopies; (ii) the age-related change in the retinal pigment epithelium; (iii) the possible interaction between the neuroretina and the retinal pigment epithelium during the aging process; (iv) the characterization and functional significance of the macrophages in subretinal space; and (v) the structural modification and possible significance of Muller cells in aging monkey retinas.

Material and Methods. Eyes from two 4-year-old, five 10-year-old, and five 20-year-old monkeys, *Macaca mulatta,* were dissected out immediately after their death and were immersed in 3% glutaraldehyde in 0.1 *M* neutral phosphate buffer for 2 hr at room temperature and washed briefly in 0.134 *M* phosphate buffer. One eye from each animal was processed for light microscopy and the other was processed for electron microscopy and scanning electron microscopy. For light microscopy, the globes were then opened by cutting several millimeters on either side of the optic disk just outside the limbus. Subsequently, the central section of the eyeball between the nasal and temporal side was dehydrated in alcohol and embedded in paraffin. Ten-micrometer sections were cut, including a full length of the retina between the two sides of the ora serrata and the optic disk. Each section was stained by hematoxylin and eosin. Only those sections in which the cytology was adequate to clearly differentiate the retinal structures were chosen for quantitative analysis. The retina, in paraffin section, between the optic disk and ora serrata on each side was divided into three equal portions, the posterior, middle, and peripheral regions. Identification of the nasal and temporal sides of the retina was made on the basis of the greater length of the retina from the optic disk to the ora serrata on the temporal side as opposed to the nasal side (13).

Eight sections from each specimen were used for quantitative analysis. To reduce bias, these sections were designated only by code numbers, and the photoreceptor cells which were clearly below the outer limiting membrane were counted by at least two different persons. After the counts, the averages and standard deviations for each group were tabulated.

For electron microscopy, the second eye from each animal was opened by cutting behind the limbus. Nasal halves of the posterior eye cups were postfixed for 2–3 hr in 1% sodium tetroxide in 0.1 *M* phosphate buffer, dehydrated in graded ethanol, cleared in toluene, and embedded in Spurr's medium (14). Ultrathin sections were placed on copper grids and double-stained with uranyl acetate and lead citrate.

For scanning electron microscopy, after a brief immersion in 3% glutaraldehyde phosphate buffer solution, the retinal portions from the temporal half of the posterior eye cups were detached from the retinal pigmented epithelium (RPE). Tissues from both sides were postfixed in 1% osmium tetroxide, dehydrated in graded ethanol, critical-point-dried in carbon dioxide, and coated with gold-palladium.

Results. The retinas of 4- and 10-year-old monkeys from the midperipheral section of the eye had a normal population density of rods and cones (Fig. 1A). Neural retina and retinal pigmented epithelium showed normal morphology. The outer and inner nuclear layers were regular and uniform. Only the apical half of cytoplasm of RPE cells contained pigment granules, and there were numerous microvilli on the apical surface of RPE. The subretinal space was devoid of any cells or cellular debris.

In contrast, the midperipheral section of retinas from 20-year-old (aged) monkeys showed markedly reduced numbers of photoreceptor cells (Fig. 1B and 1C). Although the changes were not so dramatic as shown in Fig. 1B in all of the aged retinas, the density of photoreceptor cell population decreased from posterior region to peripheral region (Fig. 2). Furthermore, the inner and outer segments of photoreceptors became short and irregular in size, shape, and orientation.

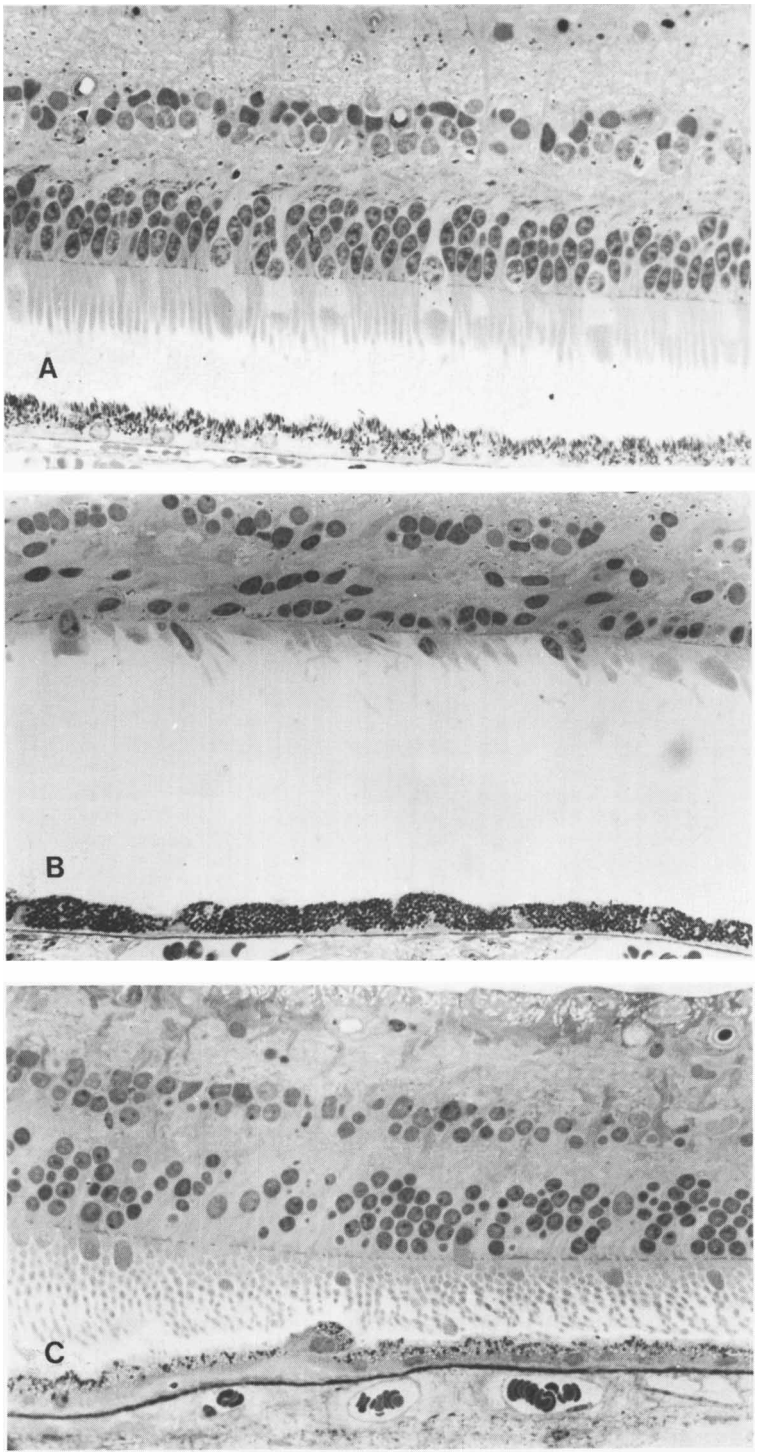

FIG. 1. Comparison of 10- and 20-year-old monkey retinas from midperipheral regions. (A) Ten-year-old monkey retina: neuroretina and retinal pigment epithelium are morphologically normal, showing a normal population density of rods and cones. The apical half of the cytoplasm of the RPE cells contains the pigment granules. LM ×750. (B) Twenty-year-old monkey retina: markedly fewer photoreceptor cells and several displaced photoreceptor cells (DPC) are evident. The cytoplasm of RPE cells is entirely filled with pigment granules. LM ×750. (C) Twenty-year-old retina: a pigmented macrophage is seen separating from RPE. LM ×750.

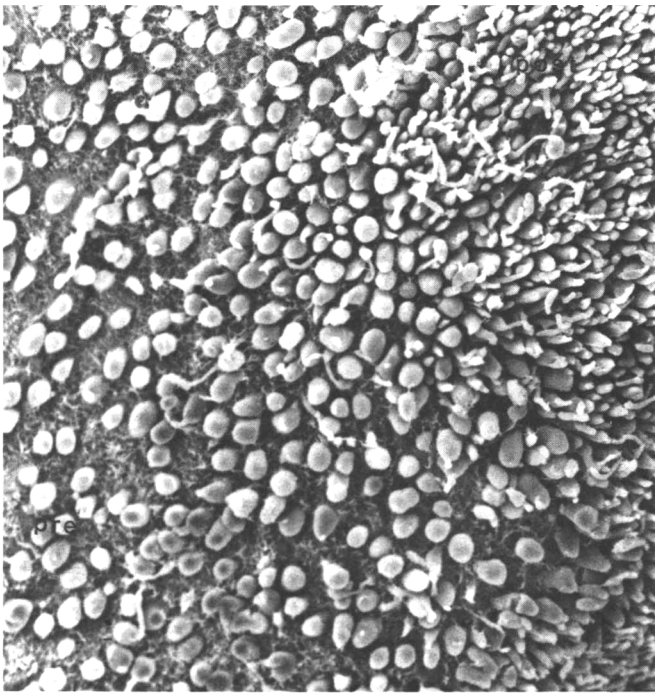

FIG. 2. Scanning electron micrograph of detached neuroretina of 20-year-old monkey showing a transitional morphological modification of photoreceptor cells. Decrease in population density from posterior (post) to peripheral (pre) regions. The outer segments of some photoreceptor cells have become either modified or abolished, whereas the inner segments appear enlarged and oval or spherical in shape. SEM ×500.

The sequence of age-related morphological changes in the retinas can be better demonstrated at the peripheral region where the changes were severe. The earlier and more severe alteration was noticed in the outer segment which was highly deformed (type I DPC) (Fig. 2). Later some of the photoreceptor cells (type II DPC) lost their outer segments completely, leaving a more spherical, shorter, and relatively smooth-surfaced inner segment.

The modifications in RPE were closely related to the changes in the underlined neural retina. Again, the severity of modification increased toward the peripheral region. In younger monkey retinas (Figs. 3A and B), the RPE cells were hexagonal in shape with an abundance of thick and thin microvilli on their apical surfaces. The RPE cells in the aged retinas, especially in the peripheral region, were either devoid of microvilli or had a few thin microvilli (Fig. 4A). Thick microvilli were not found in this region. The pleomorphic pigment granules were dispersed throughout the cytoplasm (Fig. 4B). The RPE cells varied in their size, shape, and surface features. The degree of changes in RPE cells coincided with the decrease in the photoreceptor cell population density.

Displaced photoreceptor cells (DPC) and macrophages were frequently observed in the subretinal space of the aged monkey retinas (Fig. 5A). The DPC closer to the outer surfaces of neuroretina were usually oval or spherical in shape. Some DPC (type I) had long stalks extending into the subretinal space (Fig. 5B). A narrow space around the stalks of these cells at the level of the outer limiting membrane could be seen at higher magnifications, perhaps indicating a change in intercellular relationship between DPC and surrounding Muller cells (Fig. 5C). The DPC (type II) found closer to RPE in the subretinal space were free, oval, or spherical in shape without any stalks. These cells caused crater-like indentations in the apical surface of the RPE cells (Fig. 4A). In these indentations, the microvilli were rel-

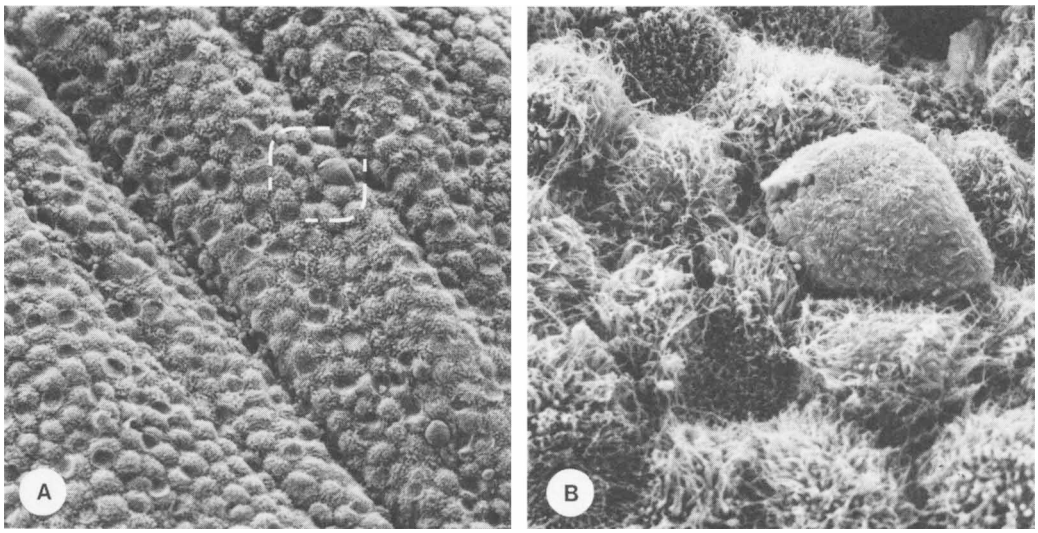

FIG. 3. Retinal pigmented epithelium from 10-year-old monkey: (A) RPE cells are of similar shape and size with an abundance of thick and thin microvilli on their apical surfaces. SEM ×234. (B) Higher magnification of area marked in 3A. Among the microvilli of RPE cells, a macrophage with very few short microvilli is seen. SEM ×1560.

atively fewer and appeared fully extended, indicating that the formation of the indentation was due to localized retraction of the RPE microvilli.

Macrophages were frequently observed in the aged subretinal space (Figs. 5A and 6). These cells varied greatly in their size, shape, and surface morphology and could be roughly

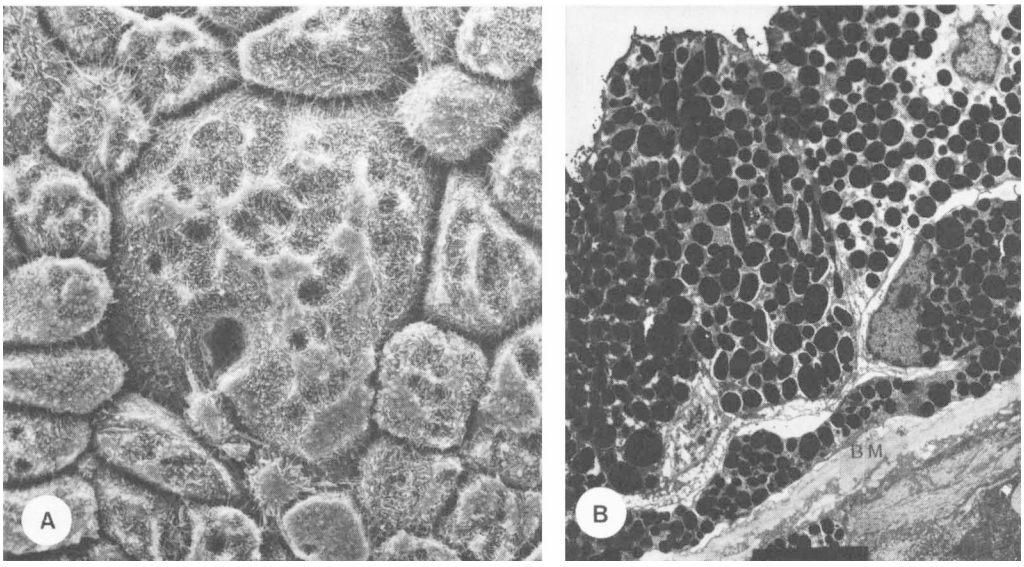

FIG. 4. Retinal pigmented epithelium from 20-year-old monkey: (A) RPE cells are pleomorphic, varying greatly in size, shape, and orientation. Crater-like indentations and a few fine, fully-extended microvilli are seen. SEM ×830. (B) RPE cell cytoplasm contains pleomorphic pigment granules which are distributed throughout the cell. In addition, a pigmented cell is present between the RPE and Bruch membrane (BM). TEM ×2490.

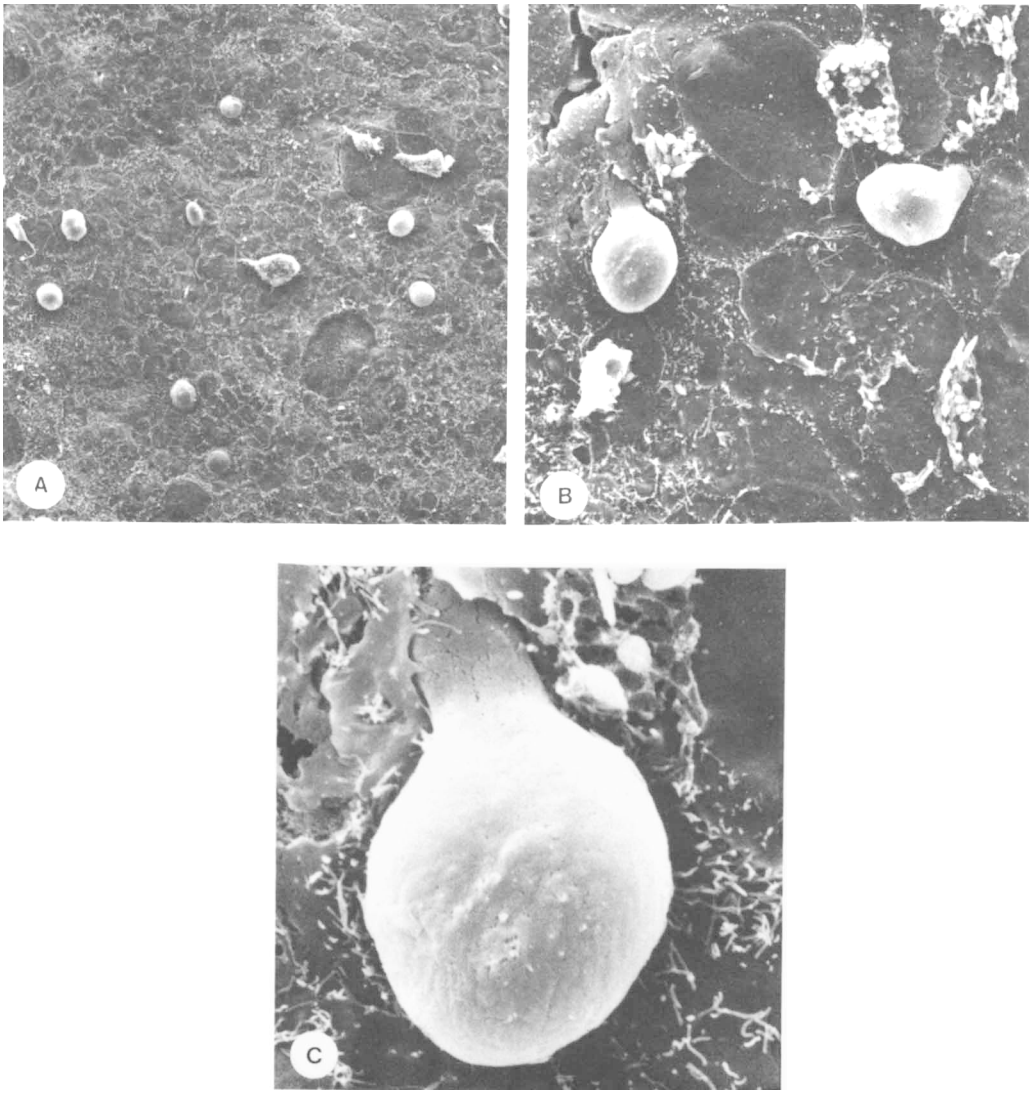

FIG. 5. Detached neural retina from a 20-year-old monkey: (A) Showing displaced photoreceptor cells (DPC), macrophages, and outer limiting membrane. SEM ×390. (B) Higher magnification showing DPC having spherical cell bodies with stalks connecting to the neural retina. Muller cells, which form the outer limiting membrane, are mostly devoid of apical microvilli. SEM ×1560. (C) Higher magnification shows the space around the stalk of DPC indicating a modification of intercellular junctional complexes between the Muller cells and photoreceptor cells. SEM ×5460.

divided into two major types. One type had numerous large microvilli and one rather larger pseudopodium-like cytoplasmic extension (Figs. 5A and 6A). Under electron microscopic examination, larger coarse granules could be seen in their cytoplasm (Fig. 6B). Some of these granules were phagosomes composed of membranes and other cellular debris, some others were lysosomes, and yet others were pigment granules. The nuclei of these cells were elongated and irregular in shape. These macrophages appeared to be active. The other type of macrophages had relatively rounded nuclei and had very few fine microvilli (Fig. 3B). Only one or two phagosomes and a few lysosomes were found in the

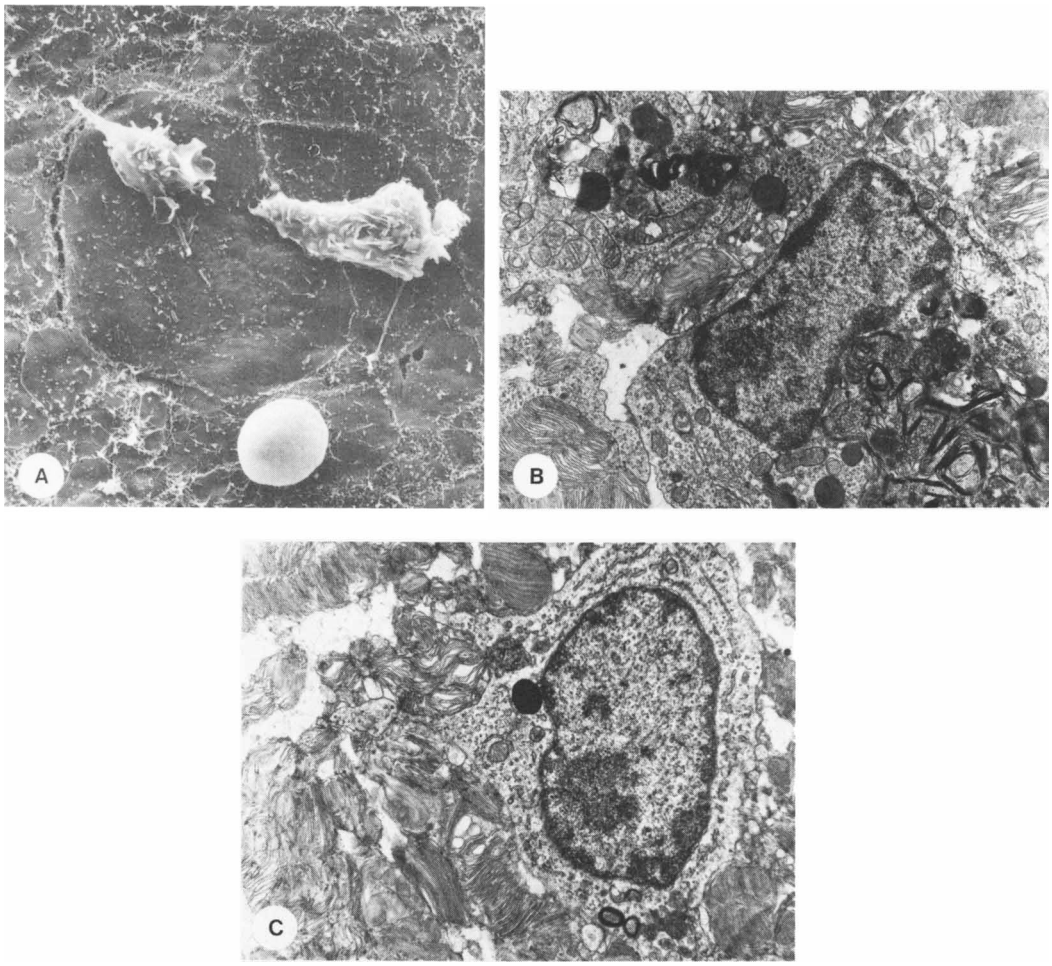

FIG. 6. (A) Higher magnification of 5A shows macrophages with numerous microvilli and pseudopodia pointing to the direction of cell movement. SEM ×1480. (B) Electron micrograph of macrophages in subretinal space of 20-year-old monkey shows an active macrophage with phagosomes and other cellular debris in its cytoplasm. EM ×14,800. (C) An inactive macrophage. EM ×14,800.

cytoplasm of these cells (Fig. 6C). These macrophages appeared to be inactive. Pigmented macrophages were observed separating from the RPE (Fig. 1C).

Modifications of Muller cells can be best demonstrated by scanning electron microscopy. The apical microvilli of the modified Muller cells were greatly extended, and they varied in size and shape. The apical surface microvilli in the affected cells were mostly abolished or were reduced to very few short and fine microvilli (Fig. 5).

The distribution of displaced photoreceptor cells is shown in Table I. Although the number of DPC increased in all regions of the retina with increasing age, the most significant change was found in the peripheral region of the 20-year-old monkey retina.

Discussion. The displacement of photoreceptor cells into the subretinal space in monkeys appeared to be identical to that of the rats (9) and humans (10). Significantly more displaced photoreceptor cells were found in human eyes of older subjects or in eyes of patients having age-related degenerative disorders (10). Displaced photoreceptor cells in rat retinas were observed more frequently in very young developing retinas and in aged retinas (9). This

TABLE I. DISTRIBUTION OF DISPLACED PHOTORECEPTOR CELLS IN MONKEY RETINA

Age (years)	Number of animals	Posterior region		Middle region		Peripheral region	
		Temporal	Nasal	Temporal	Nasal	Temporal	Nasal
4	2	0.62 ± 0.21	2.06 ± 0.33	3.12 ± 0.62	2.25 ± 0.75	5.75 ± 3.22	7.12 ± 3.68
10	5	0.8 ± 0.71	1.4 ± 0.53	1.24 ± 0.91	1.4 ± 0.53	8.0 ± 3.92	9.6 ± 2.46
20	5	4.0 ± 2.2	5.25 ± 3.6	6.6 ± 2.8	4.4 ± 2.8	20.4 ± 9.7	21.5 ± 12.01

change in monkey retina also appeared to be age related. The number of DPC increased in older retinas.

Two main types of DPC were easily identifiable by scanning electron microscopy. The type I cells which were observed closer to the outer limiting membrane had long stalks which were still attached to the outer nuclear layer, and without doubt these were photoreceptor cells. In type II DPC, although they had lost all connection with the outer nuclear layer and their synaptic bodies, inner and outer segments were either highly modified or completely abolished; they had a nuclear morphology identical to that of the photoreceptor cells. The origin of these cells has been confirmed by transmission electron microscopy in our previous studies (9–11), and it was suggested that DPC located at different levels of subretinal space represent different stages of the same phenomenon.

The decrease in density of photoreceptor cell population toward the peripheral retina is quite obvious. The displacement of photoreceptor cells and their subsequent removal from the subretinal space undoubtedly contributes to the loss of photoreceptor population and eventually causes some visual impairment in aging eyes.

The morphology of DP cells at any stage of their displacement was quite abnormal. The inner and outer segments, if present, were short and irregular in size, shape, and orientation. Similar alterations in the morphology of DPC were observed in rat and human retinas, and it was suggested that these alterations represent the disarrangement of metabolic activities in these cells, including the synthesis and assembling of the outer segment disks. It was further suggested that DPC were not normal cells, and these abnormalities may be the cause of their outward displacement (10).

DPC were found in all areas of the aged monkey retina, and their number increased toward the periphery. This distribution may, to a significant extent, contribute to the gradual reduction in the photoreceptor cell population toward the periphery. The frequency and severity of these changes appeared to be closely associated with the age of the animals.

Peripheral retinal degeneration is a common disorder of man. It includes a spectrum of peripheral retinal lesions, including cystoid degeneration, paving-stone degeneration, and lattice degeneration (15, 16). It is difficult to assess the contribution of age alone since most patients suffer from a variety of eye and systemic diseases. But in this study the animals, as far as we could determine, were free of any eye or systemic disease. Therefore, it is reasonable to assume that DPC and decrease in photoreceptor cell population are age-related phenomena.

The RPE of monkeys (17, 18), humans (19), rats (20, 21), and other animals (22, 23) have been studied extensively. The RPE cells in young monkeys were hexagonal. Although some variation in the shape of these cells in the different regions of the retina was reported, the apical surfaces of the regions had innumerable microvilli, and a dense layer of microvilli covered the whole cell surface (18). It was also suggested that the fluid exchange of the RPE cells at the apical surface is extremely active. The abundance of microvilli can be better appreciated by scanning EM. The pigment granules in RPE of a young monkey were located in the upper portion of the cells, and some pigmented granules were found in the microvilli (18).

Changes in RPE associated with age have been reported (24, 25). The reduction of microvilli on the apical surfaces of RPE cells is a gradual process and is an indication of the

change in the integrity of the apical plasma membrane which could be expected to alter the exchange of materials between the neural retina and RPE, as well as between the photoreceptors and the choroidal circulations. These changes could significantly alter the retinal metabolic equilibrium and accelerate the degenerative processes in the affected retina.

One of the main histologic differences between young and old human RPE is the increase in lipofuscin granules in RPE cells of aged retina (26–28). It is suggested that melanin granules are protective organelles of the cells, whereas lipofuscin granules are lysosomal residual inclusions in the cell (29). As the lipofuscin granule accumulation increases, pure melanin granules decrease with age (which is accompanied by the rise in the number of the complex melanolysosomal and melanolipofuscin granules) (25). These complex granules are thought to be melanin granules in the process of degradation (27). This may explain variability in size and shape of pigment granules and their distribution throughout the cytoplasm of the aged RPE. The studies of rats (30–32) and of monkeys (33) suggested that conditions such as lipid composition of shed outer segments of photoreceptors, antioxidant status of RPE cells, diet, and oxygen and light exposure contribute to the formation and accumulation of lipofuscin.

In addition to DPC, two types of macrophages were observed in the subretinal space of the aged monkey. Different types of macrophages: pigment-laden (34), pigmented, and pigment-free (35) were observed in the subretinal space. It was postulated that all macrophages in this area are blood derived and enter the retina from the capillaries in the outer nuclear layer (36). This conclusion was based on the distinct nuclear and cytoplasmic morphology of these macrophages, and it was further suggested that the presence of pigment granules in these cells is not proof that these granules were produced by these cells. La Vail (36) also rejected any role of RPE in cleaning of subretinal debris. During this study and previous studies, we have observed at least two types of macrophages having totally different morphology. Johnson and Fould (37) demonstrated pigmented macrophages detaching free from RPE and moving into the subretinal space. The role of RPE as a morphogenetic supporter during the development of the retinal outer segments (38), its basic support in healing of damaged retinal tissue (39), and its involvement in phagocytosis of the shed outer tips of the photoreceptor element (17, 40) have been well documented. Recently Hume *et al.* (41), using macrophage-specific antigen F4/80, proposed that macrophages migrate during the development of the retina and subsequently differentiate to become microglia of the retina and form a regularly spaced distribution across the retina in the inner and outer plexiform layers. These cells are involved in phagocytosis and degradation of the resulting cellular debris. It has also been suggested that plasminogen activator, a secretory product of macrophages (42), is apparently involved in neuronal cell migration (43). We are inclined to believe that macrophages present in the subretinal space may arise from different sources, including RPE, and the difference in their morphology is due to the degree of their activity.

Morphological alteration observed in Muller cells appeared to be caused by their expansion to fill the spaces produced by the displacement of photoreceptor cells. The number of Muller cells per unit area is also reduced because of fewer surviving photoreceptor cells to be supported. The shorter length and reduced number of microvilli in these cells denote the decrease of surface area and intercellular exchange between Muller cells and photoreceptor cells.

These observations shed some light on the morphological changes in aged retinas. We are in the process of studying the biochemical alterations in aged retinas of different species and hope to correlate our biochemical and morphological findings in the near future.

This study was supported by research Grants EYO 2542 and EYO 04178 from National Eye Institute of National Institutes of Health. The authors express their thanks to Mrs. Janice W. Rana and Ms. Sharon Hughes for the preparation of this manuscript.

1. McFarland RA, Fisher MB. Alterations in dark adaptation as a function of age. J Gerontol **10**:424, 1959.
2. McFarland RA, Domey R, Warren B, Ward D. Dark

adaptations as a function of age. I. A statistical analysis. J Gerontol **15**:149, 1960.
3. Wolf E, Gaeta A, Geer S. Critical flicker frequencies in flicker perimetry standards and confidence limits. Arch Ophthalmol (Chicago) **80**:347, 1968.
4. Wolf E, Nadroski AS. Extent of the visual field, changes with age and oxygen tension. Arch Ophthalmol (Chicago) **86**:637, 1971.
5. Weale RA. Senile changes in visual activity. Trans Ophthalmol Soc UK **95**:36, 1975.
6. Weibe I, Stotzer H, Seitz R. Age and light dependent changes in rat retina. Arch Pathol **362**:145, 1974.
7. Steiz R, Weisse I, Stotzer H. Retinal changes due to age and light—A comparative study in rat eyes. Klin Monatsbl Augenheilk **171**:431, 1977.
8. Lai YL, Jonas AM. Age related light-associated retinal changes in Fischer rats. Invest Ophthalmol Visual Sci **17**:634, 1978.
9. Lai Y. Outward movement of photoreceptor cells in normal rat retina. Invest Ophthalmol Visual Sci **19**: 849, 1980.
10. Lai YL, Lug R, Masuda K, Liu YP. Mechanism and significance of photoreceptor cell loss in the Fischer rat retina. In: Hollyfield JG, ed. The Structure of the Eye. Amsterdam/New York, Elsevier/North-Holland, pp133–139, 1982.
11. Lai YL, Lug R, Yao PC, Hayasaka S, Hyasaka, I. Studies of the pathogenic mechanisms of light on rat retina. Acta Anat **107**:407, 1980.
12. Mangum MD, Lug R, Lai YL. Subretinal photoreceptor cells. Invest Ophthalmol Visual Sci **19**(Suppl): 191, 1980.
13. Hogan MJ, Alvardo JA, Weddell JE. Histology of the Human Eye. Philadelphia, Saunders, 1971.
14. Spurr AR. A low-viscosity epoxy resin embedding medium for electron microscopy. J Ultrastruct Res **26**:31, 1969.
15. Wolter RJ, Wilson WW. Degeneration of the peripheral retina. Amer J Ophthalmol **47**:153, 1959.
16. Foos RY, Spencer LM, Straatsma BR. Trophic degeneration of the peripheral retina. In: Symposium on Retina and Retinal Surgery Transections of the New Orleans Academy of Ophthalmology. St. Louis, Mosby, pp90–102, 1969.
17. Young RW. Shedding of discs from rod outer segments in the rhesus monkey. J Ultrastruct Res **34**:1901, 1971.
18. Sakuragawa M, Kuwabara T. The pigment epithelium of the monkey. Topographic study by scanning and transmission electron microscopy. Arch Ophthalmol (Chicago) **94**:85, 1976.
19. Spitznas M, Hogan MJ. Outer segment and photoreceptors and retinal pigment epithelium. Arch Ophthalmol (Chicago) **84**:810, 1970.
20. Tso MOM, Friedman E. The retinal pigment epithelium. I. Comparative histology. Arch Ophthalmol (Chicago) **78**:641, 1967.
21. Hansson HA. Ultrastructural studies on rat retina damaged by visible light. Virchows Arch B **6**:247, 1973.
22. Steinberg RH. Scanning electron microscopy of the bullfrog's retina and pigmented epithelium. Z Zellforsch Mikrosk Anat **143**:451, 1973.
23. Kroll AJ, Machemer R. Experimental retinal detachment in the owl monkey. 3. Electron microscopy of the retina and pigment epithelium. Amer J Ophthalmol **66**:410, 1968.
24. Friedman E, Tso MOM. The retinal pigment epithelium. II. Histologic changes associated with age. Arch Ophthalmol (Chicago) **79**:315, 1968.
25. Burns LF, Hilderbrand ES, Eldridge S. Aging human RPE: Morphologic analysis of macular, equatorial and peripheral cells. Invest Ophthalmol Visual Sci **25**:195, 1984.
26. Wing GL, Blanchard GC, Weiter JJ. The topography and age relationship of lipfuscin concentration in the retinal pigment epithelium. Invest Ophthalmol Visual Sci **17**:600, 1978.
27. Feeney L. Lipofuscin and melanin of human retinal pigment epithelium. Fluorescence, enzyme cytochemical and ultrastructural studies. Invest Ophthalmol Visual Sci **17**:583, 1978.
28. Mishima H, Hasche H, Kondo K. Age changes in the fine structure of human retinal pigment epithelium. Japan J Ophthalmol **22**:476, 1978.
29. Sohol RS. Age pigments. Amsterdam, Elsevier/North-Holland, pp102–155 and 317–334, 1981.
30. Katz ML, Stone WL, Dartz EA. Fluorescent pigment accumulation in retinal pigment epithelium of antioxidant-deficient rat. Invest Ophthalmol Visual Sci **17**:1049, 1978.
31. Farnsworth CC, Stone WL, Dratz EA. Effects of vitamin E and selenium deficiency on the fatty acid composition of rat retinal tissue. Biochem Biophys Acta **552**:281, 1979.
32. Robinson WG Jr, Kuwabara T, Bieri JG. Deficiencies of vitamin E and A in rat. Retinal damages and lipfuscin accumulation. Invest Ophthalmol Visual Sci **19**:1030, 1980.
33. Malinow MR, Feeney-Burns L, Peterson LH, Klein M, Neuringer M. Diet-related macular anomalies in monkeys. Invest Ophthalmol Visual Sci **19**:857, 1980.
34. Tso MOM, Santos-Anderson RM, Vainisi SJ. Heredofamilial retinal dystrophy in Guinea baboons. I. A histopathological study. Arch Ophthalmol (Chicago) **101**:1597, 1983.
35. Farber DB, Souza DW, Chase DG. Cone visual cell degeneration in ground squirrel retina: Disruption of morphology and cyclic nucleotide metabolism by Iodoacetic acid. Invest Ophthalmol Visual Sci **24**:1236, 1983.
36. LaVail MM. The retinal pigment epithelium in man and rat with inherited retinal degeneration. In: Zinn KM, Marmor MG, eds. Retinal Pigment Epithelium. Cambridge, Harvard Univ. Press, p293, 1979.

37. Johnson NF, Fould WS. Observations on the retinal pigment epithelium and the retinal macrophages in experimental retinal detachment. Brit J Ophthalmol **61**:564, 1977.
38. Kuwabara T, Weidman TA. Development of the prenatal rat retina. Invest Ophthalmol **13**:725, 1974.
39. Kuwabara T. Retinal recovery from exposure to light. Amer J Ophthalmol **70**:187, 1970.
40. Young RW, Bok D. Participation of the retinal pigment epithelium in the rod outer segement renewal process. J Cell Biol **42**:392, 1969.
41. Hume DA, Perry VH, Gordon S. Immunohistochemical localization of a macrophage specific antigen in developing mouse retina: Phagocytosis of dying neurons and differentiating glial cells to form a regular array in the plexiform layers. J Cell Biol **97**:253, 1983.
42. Hume DA, Gordon S. Macrophage biochemistry. Life Chem Rep **1**:1, 1982.
43. Moonan G, Wagemans MP, Selak I. Plasminogen activator—Plasmin system and neuronal migration. Nature (London) **298**:753, 1982.

Received September 5, 1985. P.S.E.B.M. 1986, Vol. 181.
Accepted November 11, 1985.