Retinal Detachment in the Cat: The Outer Nuclear and Outer Plexiform Layers

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The retinae of cats were surgically detached for ½ hr to 14 months, and the outer nuclear (ONL) and outer plexiform layers (OPL) were studied by light and electron microscopy. The longer the duration or the greater the height of detachment the more likely was the occurrence of cell death. Histologic signs of degeneration were present 1 hr after detachment. The number of photoreceptor nuclei in the ONL decreased significantly by 1 month. Loss of cells in the ONL occurred by necrosis and by the migration of photoreceptor cell bodies into the subretinal space. The OPL degenerated by the necrosis of cell processes and synaptic terminals and by the retraction of the synaptic terminals. By 2 weeks most synaptic terminals were necrotic or in the process of retracting. Photoreceptor synaptic contact with second order neurons was diminished by 30 days and was essentially absent by 50 days. Müller cells proliferated and hypertrophied; their nuclei and cell processes filled the intraretinal spaces left by the degenerating photoreceptors. In addition, Müller cells protruded into the subretinal space and formed multiple layers of cell bodies and processes between the retina and retinal pigment epithelium. By 14 months these subretinal Müller cell processes covered the entire detached retina, and appeared morphologically like an astroglial scar. Similar changes in human retinal detachments may significantly influence the degree of visual recovery after retinal reattachment, especially in retinae detached for more than a few days. Invest Ophthalmol Vis Sci 24:927–942, 1983

Although it is known from the results of several studies[1–8] that outer segments degenerate after retinal detachment, and may regenerate after reattachment, it is not clear if this is true for other parts of the photoreceptor cell. In the dog retina the photoreceptor cell bodies (outer nuclear layer) and synaptic terminals (outer plexiform layer) may survive up to six months after detachment.[2] In contrast, in the rabbit retina there is some disruption of the outer nuclear layer within three days of detachment, a reduction in the number of synaptic terminals in the outer plexiform layer as detachment duration increases, and an eventual degeneration of most of the neural retina.[3–5] Some of these species differences in outer nuclear and outer plexiform layer degeneration may be due to differences in vascularization of the retina. The most rapid degeneration occurs in rabbits that are described as having an avascular retina.[9] Dogs,[2] monkeys,[6] humans,[10] and cats,[11] on the other hand, all have extensive capillary networks within their retinae, and it is in these species that the retina is apparently spared total degeneration after detachment. The degeneration of receptor cell bodies or synaptic terminals would have obvious consequences for the recovery of normal vision after retinal reattachment.

In this paper we describe the morphologic changes that occur in the outer nuclear layer (ONL) and outer plexiform layer (OPL) of the cat retina after experimental retinal detachments of ½ hr to 14 months duration.

Materials and Methods

Retinae from 26 cats were detached surgically for ½ hr to 14 months before they were fixed and processed for light and electron microscopy. ^{3}H-thymidine was injected intraocularly into selected animals to determine if cellular proliferation occurs in response to retinal detachment. Detailed descriptions of the methods are given in a previous paper.[1]

For this study retinal tissue was examined from areas representing four different conditions: (1) control areas consisting of tissue from normal cat retinae, from eyes which had undergone lensectomy and vitrectomy, and from attached, normal-appearing areas adjacent to areas of detachment; (2) transition zones

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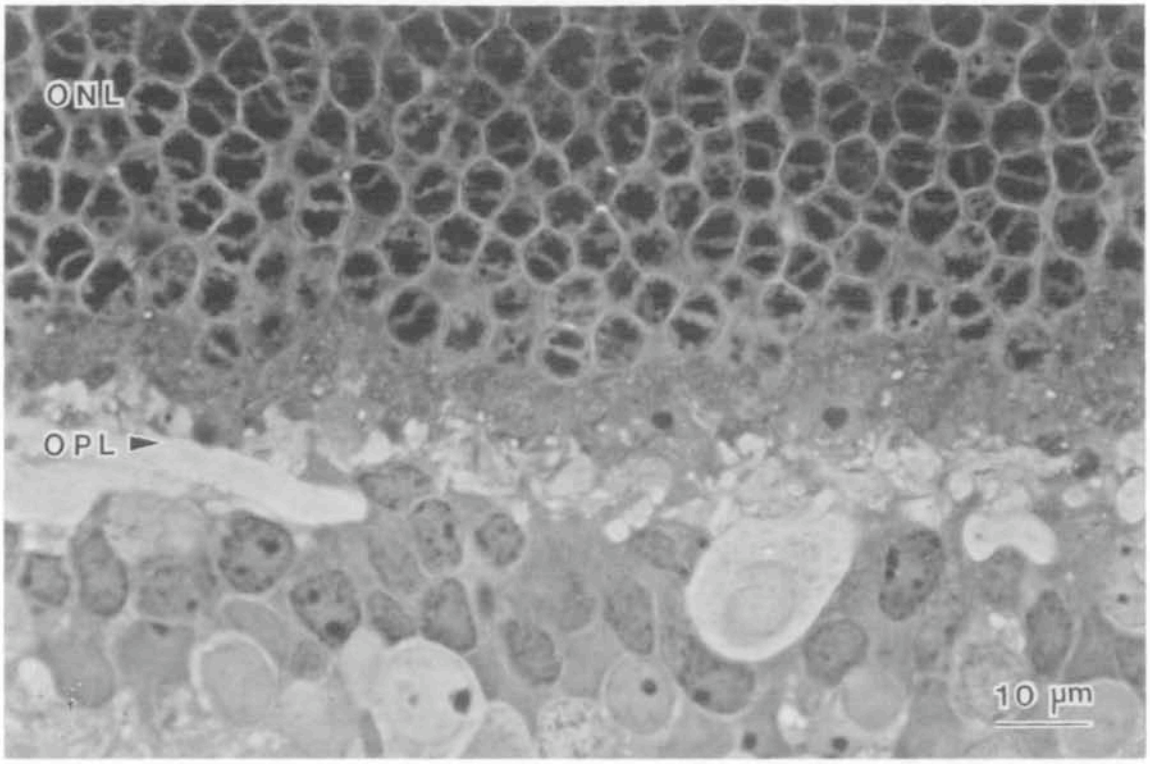

Fig. 1. Light micrograph of part of the outer nuclear layer (ONL) and the outer plexiform layer (OPL) from an attached retina.

between attached and detached retina; (3) shallow detachments that were defined arbitrarily as a separation between the retina and RPE of less than three retinal thicknesses; and (4) high detachments that were defined as a separation of greater than three retinal thicknesses. The clinically defined "bullous detachment" is included in the category of highly detached retina.

The number of photoreceptor nuclei in the ONL per millimeter of retina was determined for attached controls, ½ and 1 hr, 1, 2, 3, 13, 30, and 50 day, 3, 6, and 14 month detached retinae. Using 1-μm thick tissue sections, a minimum of five 0.2 mm lengths of retina was counted for each data point. Data points for the attached controls were taken from the posterior retina, the superior midzone (equatorial region) and from the superior periphery (between 1–2 mm posterior to the ora serrata). Data points for the detached retinae were obtained from representative posterior or equatorial regions. All counts were corrected according to the method of Abercrombie.[12]

Results

Figures 1 and 2 show the appearance of normal cat retina taken from control regions defined above. These figures can be used for comparison to regions of retinal detachment.

One Half-hour to Three-day Detachments

In addition to the rapid degeneration of the outer segments, the photoreceptor cells' synaptic terminals also show a rapid response to retinal detachment. Figure 3 shows a gradation of staining intensity in the transition from attached to detached retina 1 hr after the detachment procedure. Receptor terminals in the zone of detachment stain much lighter and have a vacuolated appearance in comparison to control retinae (Fig. 1).

A decreased basophilia seen by light microscopy at 3 days is caused by vacuolization of the cell bodies and terminals of the photoreceptors, and of the processes within the outer plexiform layer (Figs. 4, 5–8). Within the outer nuclear layer the photoreceptor cell bodies often show a distension of the nuclear envelope and endoplasmic reticulum, a loss of cytoplasmic ground substance, deterioration of mitochondria, and the presence of multivesicular bodies (Figs. 4, 5). Mitochondria of the receptor terminals are also distended and show a loss of internal structure. Multivesicular bodies are common in the terminals as is the loss of cytoplasmic ground substance (Fig. 6).

Not all photoreceptor cells degenerate at the same rate—some may not degenerate at all while others begin to show signs of degeneration only in much longer detachments. It appears that rod cell bodies

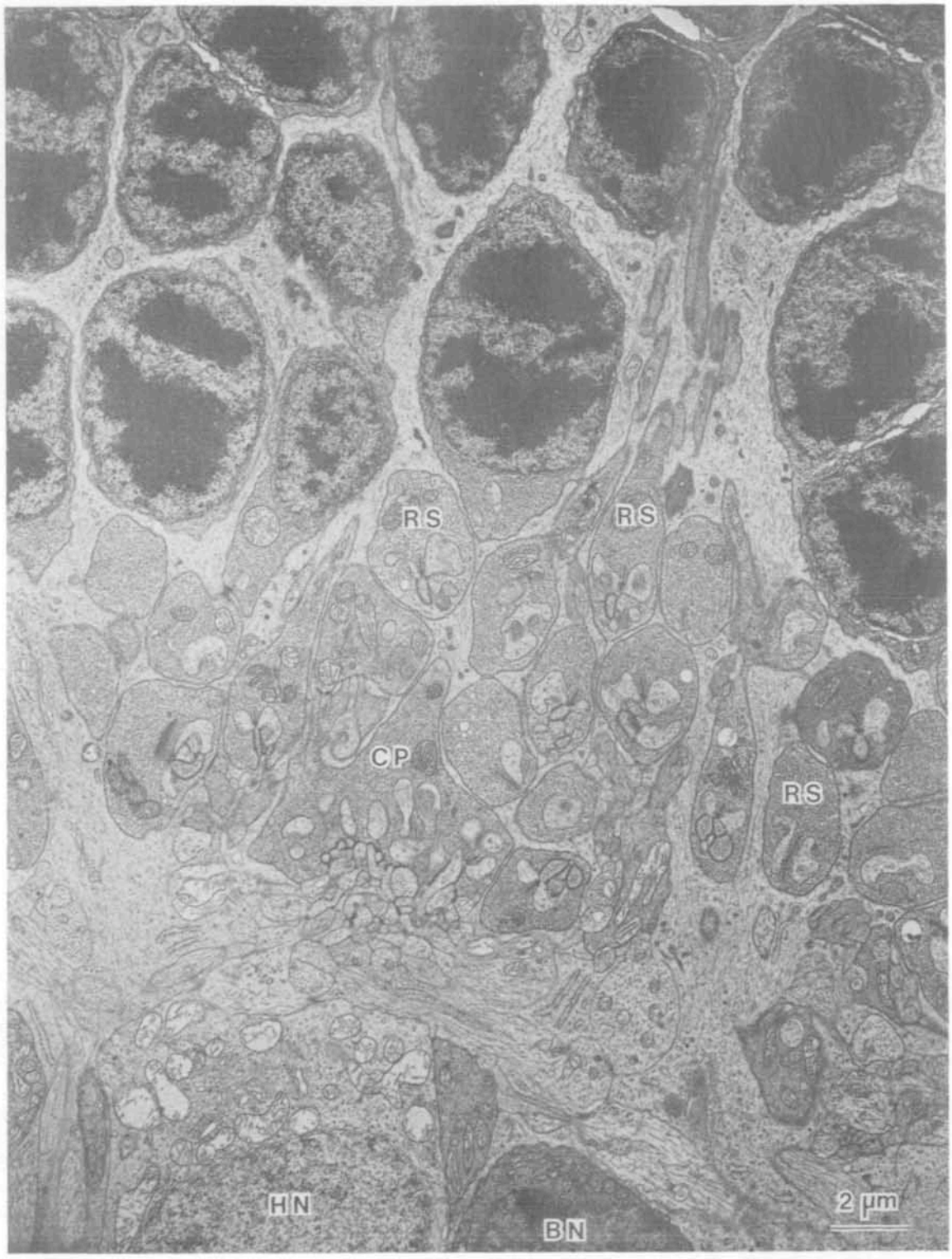

Fig. 2. Low power electron micrograph of the outer plexiform layer of a control (lensectomized and vitrectomized) retina. Rod spherules (RS) and a cone pedicle (CP) are indicted. A horizontal cell nucleus (HN) and a bipolar cell nucleus (BN) designate the outer boundary of the inner nuclear layer.

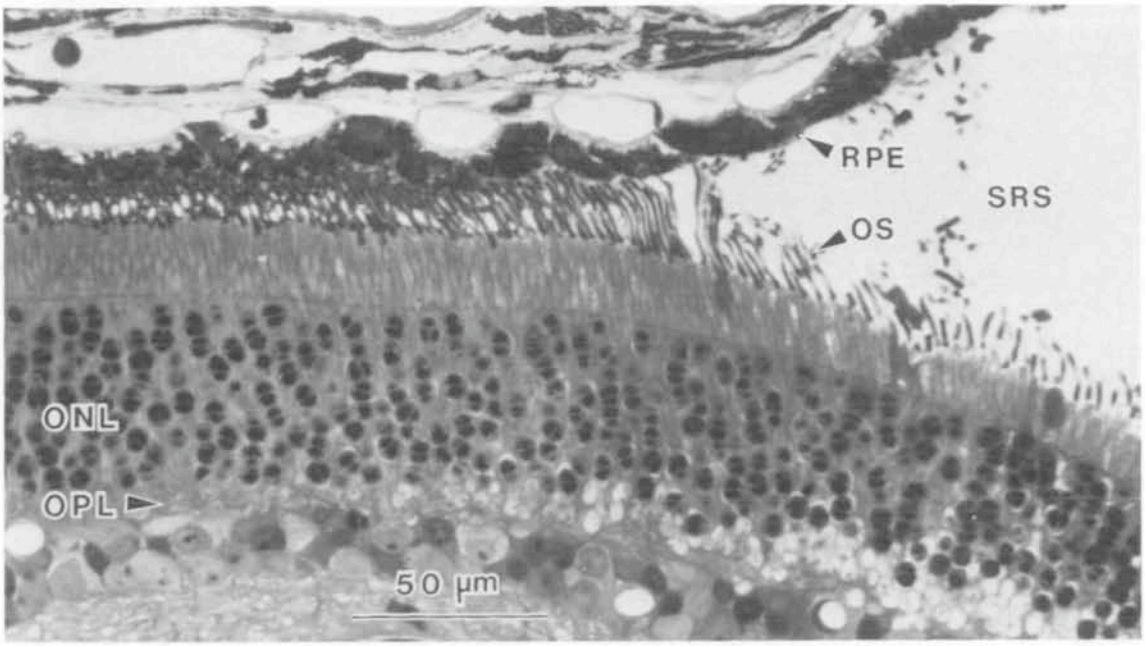

Fig. 3. Light micrograph of the transition zone from attached to detached retina 1 hr after detachment. The normal interdigitation of the retinal pigment epithelium (RPE) and the photoreceptor outer segments (OS) is disrupted in the detachment region, increasing the size of the subretinal space (SRS). The staining intensity of the outer plexiform layer (OPL) decreases in the detachment region. Outer nuclear layer = ONL.

and terminals show a more rapid reaction to detachment than do those of cones. Figures 4 and 5 show both rod and cone cell bodies and inner segments after 3 days of detachment. Cone somata can be recognized by their location next to the outer limiting membrane and by their dispersed pattern of nuclear heterochromatin. Rod somata always show two or three distinct clumps of heterochromatin. Whereas all of the rods in these areas show signs of degeneration and deterioration, the cone cell bodies retain their general structure and their organelles appear generally well preserved, although reduced in number. The same applies to the cone terminals. After 3 days many rod terminals have few organelles, and appear as empty bags with only remnants of mitochondria, scattered vesicles and synaptic ribbons remaining in their cytoplasm (Fig. 7). Synaptic ribbons and a small halo of closely apposed synaptic vesicles are among the last organelles to degenerate in the rod terminals. These ribbons appear shorter than those found in normal rod spherules in single thin sections (compare Figs. 2 and 7). The cone terminals at this time are also affected but in a different way inasmuch as they contain a population of large (85–100 nM diameter) vesicles (Figs. 6, 8) not found in normal retina. Otherwise, they appear normal in contrast to the rods.

The processes of the second order neurons also respond to the detachment. There is vacuolization of large horizontal cell processes within the OPL (Fig. 6), and some OPL processes appear surrounded by large amounts of extracellular space.

In addition to the degenerative changes, there is also a proliferative response of the retina to detachment. Twelve hours after detachment, ^{3}H-thymidine-labeled cells occur in autoradiograms. We classified these cells as pericytes, capillary endothelial cells and microglia on the basis of their histology, location within the retina and staining characteristics. The nuclei of microglia, monocytes and macrophages stain violet while Müller nuclei stain blue with Humphrey and Pittman's stains for light microscopy.[13] About 24 hours after detachment the retina contains large numbers of cells with the appearance of monocytes that probably account for the large number of macropghages within the retina about 3 days after detachment. ^{3}H-thymidine-labeled Müller cell nuclei are present by 2 days after detachment (Fig. 9). At this time, the Müller cell nuclei are occasionally found in the outer plexiform layer, having apparently migrated from their normal location at the IPL-INL border. Mitotic figures are present in the inner nuclear, outer plexiform and outer nuclear layers as early as 3 days after detachment (Fig. 10).

Three-day to Two-week Detachments

The distance between the RPE and the retina affects the response of the photoreceptor cells to de-

tachment. This is exemplified by 13-day shallow and high detachments shown in Figures 11 and 12. Although the outer and inner segments are affected severely in both regions, in the shallow detachment the cell bodies show fewer signs of degeneration and the terminals show less vacuolization but increased basophilia. Rod terminals in such regions lose their

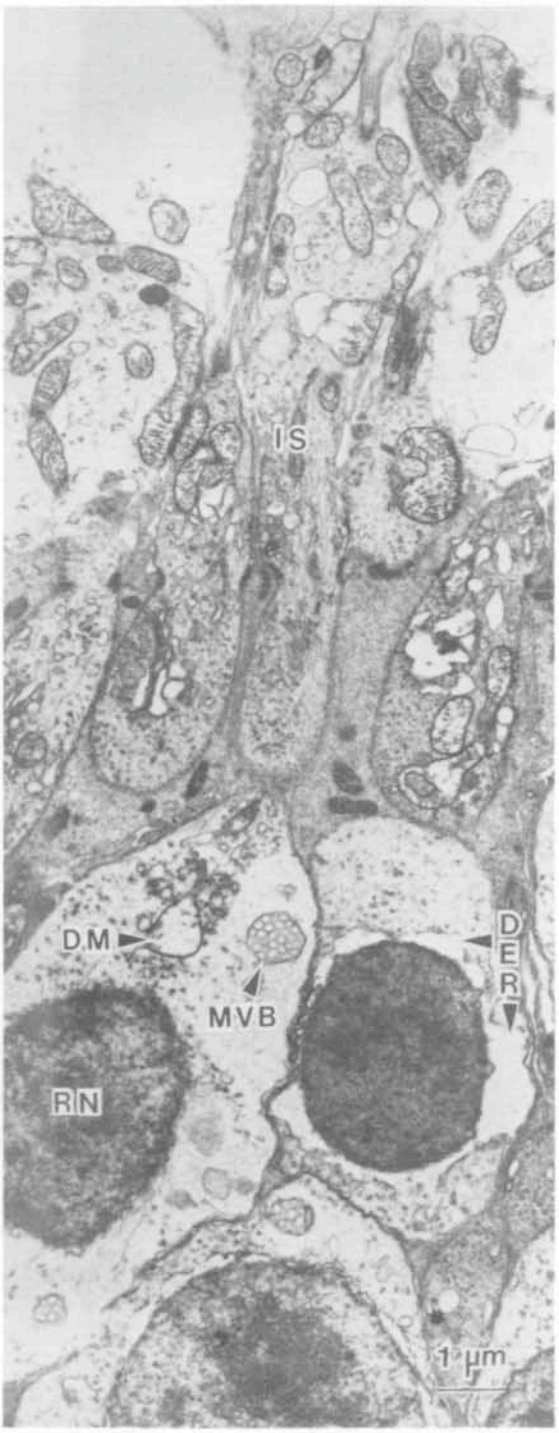

Fig. 4. Electron micrograph of a rod nucleus (RN), cell body, and inner segment (IS) 3 days after detachment. The outer segment has degenerated and this rod and all of the others in this area show signs of necrosis: multivesicular bodies (MVB), distended mitochondria (DM) and endoplasmic reticulum (DER), and a loss of cytoplasmic ground substance.

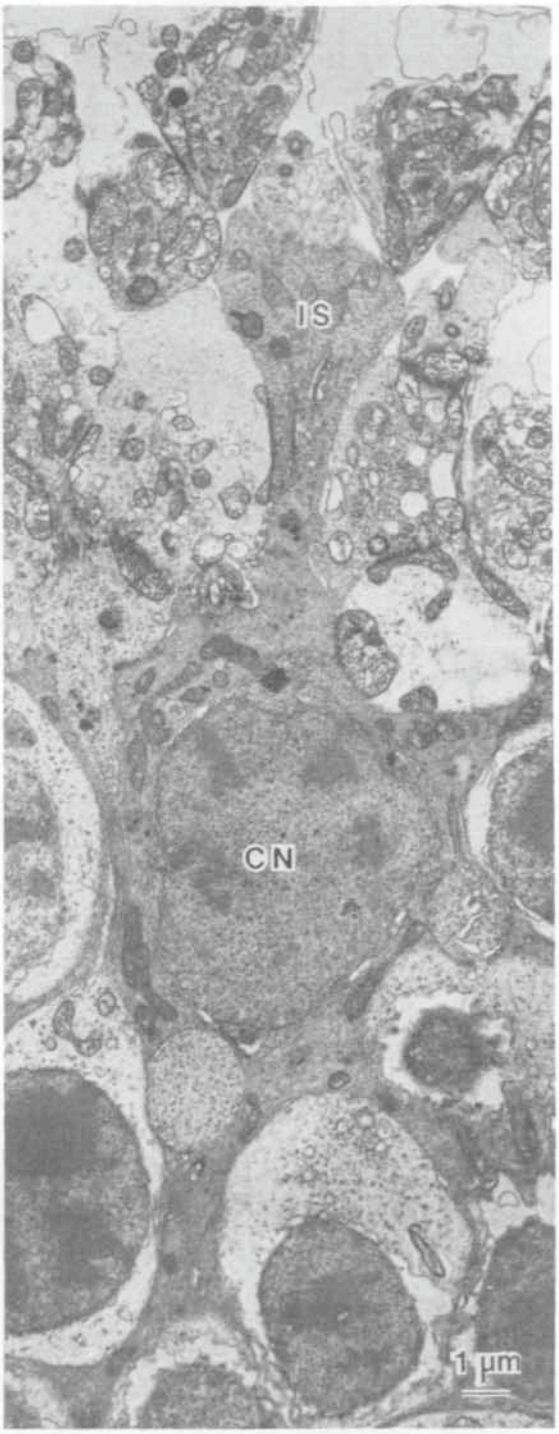

Fig. 5. Electron micrograph of a cone nucleus (CN), cell body, and inner segment (IS) 3 days after detachment, and located near the rod in Figure 4. Although the outer segment has degenerated, the rest of the cone is relatively intact compared to the rods. All of the rods in this region are necrotic.

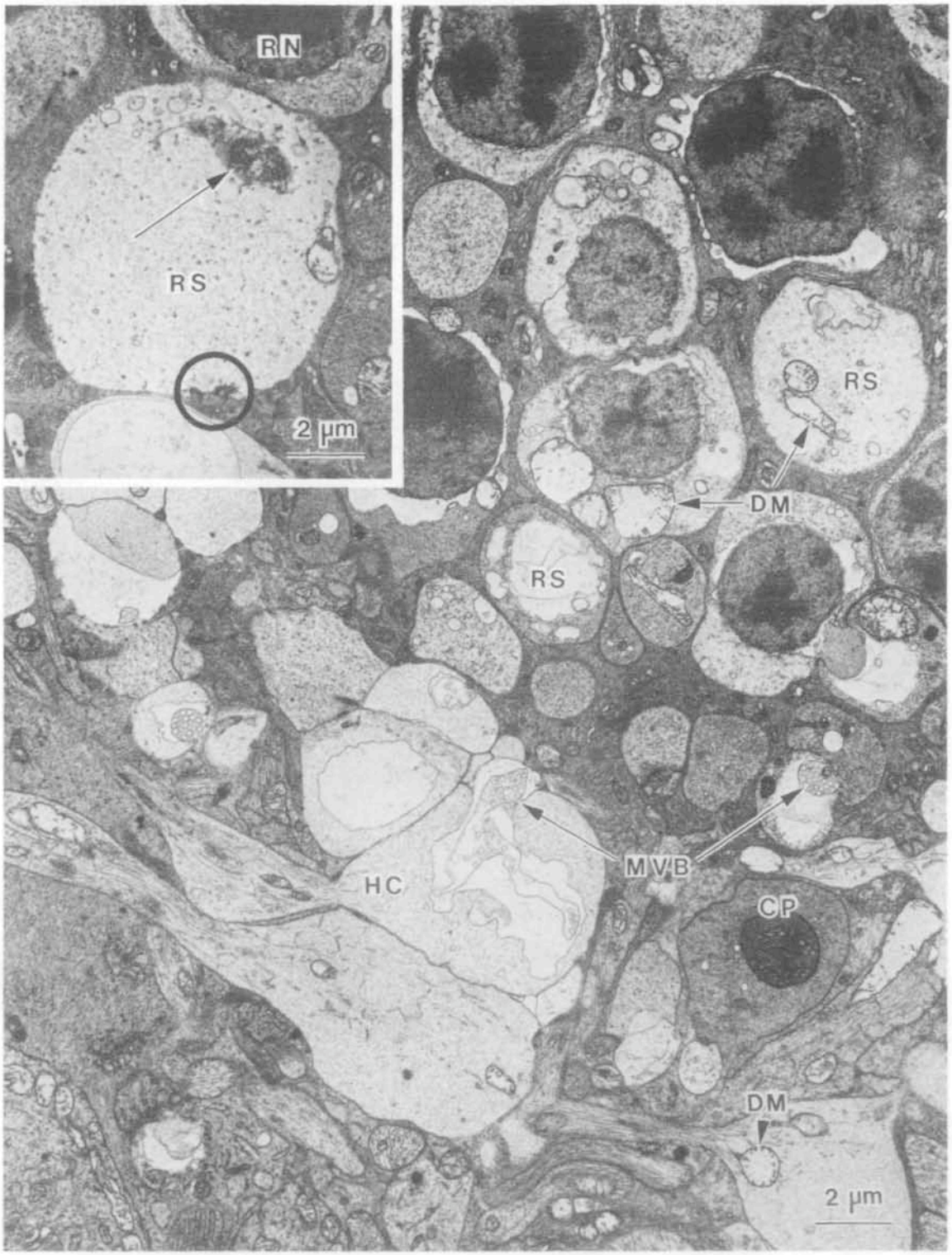

Fig. 6. Low power electron micrograph of the outer plexiform layer of a retina detached for 3 days. Many rod spherules (RS) and horizontal cell processes (HC) stain irregularly and contain vacuoles, distended mitochondria (DM), and multivesicular bodies (MVB). The cone pedicle (CP) is relatively intact compared to the rod spherules. **Fig. 7.** Electron micrograph of a rod spherule (RS) 3 days after detachment. This swollen terminal contains distended mitochondria and shortened synaptic ribbons, with halos of synaptic vesicles (circle), abutting a flattened plasma membrane. A portion of the rod nucleus (arrow) remains. Normal rod nucleus = (RN).

"spherule" shape and appear retracted but not vacuolated; synaptic vesicles are numerous but the ribbons are short and the deep invaginations characteristic of rod terminals are absent (Fig. 13). There are still postsynaptic processes closely apposed to these terminals, usually occurring in a shallow depression of the terminal membrane. We did not identify any cone terminals that appeared to be retracting at this or any other time in our study.

Two-week to Two-month Detachments

Although the cone terminals do not appear as severely affected by detachment during the first 2 weeks, they are not spared from degeneration because cone terminals were not found in detachments of 50 days or longer. By 50 days receptor terminals could no longer be identified by light microscopy (Fig. 14), and morphologic evidence of synaptic contact between the photoreceptors and the second order neurons was rarely found by electron microscopy. As the terminals degenerate, the OPL becomes primarily occupied by Müller cell processes. By 30 days large numbers of Müller cells in the outer plexiform and nuclear layers are easily recognized by their large, deeply indented nuclei with dispersed heterochromatin and by the presence of many 10 nm diameter cytoplasmic filaments (Fig. 15). There appears to be an increase in the amount of rough endoplasmic reticulum in these Müller cells. As detachment duration increases, the Müller cell processes also comprise more of the outer nuclear layer than in control animals.

In retinae detached for 30 days, Müller cell processes project past the OLM into the subretinal space through localized disruptions of the outer limiting membrane, with Müller nuclei sometimes appearing there as well. This occurs commonly in detachments of 50 days or longer (Fig. 16) and, at this time, Müller cell processes extend laterally in the subretinal space covering more of the detached retina.

A significant decrease in photoreceptor cell numbers occurred between 13 and 30 days in our study. By 30 days the number of nuclei is below that found in the far periphery of the controls (Fig. 17) and all of our counts in detached retinae were taken from more central locations.

Two- to Three-month Detachments

As detachment duration lengthens the most dramatic change in the ONL is the occurrence of large vacuoles or spaces and a concomitant decrease in the

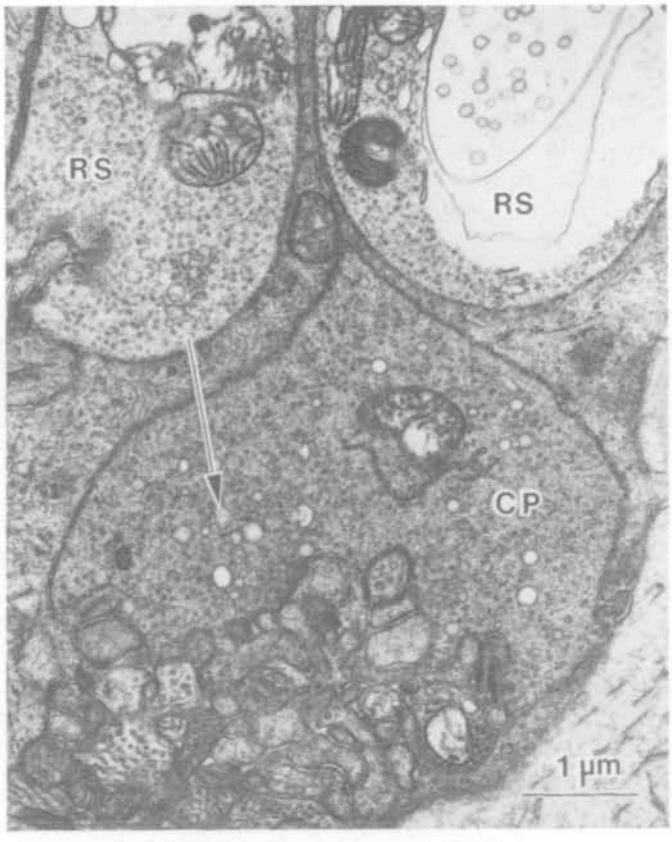

Fig. 8. Electron micrograph of a cone pedicle (CP) 3 days after detachment. Although many rod spherules (RS) are necrotic in this area, the cone pedicles appear relatively normal. Cone pedicles do contain an abnormal population of large (85–100 nm diameter) vesicles (arrow).

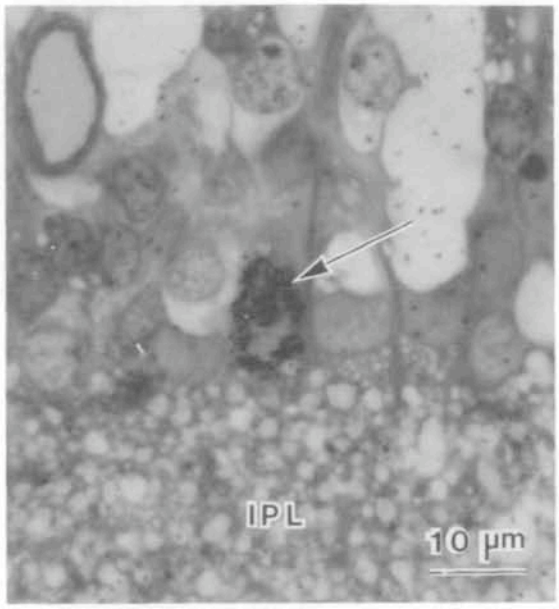

Fig. 9. Light microscope autoradiogram of a Müller nucleus (arrow) labeled with ^{3}H-Thymidine two days after retinal detachment. Inner plexiform layer = IPL.

number of photoreceptor nuclei. There is a progressive loss of cytoplasm and organelles in some photoreceptors until the nucleus appears suspended in a cell-size vacuole (Figs. 4–6, 12, 18, 19). There is a concomitant condensation of the nuclear heterochromatin in these cells. As adjacent cells degenerate their plasma membranes breakdown (Fig. 18) producing large empty spaces in the ONL (Fig. 19) containing the remnants of mitochondria, intracellular membranes and scattered vesicles. Macrophages within the retina appear to phagocytose the remnants of these cells (Figs. 19, 20).

In addition to degeneration, photoreceptor cell bodies are lost from the ONL by migration beyond the outer limiting membrane into the subretinal space (Fig. 21). A few cell bodies are found in the subretinal space as early as 24 hours after detachment but their number increases greatly with the duration of detachment.

By 90 days after detachment, a few regions of the retina do not have any remaining photoreceptor cells. In most areas, however, counts of photoreceptor nuclei show an additional decrease from 30 day values to a level less than 20% of the control areas (Fig. 17). As cell death and migration continue in the ONL (Figs. 17, 21), Müller cell processes fill in the space formerly occupied by the photoreceptors. Rudiments of inner segment ellipsoids are recognized on the remaining photoreceptors, and there is some separation of the outer and inner nuclear layers. We rarely found synaptic contacts between the remaining photoreceptors and the bipolar or horizontal cells in tissue studied by electron microscopy.

Three- to 14-month Detachments

After several months (Figs. 21–23) the outer nuclear layer is composed of scattered photoreceptor nuclei interspersed with the Müller cell processes. Regions void of photoreceptor cells are more common in retinae detached longer than 90 days.

By 14 months subretinal Müller cell nuclei and processes cover all of the detachment zone (Fig. 23). Basal lamina lies adjacent to many of these cytoplasmic processes. Photoreceptor cell bodies and RPE cells are sometimes mixed in with the multiple layers of Müller cell processes in the subretinal space.

By 14 months there are very few macrophages and ^{3}H-thymidine-labeled cells in the detached retina.

Discussion

Detachment of the cat retina from the adjacent retinal pigment epithelium has dramatic effects not only at the photoreceptor—pigment epithelial interface but also within the outer nuclear and outer plexiform layers. The ONL changes include necrosis of

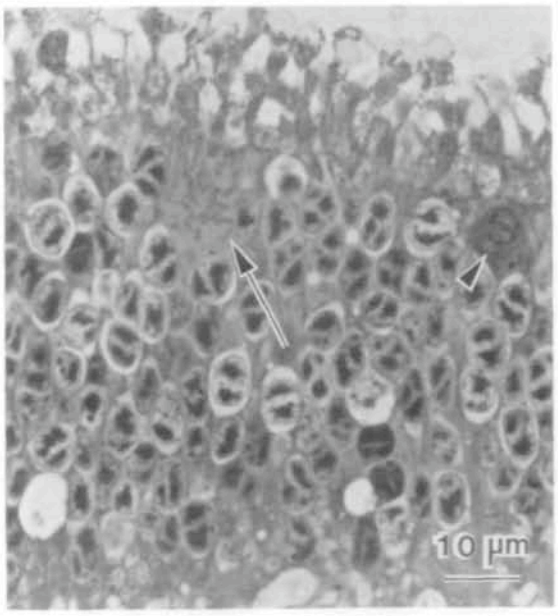

Fig. 10. Light micrograph of a mitotic figure (arrow), assumed to be a Müller cell, and a microglial cell (arrowhead) in the outer nuclear layer. Three days, high detachment.

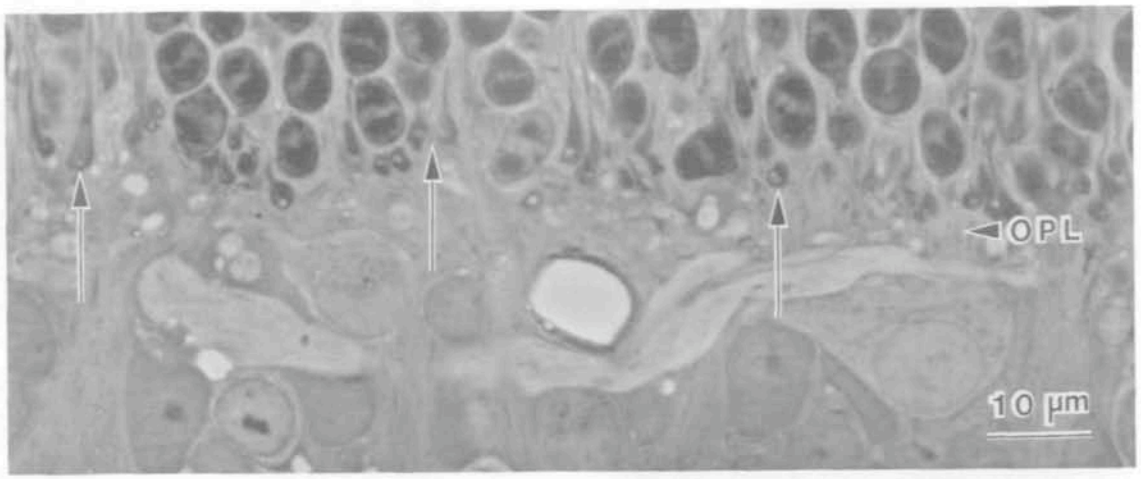

Fig. 11. Light micrograph of the outer plexiform layer (OPL) from a shallow, 13 day detachment. This figure and Figure 12 are from the same tissue section, separated by about 2 mm. In this figure, many photoreceptor synaptic terminals are retracted (arrows) and are more basophilic than normal.

photoreceptor cells and the migration of cell bodies into the subretinal space. The OPL also deteriorates by necrosis and by the retraction of synaptic terminals. Synaptic contact with the second order neurons is essentially severed by 50 days after detachment. Müller cells proliferate and their cell processes and nuclei fill the intraretinal spaces left by the degenerating photoreceptors. They also protrude into the subretinal space forming multiple cytoplasmic layers between the RPE and the detached retina. Photoreceptor and RPE cell bodies also migrate into the subretinal space where they intermingle with the Müller cells.

Although the experimental evidence is very limited, in some cases photoreceptors can regenerate their outer segments after retinal reattachment.[8] The extent of photoreceptor outer segment regeneration undoubtedly affects the highly variable degree of visual recovery found after retinal reattachment in humans.[14-17] Similarly, the changes we have described here may also significantly influence the degree of visual recovery, especially in retinae detached for more than a few days.

Müller Cells

In other retinal pathologies (such as absolute glaucoma, pigmentary degeneration of the retina, pulse-

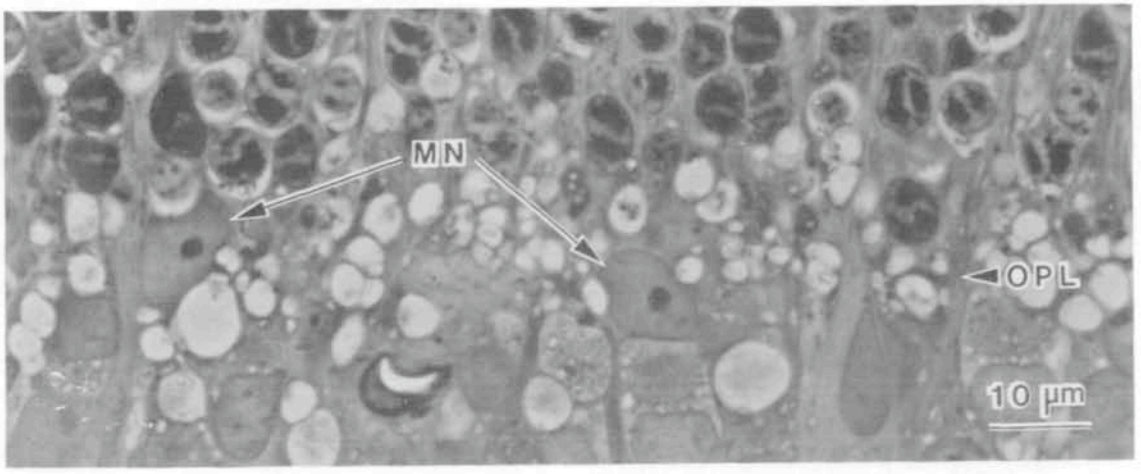

Fig. 12. Light micrograph of the outer plexiform layer (OPL) from a high, 13-day detachment. This figure and Figure 11 are from the same tissue section, separated by about 2 mm. In this figure, many cells are necrotic and are less basophilic than normal. Müller cell nuclei (MN) are in the OPL.

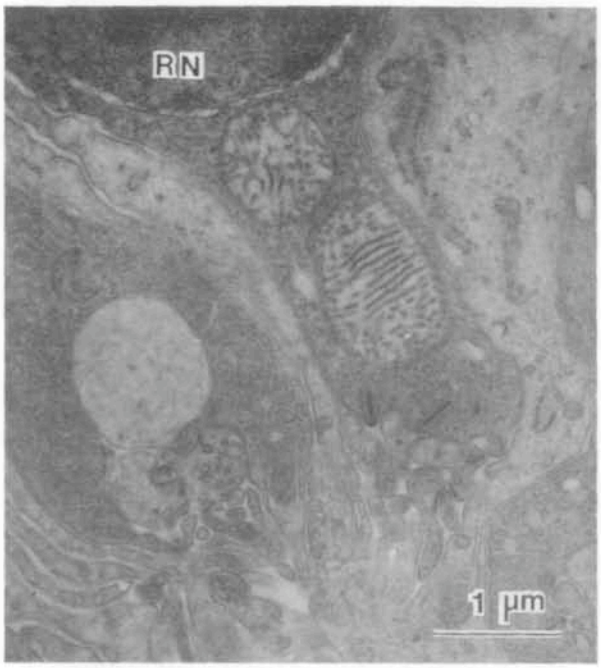

Fig. 13. Electron micrograph of a rod terminal in a shallow 13 day detachment. This terminal has lost its normal spherule shape and appears retracted, but not necrotic. Synaptic vesicles are numerous but the synaptic ribbons are shortened and the deep invaginations characteristic of normal rod terminals are absent. Rod nucleus = RN.

less disease, diabetic retinopathy, and retinal lesions[18,19]), Müller cells are known to proliferate and fill the intraretinal spaces left by degenerating neural elements. In humans with secondary retinal detachments Müller cells have been shown to fill the intraretinal spaces as the number of photoreceptor nuclei decreases.[20] In our study Müller cells that have proliferated and hypertrophied fill the intraretinal space left after photoreceptor somata and synaptic terminals degenerate. In detachments of 50 days or longer, the photoreceptors are isolated from the second order neurons by Müller cell cytoplasmic processes in the OPL. Glial cells elsewhere in the CNS proliferate after injury and form glial scars that may actually inhibit the re-establishment of connections between neurons.[21–24] Müller cells may act in an analogous way by inhibiting the reconnection of receptors and second order neurons after reattachment of long-term retinal detachments.

Müller cell hypertrophy and proliferation also lead to the formation of multiple layers of cell bodies and processes in the subretinal space. By 30 days this occurs in localized regions but by 14 months the Müller cell processes extend over the entire detached retina. Müller cells have also been reported to protrude into the subretinal space in detached owl monkey retinae.[25,26] In that species, however, the Müller cell processes remain localized while RPE cells and astrocytes form a subretinal membrane over the detachment zone. Although RPE and photoreceptor cells migrate into the subretinal space of the cat,[1] it is principally the Müller cell processes that comprise the subretinal membrane. We did not find astrocytes in the subretinal space nor elsewhere in the retina except in their normal location associated with the ganglion cell axons.[27] Although the origin of these subretinal cells may vary between species, their contribution to massive periretinal proliferation is clear.[25,26]

The growth of Müller cells into the subretinal space is analogous in many respects to the formation of an astroglial scar after spinal cord axotomy.[23,24,28–30] In both cases the cells involved are glia, both are secondary pathologic responses, and both appear as overlapping cytoplasmic processes (with basal laminae) growing parallel to and covering neurons at the

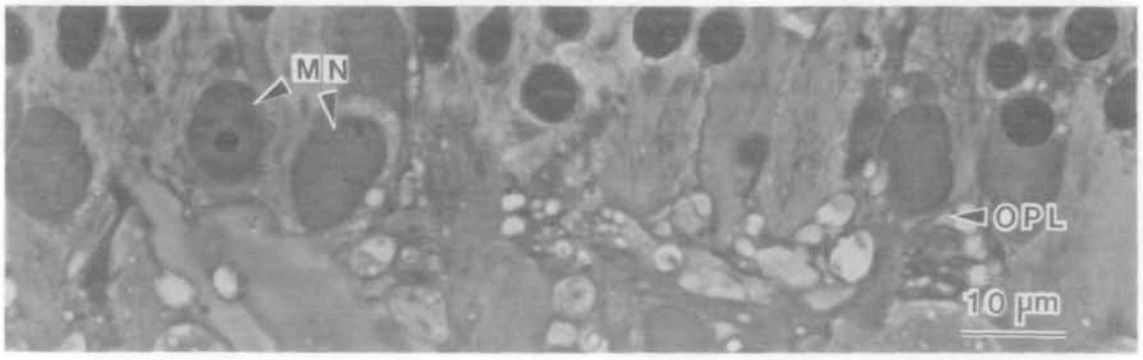

Fig. 14. Light micrograph of the outer plexiform layer (OPL) of a retina detached for 50 days. Synaptic terminals are very rare. The OPL contains some processes of the second order neurons, Müller cell nuclei (MN) and processes. Photoreceptor synaptic contact with the second order neurons is virtually eliminated by this time.

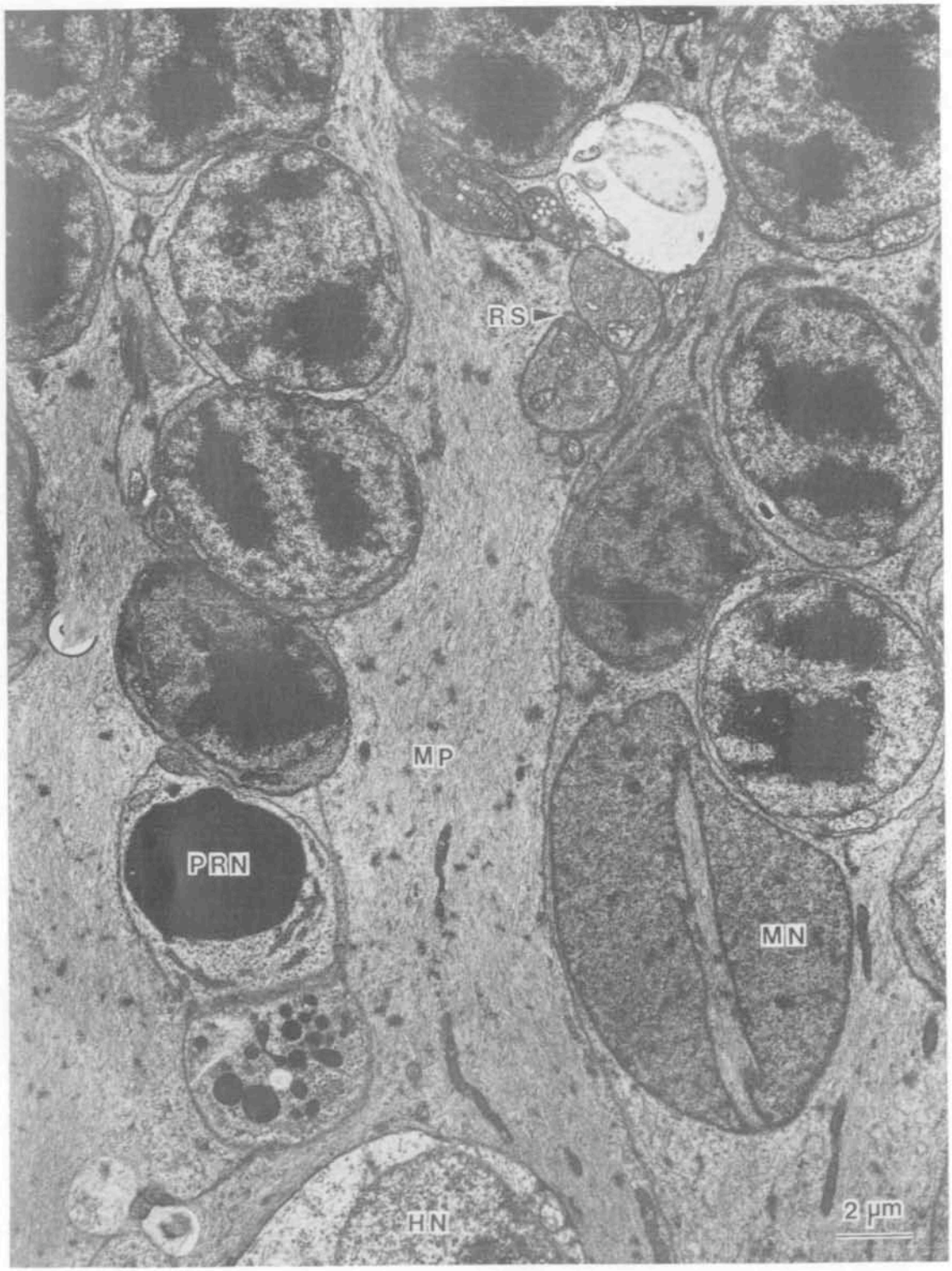

Fig. 15. The region of the outer plexiform layer in a retina detached for 30 days. The OPL is nearly absent in some regions by this time. Only a few rod spherules (RS) can be found. The OPL is filled with Müller cell nuclei (MN) and processes (MP) containing many 10 nm diameter filaments. Pyknotic rod nuclei (PRN) are often present. The inner boundary of the OPL is at the bottom of the figure. Horizontal cell nucleus = HN.

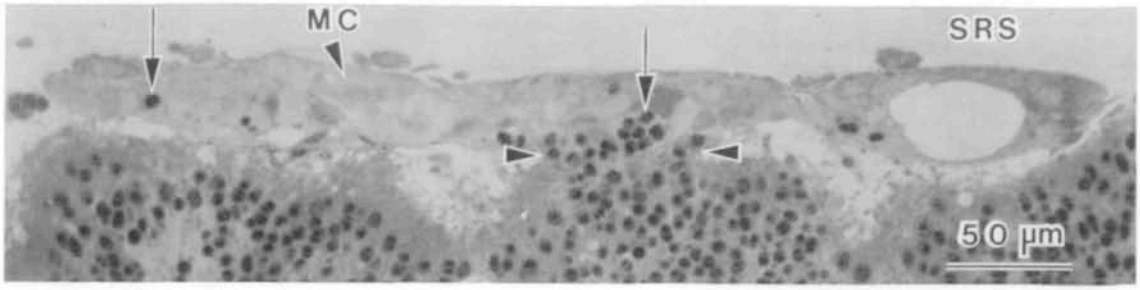

Fig. 16. Low power light micrograph of a retina detached for 50 days showing Müller cells (MC) protruding into the subretinal space (SRS). The arrowheads indicate a localized disruption of the adherens junctions that comprise the outer limiting membrane. Some photoreceptor nuclei (arrows) are found with the Müller cells in the subretinal space.

border of a disrupted tissue. An astroglial scar may block the regeneration of spinal cord axons.[23,24] Similarly, subretinal Müller cells may block the regeneration of photoreceptor outer segments and contribute to poor visual recovery after reattachment. Indeed, our preliminary results with reattached cat retinae indicate that they do act as a barrier between regenerating photoreceptors and the RPE.[1]

ONL Degeneration

After retinal detachment in dogs the ONL may survive for as long as 6 months.[2] In detached owl and rhesus monkey retinae cystoid spaces in the INL substantially reduce the number of cells in the adjacent ONL, although the authors of those studies reported little evidence of cell death in the ONL before 14 weeks.[6-8] The detached rabbit retina showed widespread loss of neural elements by 9 months in one study[3] and, in another study, was reduced to a membrane consisting of a monolayer of cells after 4 months.[4] Degeneration of photoreceptor nuclei also occurs in human retinae with secondary, nonrhegmatogenous, retinal detachments.[20] Some of these differences in ONL degeneration reported in various species may be attributed to differences in vascularization of the retina.[2,6,9-11]

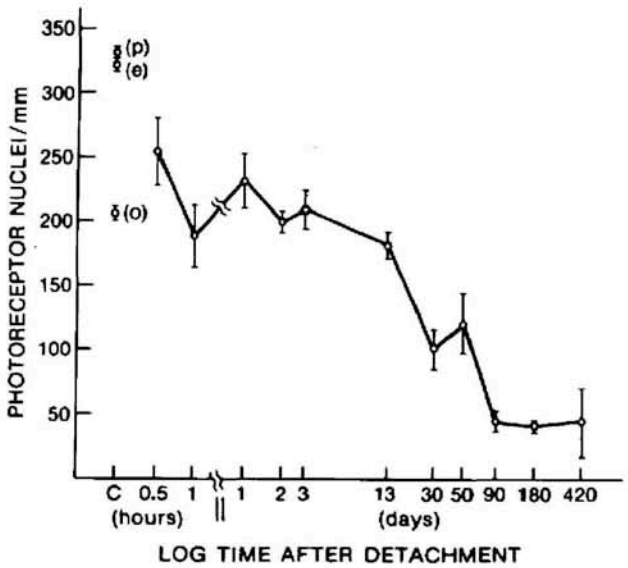

Fig. 17. This graph relates the number of photoreceptor nuclei in the outer nuclear layer to the time after retinal detachment (error bars = ±1 standard deviation from the mean). The points indicated by C (= Control, attached retina) on the ordinate are from posterior retina (P), equatorial retina (E) and from between 1–2 mm posterior to the ora serrata (O). All counts after retinal detachment are from equatorial or posterior retina. By 30 days after detachment, there is a significant reduction in the number of photoreceptors.

In the cat we found a significant decrease in the number of photoreceptor nuclei after 1 month of detachment (Fig. 17). The apparent decline immediately following detachment is due to edema (thus decreasing the photoreceptor density) and not to the loss of receptor nuclei. Unlike the owl and rhesus monkeys,[6-8] the edema within the detached cat retina appears to stabilize and does not progress to the formation of cystoid spaces. In the cat, the deterioration of the ONL proceeds mainly by necrosis and by the migration of photoreceptor cells into the subretinal space.

Machemer[6] reported that in the owl monkey the formation of cystoid spaces and the degeneration of outer segments are more pronounced in high detachments and in those of long duration. In the detached cat retina, necrosis of the photoreceptors is correlated with the depth and duration of retinal detachment. The higher the detachment or the longer the duration the more likely it is to occur. But, necrotic cells are not present in some regions of long-term, bullous detachments. This may be due to fluctuations in the height of detachment throughout the detachment period or may reflect variations in the local microenvironment. Whether these degenerative changes are

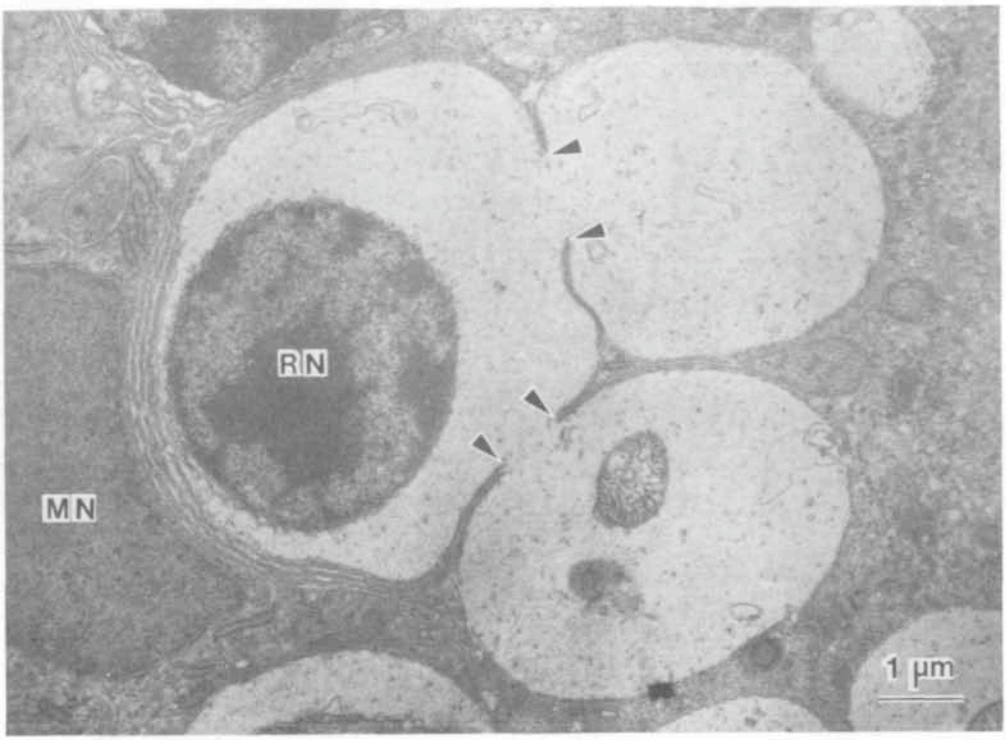

Fig. 18. Electron micrograph of degenerated photoreceptor cell bodies in an 83-day detachment. The plasma membranes (arrowheads) separating a rod (RN) and adjacent degenerating cells are disrupted. Müller nucleus = MN.

reversible, if the retina is reattached prior to cell death, is not known.

A noteworthy occurrence, even in regions with necrotic rods, is the relatively well-preserved appearance of cone inner segments, cell bodies, and synaptic terminals. Even though we found substantial numbers of cones, we did not find any that appeared necrotic at any detachment time. It is possible that in some instances of long-term macular detachments in humans, the partial return of vision after reattachment[17] may be due to the ability of cone cell bodies to survive.

The migration of photoreceptors into the subretinal space has been reported to occur in developing

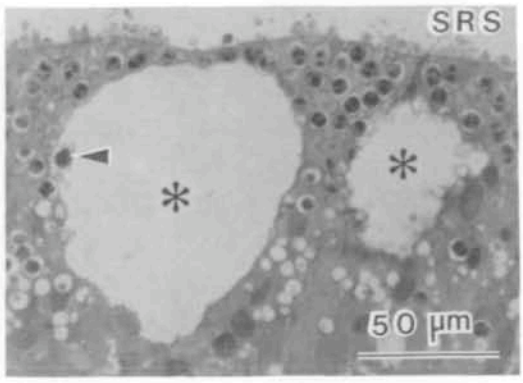

Fig. 19. Light micrograph showing outer nuclear layer degeneration in an 83-day detachment. As adjacent photoreceptors degenerate, large spaces (asterisks) appear in the outer nuclear and outer plexiform layers. Intraretinal spaces such as these are more common in high detachments. Macrophages (arrowhead) occur in these spaces. Subretinal space = SRS.

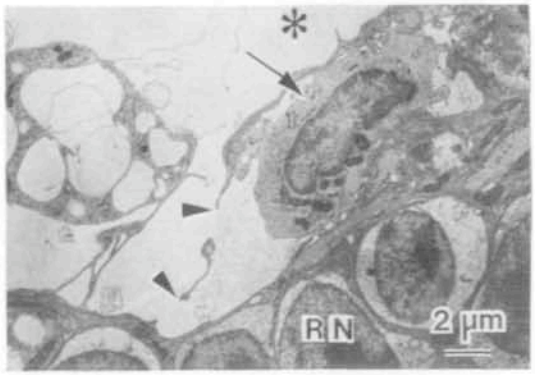

Fig. 20. Electron micrograph of a macrophage (arrow) in an 83-day detachment. The macrophage is at the edge of an intraretinal space (asterisk) similar to those shown in Figure 19. Degenerating plasma membranes (arrowheads) are shown. Rod nucleus = RN.

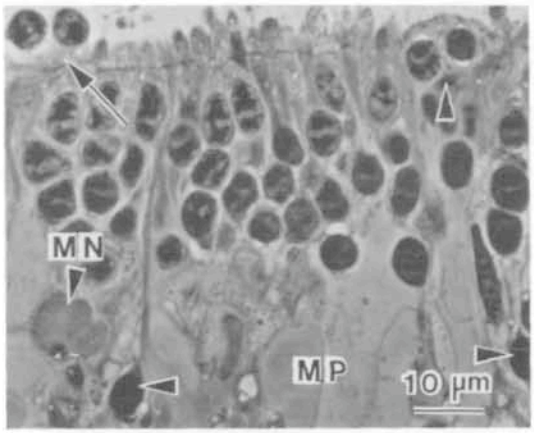

Fig. 21. Light micrograph of the outer nuclear layer 90 days after detachment. Many photoreceptors are missing from the ONL and the space is now occupied by Müller cell processes (MP) and nuclei (MN). The vitread border of the ONL is indicated by the two horizontal arrowheads that point to two remaining photoreceptor nuclei. Two photoreceptor cell bodies (arrow) are located in the subretinal space. Two other photoreceptors (vertical arrowhead) appear under a bulge in the outer limiting membrane.

and aged rat retinae,[31] and in aged human retinae.[32] This has also been reported in detached owl monkey retinae, but only where glial cells have disrupted the OLM and only after 4 weeks of detachment.[25] In the cat, beginning as early as 24 hours after detachment, photoreceptor cells appear to migrate past the OLM in the absence of any disruption from Müller cells. This migration of individual photoreceptor cells seems to be independent of the height and duration of detachment. Photoreceptors found in the subretinal space have normal nuclei and scant cytoplasm, so this does not appear to be a means of disposing of necrotic cells. The cells appear to gain access to the subretinal space through disruptions of the adherens junctions comprising the OLM. In addition, we also see photoreceptor cells enmeshed in the Müller cell processes forming the subretinal membrane.

OPL Degeneration

In humans with secondary retinal detachments,[20] and in rabbits with experimental retinal detachments,[5] there is a reduction in the number of photoreceptor synaptic terminals with time. However, neither of these studies reported the mechanism(s) by which the reduction occurred.In the detached cat retina we found both necrotic photoreceptor terminals and terminals that appear to be retracting towards their cell bodies. Necrosis of the terminals occurs most often in high detachments while the retraction occurs most often in shallow detachments. Both are extensive by 2 weeks after detachment. The loss of synaptic terminals is followed by the hypertrophy of Müller cell processes within the OPL. Similar hypertrophy has been observed in detached rabbit retinae.[5]

We have some morphologic evidence suggesting that transneuronal degeneration or atrophy may occur in 2nd order neurons during degeneration of the receptor terminals. We have found necrotic and pyknotic cells in the inner nuclear layer and ganglion cell layer by 30 days after detachment. Whether or not this is a direct effect of the loss of synaptic input from the photoreceptors or a more general response to detachment is not known.

By 50 days after detachment, virtually all of the synaptic terminals have degenerated and the OPL is filled with Müller cell processes. On the basis of morphologic evidence, there is essentially no synaptic communication between photoreceptors and second order neurons by this time.

In the preceding paper[1] we identified two major anatomical effects of retinal detachment in the cat: RPE cell proliferation and migration, and degeneration of the photoreceptor outer and inner segments. In this paper, we have shown three additional anatomical effects of detachment: (1) ONL degeneration, (2) photoreceptor synaptic terminal degeneration, and (3) Müller cell proliferation, hypertrophy, and scar formation. These five effects all vary with respect to region, depth and duration of detachment. Variability in these five effects probably contributes to the high degree of variability seen in the recovery of vision after retinal reattachment in humans.[14-17] In ad-

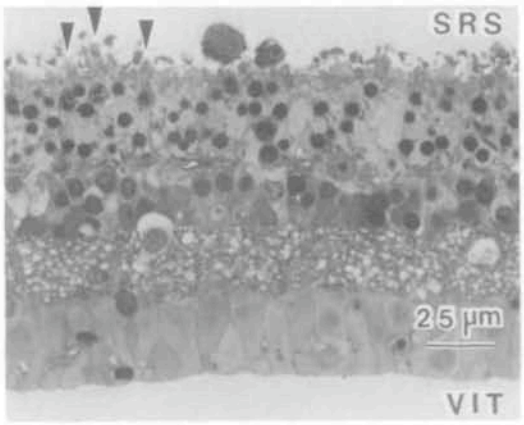

Fig. 22. Low power light micrograph of a 6-month detachment showing a region in which some photoreceptor cells survive, although they are greatly reduced in number. Cone inner segments and cell bodies (arrowheads) appear less disrupted than adjacent rods. Subretinal space = SRS, and vitreous cavity = VIT.

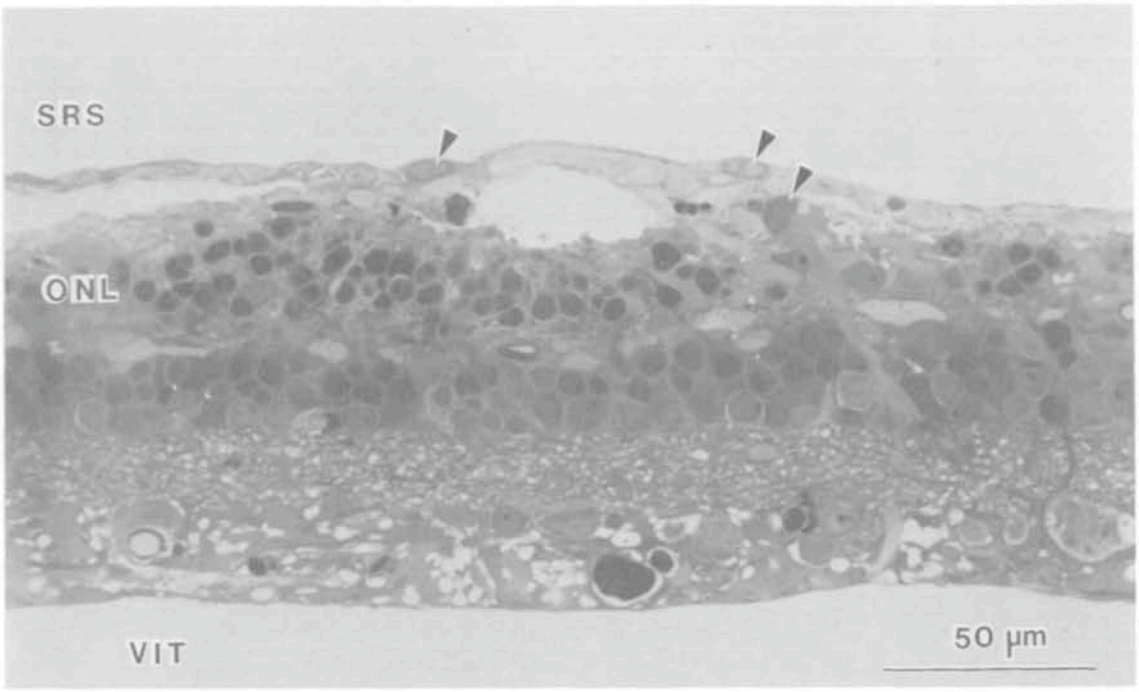

Fig. 23. Low power light micrograph of a retina detached for 14 months. Müller cell nuclei (arrowheads) and processes cover the photoreceptors in the subretinal space (SRS). Regions of the outer nuclear layer (ONL) without photoreceptor cell bodies are common. Vitreous cavity = VIT.

dition to the effects of retinal detachment in the outer retina, we strongly suspect that the inner nuclear layer, inner plexiform layer, ganglion cell layer and, perhaps, more central areas of the visual system may be affected as well.

Key words: retina, retinal detachment, outer nuclear layer, photoreceptor, neuron, outer plexiform layer, synaptic terminal, necrosis, degeneration, proliferation, Müller cell, glial scar

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