

Apoptosis in human retinal degeneration

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This paper was presented in part at the one-hundred and thirty-second Annual Meeting of the American Ophthalmological Society, May 19-20, 1996 at Asheville, North Carolina, USA.

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Acknowledgment

The study is supported in part by Research Grant CUHK405/95M, "Apoptosis of Photoreceptor Cells" and Research Grant CUHK295/96M, "Neuronal Rescuers for Apoptotic Degeneration of Retinal Ganglion Cells" from Research Grants Council of Hong Kong, Fight for Sight Foundation and Mr & Mrs Lew Wasserman

Abstract

Aim: This paper examined the role of apoptosis in human retinal degenerations including pathologic myopia, age-related macular degeneration, serous retinal detachment, retinal lattice and paving stone degeneration.

Materials and methods: Thirty-seven autopsy human eyes and seven surgically enucleated human eyes with one of the above mentioned retinal degenerations were studied by histopathology and by TdT mediated biotin-dUTP nick-end labelling (TUNEL) technique.

Results: TUNEL labelling characteristic DNA fragmentation of apoptosis was observed in photoreceptor cells in 2 of the 4 eyes with pathologic myopia and in 4 of 16 eyes with age related macular degeneration, two of which were exudative and two of which were atrophic. However, only few scattered photoreceptor cells were labelled in 4 of 8 eyes with serous retinal detachment secondary to malignant melanoma of choroid. Moreover, none of the photoreceptor cells in the 4 eyes with retinal lattice degeneration and 6 eyes with retinal paving stone degeneration were labelled.

Conclusions: Apoptosis is one of the important pathways of photoreceptor cell degeneration in pathologic myopia and age-related macular degeneration.

embryogenesis, the size and shape of organs are regulated by selective deletion of cells by apoptosis. In physiological programs, apoptosis leads to hormone-mediated regression of uterine epithelium in menstruation, regression of lactating mammary gland, deletion of certain lymphocytic clones, and others. In pathologic conditions, apoptosis is seen in radiation injury, tumor regression in retinoblastoma, ageing conditions such as Alzheimer's disease and hereditary degenerations such as retinitis pigmentosa. This process is characterized biochemically by double-stranded DNA degradation in which the genome is cleaved at the internucleosomal sites, producing fragments of multiples of 180 - 200 base pairs, which may be demonstrated by agarose gel electrophoresis as a ladder pattern. The endonuclease, which brings about the DNA degradation, is calcium- and magnesium-dependant. This process appears to require *de novo* protein synthesis and may be triggered by a rise in intracellular calcium levels. Morphologically, apoptotic cells characteristically exhibit condensation of chromatin at the nuclear periphery, nuclear disintegration, reduction in nuclear size with formation of apoptotic bodies and progressive degeneration of the residual nuclear and cytoplasmic structures.

This form of cell death has recently been recognized in conventional histologic sections of various organs by Gavrieli and associates⁵ by an *in situ* method of visualization of nuclear DNA fragmentation. This DNA nicked-end labelling with biotinylated dUTP after incubation with a terminal deoxynucleotidyl transferase (TUNEL) is useful to identify fragmented DNA and apoptosis. TUNEL labelling detects DNA fragmentation at the single cell level.

In recent ophthalmic literature, apoptosis of photoreceptor cells has been observed in embryologic development of human retina,⁶ photic retinopathy,⁷ retinoblastoma,⁸ retinitis pigmentosa,⁹ hereditary retinal dystrophy of RCS rats,¹⁰ retinal degeneration of rd and rds mice,¹¹ and transgenic mice expressing a rhodopsin mutation that causes retinitis pigmentosa in human and others.¹² In a more recent article, degeneration of photoreceptor cells, especially the cone cells, was observed in human traumatic detached retina.¹³

This article presents further evidence of apoptosis cell death in the human photoreceptor degeneration in myopic macular degeneration, age-related macular degeneration, and serous detachment of retina secondary to choroidal malignant melanoma. It appears that apoptotic cell death is a common form of photoreceptor cell death in many retinal degeneration.

Introduction

Photoreceptor cell death is a hallmark of a number of types of macular degeneration, such as age-related macular degeneration, myopic macular degeneration, photic maculopathy, traumatic maculopathy, cone-rod dystrophy and others.¹⁻³ It is also found in some forms of peripheral retinal degeneration, such as paving stone degeneration and lattice degeneration. However, the mechanisms of photoreceptor cell death have not been determined. Understanding the mechanisms of the photoreceptor cell death should lead to additional avenues for photoreceptor rescue.

Apoptosis, also termed programmed cell death, is a specific form of cell demise initiated by an endogenous cellular process.⁴ Apoptosis (from the Greek word, "falling off") is widely observed in the biological world, ranging from the falling of leaves in the autumn to metamorphosis of caterpillar to butterfly, to regression of the lactating mammary glands. This type of programmed cell death is believed to be triggered by a gene or sets of genes and is commonly seen in embryological, physiological or pathological processes. In

Methodology

Case selection

Thirty-seven enucleated human eyes, 30 from autopsy of Chinese patients at the Prince of Wales Hospital in Hong Kong and 7 from surgical enucleation from the Georgiana Theobald Ophthalmic Pathology Laboratory, UIC Eye

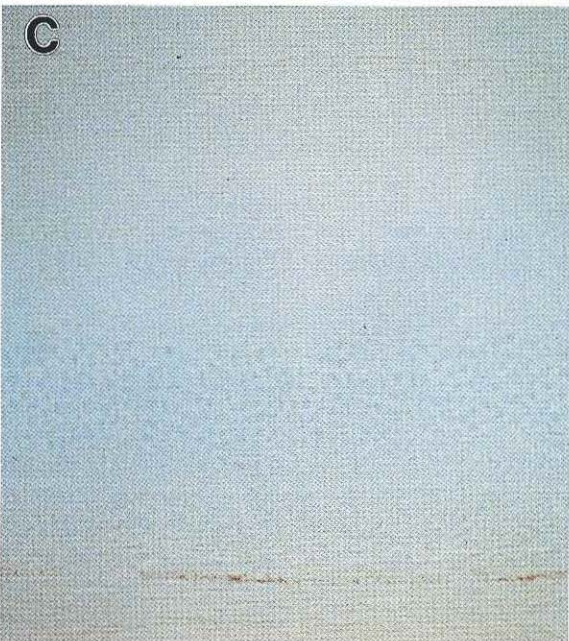
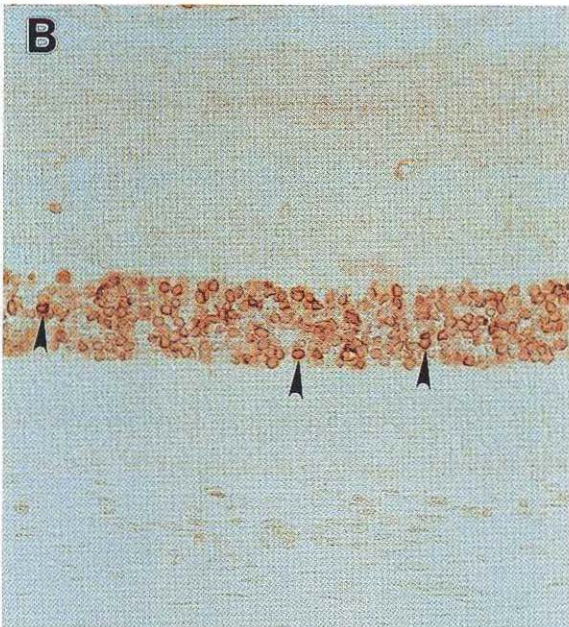
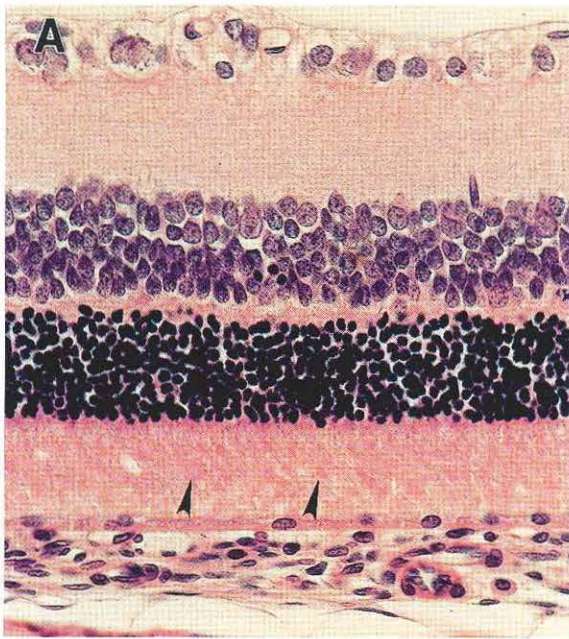


Figure 1. Retina of RCS rat (positive control and negative control).

- A. Retina of a 35-day-old RCS rat, the outer and inner segments were grossly misaligned (arrowheads). (H&E, x400)
- B. A great majority of the photoreceptor nuclei were labelled by the TUNEL technique. Most of the nuclei were labelled with a ring configuration (arrowheads). (x400)
- C. Negative control for TUNEL technique. (x400)

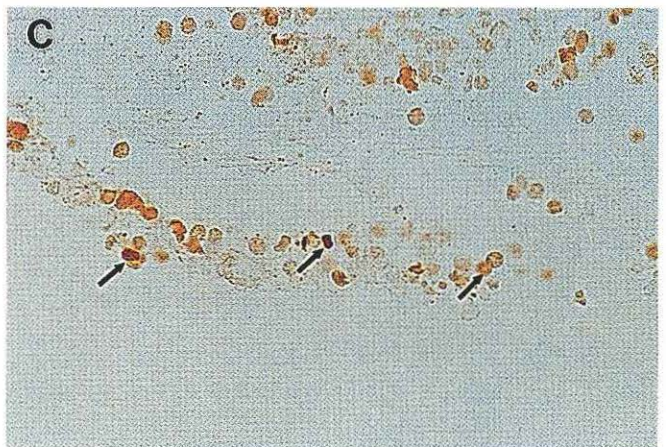


Figure 2. Pathologic myopia

- A. In the macular area, markedly atrophic choroid and RPE were noted (arrowheads). The overlying ONL was reduced to 1 to 2 nuclei thick (arrow). (H&E, x100)
- B. Most photoreceptor cells had lost their outer segments (arrows). (H&E, x400)
- C. Scattered photoreceptor cells were labelled (arrows) by TUNEL technique showing evidence of apoptosis. (x400)

Centre, Chicago, were examined in this study. Four eyes exhibited pathologic myopia with axial length greater than 28 mm. Sixteen eyes had age-related macular degeneration (ARMD). Four eyes showed peripheral retinal lattice degeneration. Six had peripheral retinal paving stone degeneration and 7 eyes exhibited serous retinal detachment secondary to choroidal malignant melanoma.

Tissue preparation

All eyes were cut in horizontal strips (6 x 9 mm) with optic discs and macula fixed in 10% buffered formaldehyde, dehydrated and embedded in paraffin. Serial paraffin sections of six micron thick were cut. The sections were stained with hematoxylin-eosin and were examined by light microscopy.

TdT-mediated biotin-dUTP nicked-end labelling (TUNEL)

We studied these human eyes by the TdT-mediated biotin-dUTP nicked-end labelling (TUNEL) technique. Apoptosis Detection Kit (S7100-Kit, Oncor Co., Inc.) was used for DNA nick-end labelling. For positive control, sections from the retina of a 35-day-old RCS rat were used in each group (Figure 1). In addition, one normal retina from a 65-year-old human (the time interval between death and eyeball fixation was 72 hours) was used for TUNEL labelling to determine if post-mortem body storage time might have an effect on TUNEL labelling. As a negative control, adjacent serial sections of retinas were processed for TUNEL labelling following the standard procedure but omitting incubation with TdT or biotinylated dUTP in TdT buffer during DNA nick-end labelling.

Results

Pathologic myopia

In 4 autopsy eyes, a diagnosis of pathologic myopia was made by gross and histopathologic features. Grossly, these eyes showed increased axial length which ranged from 28 to 31mm with posterior staphyloma and scleral thinning. A tilted optic disc, myopic crescent, and liquefaction and posterior detachment of the vitreous were observed in all 4 eyes. The peripheral retina in these eyes displayed extensive pigmentary degeneration. Paving stone retinal degeneration was observed in 1 eye. Histopathologically, the retina was markedly thinned in all 4 eyes, especially in the posterior pole. Schisis of retinal nerve fiber layer was noted in the equatorial area in 2 eyes. The inner nuclear layer was unremarkable in 4 eyes. Reduction of the outer nuclear layer (ONL) was noted in all 4 eyes, especially at the posterior staphylomatous area. In focal areas of the macula, the ONL was reduced to 1 to 2 nuclei thick (Figure 2). There was shortening of the outer segments and inner segments or focal total loss of these photoreceptor elements (Fig 3 and 4). Some photoreceptor cells were dislodged into the sub-retinal space. The peripheral retina showed cystoid degeneration in all 4 eyes. The RPE cells were remarkably atrophic or absent focally in the posterior pole. The markedly atrophic choroid exhibited attenuation and absence of the choriocapillaris at the posterior pole. The scleral thickness was markedly reduced in these eyes, especially at the posterior pole.

In the TUNEL labelling study, 2 of 4 eyes with pathologic myopia showed positively labelled photoreceptor nuclei, some of which were labelled ho-

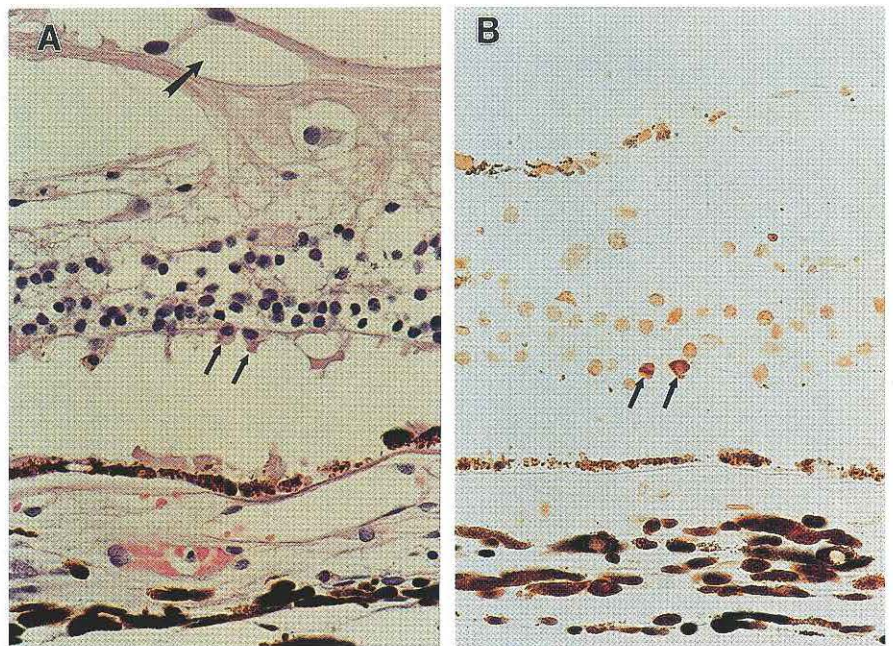


Figure 3. Pathologic myopia

- A. At the equatorial area, note absence of choriocapillaris and markedly atrophic RPE. A few remaining photoreceptor nuclei extruded from the outer limiting membrane into the subretinal space. (arrows). (H&E, x400)
B. The photoreceptor nuclei, extruded from the outer limiting membrane, were labelled (arrows) by TUNEL technique. (x400)

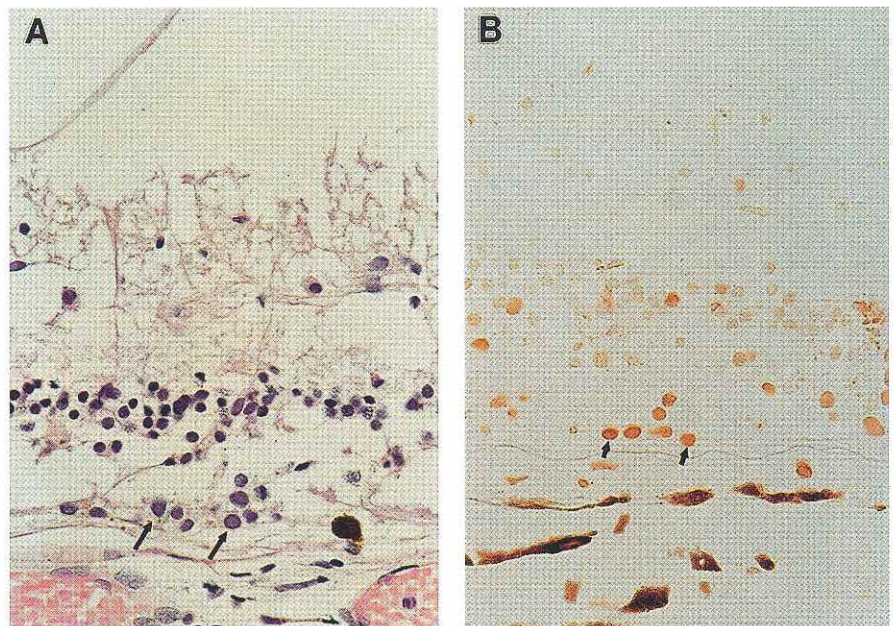


Figure 4. Pathologic Myopia

- A. Temporal to the macular area, some of the photoreceptor cells were devoid of outer and inner segments and lined the Bruch's membrane. (arrows). (H&E, x400)
B. These photoreceptor nuclei were labelled (arrows) by TUNEL technique. (x400)

mogeneously, and others were labelled with a ring configuration. The scattered labelled photoreceptor cells were more prominent at the macular area than those at the equatorial and peripheral retina. Loss of the photoreceptor elements was a common feature in the labelled photoreceptor cells. Some dislodged photoreceptor cells in the sub-retinal space were also labelled. The TUNEL positive photoreceptor nuclei were usually observed in areas where marked reduction of the thickness in the ONL was noted. In addition, a few cells in the inner nuclear layer (INL) were also labelled in 1 eye.

Two of the four eyes with pathologic myopia showed no TUNEL labelling in any of their retinal cells. One of them had cataract extraction operation before death.

Age-related macular degeneration

Sixteen eyes were diagnosed with exhibiting ARMD by histopathologic criteria. All eyes had normal inner limiting membrane, nerve fiber layer, ganglion cell layer, and INL, and pathologic findings were limited to the outer retinal layers. There was mild to severe reduction of ONL thickness in the macular area in 12 eyes. In each of these 12 eyes, atrophic RPE, drusen, (Figures 5 and 6), and irregularly thickened Bruch's membrane consistent with the atrophic form of ARMD were observed. In each of the 4 eyes, a sub-retinal or sub-RPE neovascular membrane was noted (Figure 7). The ONL of these eyes was reduced to 1 or 2 nuclei thick or totally disappeared focally.

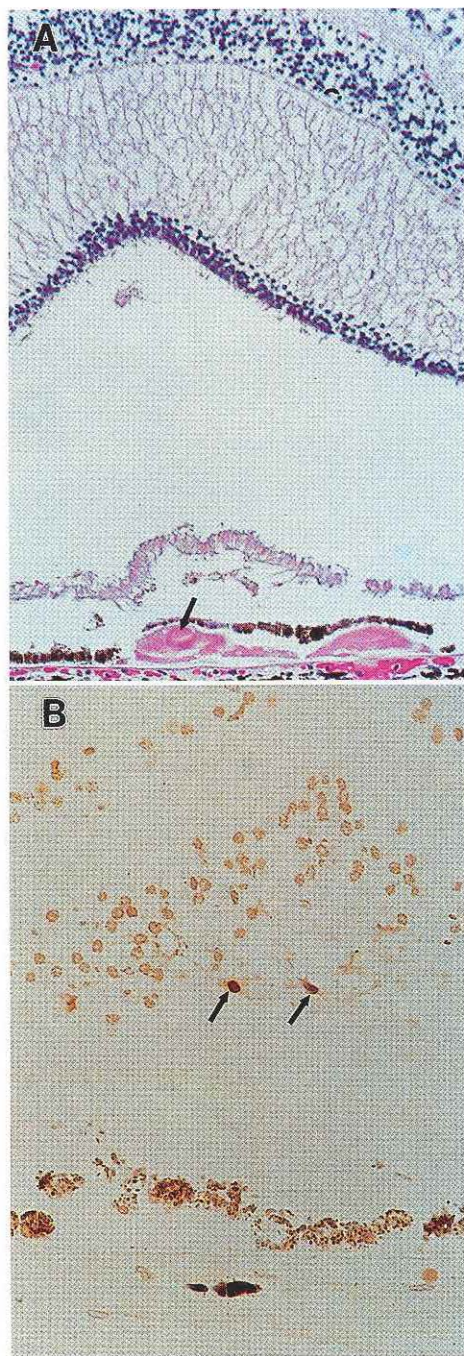


Figure 5. Drusen of Retinal Pigment Epithelium
 A. Large drusen (arrow) overlaid by thinned RPE, and moderate thinning of the outer nuclei layer were seen. (H&E, x200)
 B. Scattered photoreceptor nuclei were labelled (arrows) by TUNEL technique. (x400)

Shortening of the outer and the inner segments of photoreceptor cells or total loss of these structures was common. Some photoreceptor cells were dislocated into the sub-retinal space. Fragmentation and margination of the chromatin in photoreceptor cells were also noted occasionally.

In the TUNEL labelling study, 4 of 16 ARMD eyes showed positively labelled photoreceptor cells. Two of these 4 exhibited an exudative form of ARMD and the other 2 had atrophic form of ARMD. The labelled photoreceptor cells showed a scattered distribution. Most were labelled homogeneously, and a few were labelled with a ring configuration. Some labelled photoreceptor cells were found in the sub-retinal space. Loss of the photoreceptor elements was a characteristic of these labelled photoreceptor cells. The labelled photoreceptor nuclei were usually observed in the areas where marked reduction of thickness in the ONL was seen. In addition to the labelled photoreceptor cells, a few cells in the INL were also labelled in 1 eye.

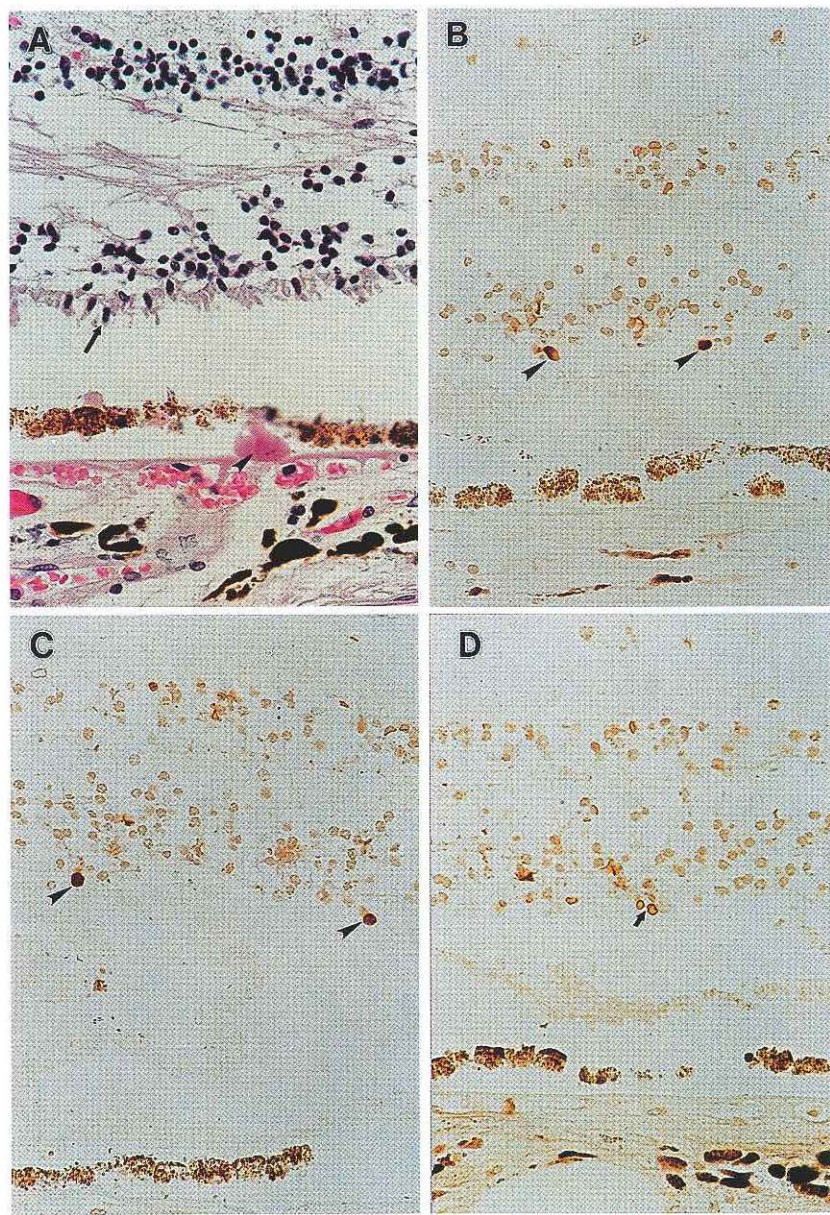


Figure 6. Atrophic Macular Degeneration

- A. Macular area showing moderate thinning of the overlying outer nuclear layer. One drusen (arrowhead) was noted beneath thinned RPE. Some photoreceptor nuclei were dislocated into the inner segments (arrows). (H&E, x400)
 B. B, C and D scattered photoreceptor nuclei were labelled intensely homogeneously (arrowheads) or with a ring configuration (arrow) by TUNEL technique. (x400)

Serous retinal detachment

Clinical diagnosis of serous retinal detachment secondary to choroidal malignant melanoma was made in 7 eyes and confirmed histopathologically. All of the choroidal malignant melanomas were of the mixed cell type. The melanomas were observed on the posterior pole in 6 eyes, and 1 tumor arose from the ciliary body and anterior peripheral choroid. The size of the tumors varied from 7 x 7 x 6 mm to 16 x 14 x 11 mm, and all the malignant melanomas invaded Bruch's membrane and extended into the sub-retinal space and the overlying retina. The tumor extended into the vitreous cavity in 2 cases and into the optic nerve head in 3 cases. The optic nerve heads were atrophic and gliotic in 2 eyes. In 2 other eyes, the optic nerve heads were hemorrhagic and swollen. In 4 of 7 eyes, vitreous hemorrhage was observed.

The RPE overlying the tumors showed marked atrophic degeneration or reactive proliferation. Drusenoid deposits on the Bruch's membrane were noted in 6 eyes. In all 7 cases, the retina overlying the tumor showed cystoid degeneration. The architecture of the retina was markedly disrupted in 3 eyes. Extensive serous retinal detachment with pigment-laden macrophages scattered throughout the sub-retinal space was found in all eyes (Fig 8). Extensive or focal loss of photoreceptor cells in the serously detached retinas was seen in all retinas.

In the TUNEL study, few scattered photoreceptor cells were labelled in 4 eyes. Some labelled photoreceptor cells were dislocated into the sub-retinal space, and showed loss of the photoreceptor elements. Labelled photorecep-

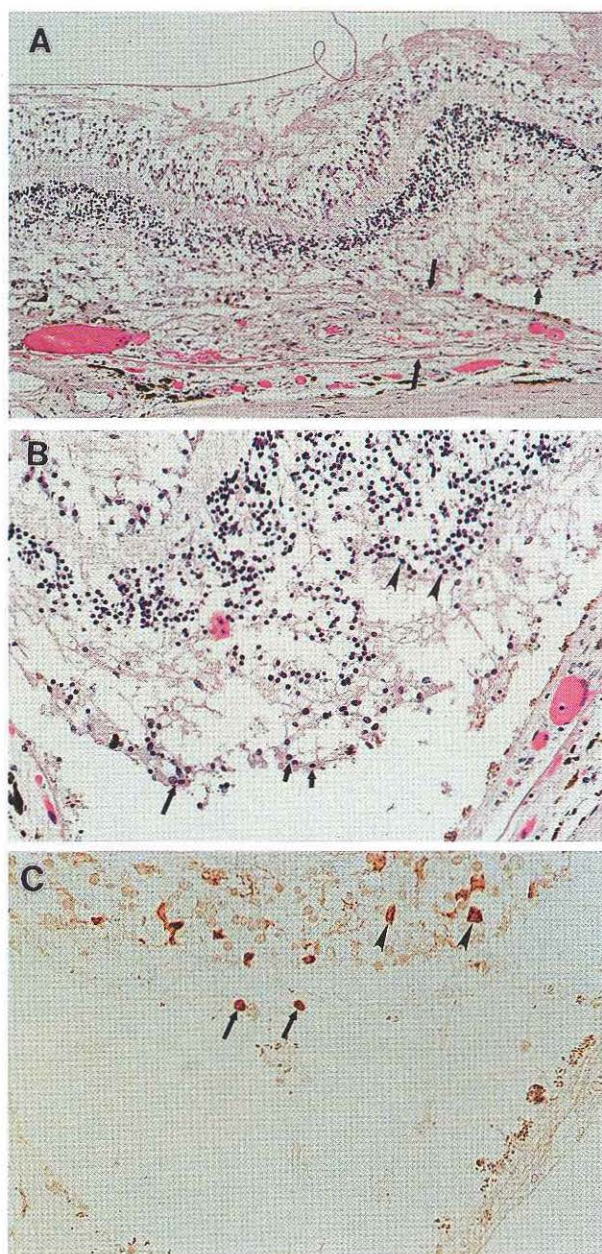


Figure 7. Age-related exudative macular degeneration.

- A distinct fibrovascular membrane was noted in the sub-retinal space. (between long arrows). (H&E, x100)
- Photoreceptor cells in the marked atrophic outer nuclear layer, which had only one or two rows of remaining photoreceptor cells, exhibited loss of outer and/or inner segments (short arrows). Margination of the chromatin in photoreceptor nuclei was noted (long arrow). (H&E, x200)
- Scattered photoreceptor nuclei were labelled (arrows) and some cells of INL were also labelled (arrowheads) by TUNEL technique. (x400)

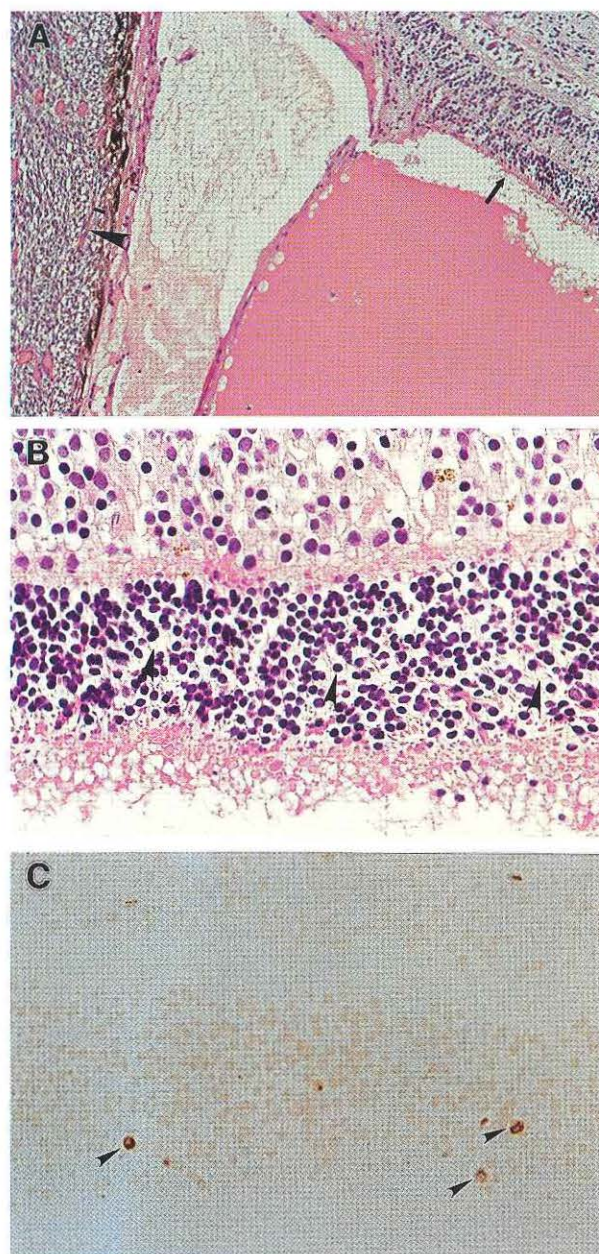


Figure 8. Serous retinal detachment secondary to malignant melanoma of choroid.

- Serous retinal detachment (arrowhead) secondary to malignant melanoma of choroid (arrow, mixed cell type). (H&E, x100)
- In the detached retina, edema of ONL was noted (arrowheads). (H&E, x400)
- Scattered photoreceptor nuclei were labelled with a ring configuration (arrowheads) by TUNEL technique. (x400)

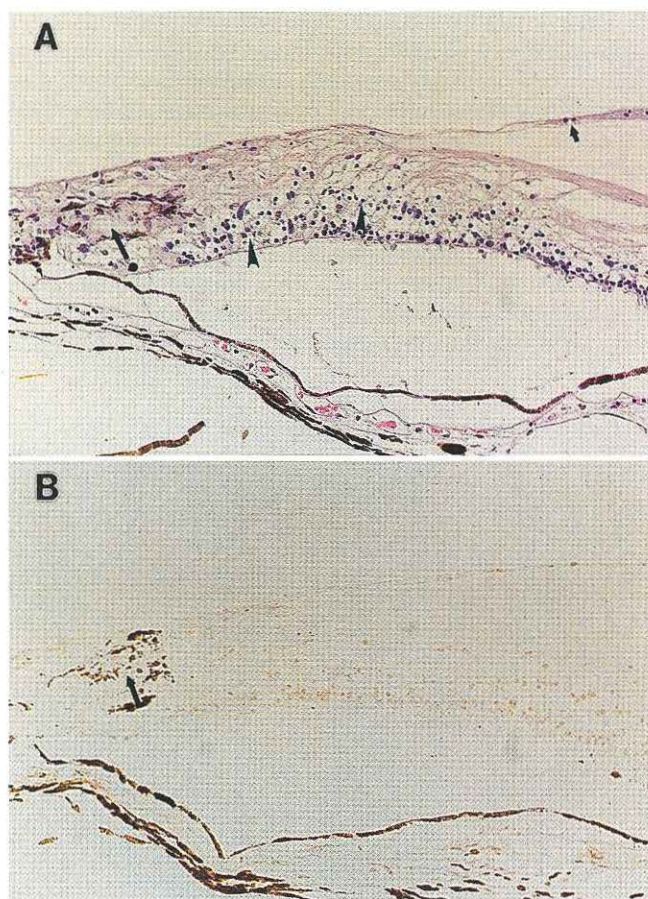


Figure 9. Peripheral retinal lattice degeneration.

- A. In the degenerated area, disorganised retina with marked thinning of the inner and outer nuclear layers was seen (arrowheads). A sclerotic and occluded retinal artery within the lesion was surrounded by proliferated RPE cells (long arrow). A preretinal glial membrane overlying the lesion was noted (short arrow). (H&E, x200).
 B. No retinal cells were labelled by TUNEL technique. (x200)

tor cells were usually observed in areas where marked reduction of thickness of the ONL was seen. Scattered labelled tumor cells were also noted in 2 of the 7 choroidal malignant melanomas.

Retinal lattice and paving stone degeneration

Peripheral retinal lattice degeneration was observed in 4 eyes that were otherwise normal. Grossly, the lesions appeared as circumscribed atrophic areas with sharp edges, located between the equator and the ora serrata. A few whitish blood vessels crossed the lesional areas, where pigment deposition was also observed. Histopathologically, the retinas were moderately thinned and showed atrophy and degeneration of all retinal layers, especially the inner nuclear layer (Figure 9). Thickened and sclerotic retinal blood vessels were focally surrounded by proliferated pigment epithelial cells. The overlying vitreous was liquefied with condensation and adherence of vitreous strands at the edges of the lesions. In some eyes, a glial membrane overlying the anterior surface of the atrophic retina was also seen.

Retinal paving stone degeneration was observed in 6 eyes which were otherwise normal. Grossly, these peripheral retinal lesions were ovoid in shape, occurring singly or in groups. They were located posterior to the ora serrata. Prominent choroidal vessels were observed at the base of the lesions. Microscopic examination of the lesions revealed thinning of the retina, especially the outer nuclear layer with distinct atrophy of RPE and absence of choriocapillaris (Figure 10). The atrophic retina was adherent to the Bruch's membrane. No inflammatory response was found in the retina. In the TUNEL labelling study, eyes with peripheral retinal lattice degeneration and paving stone degeneration failed to show any positively labelled retinal cells.

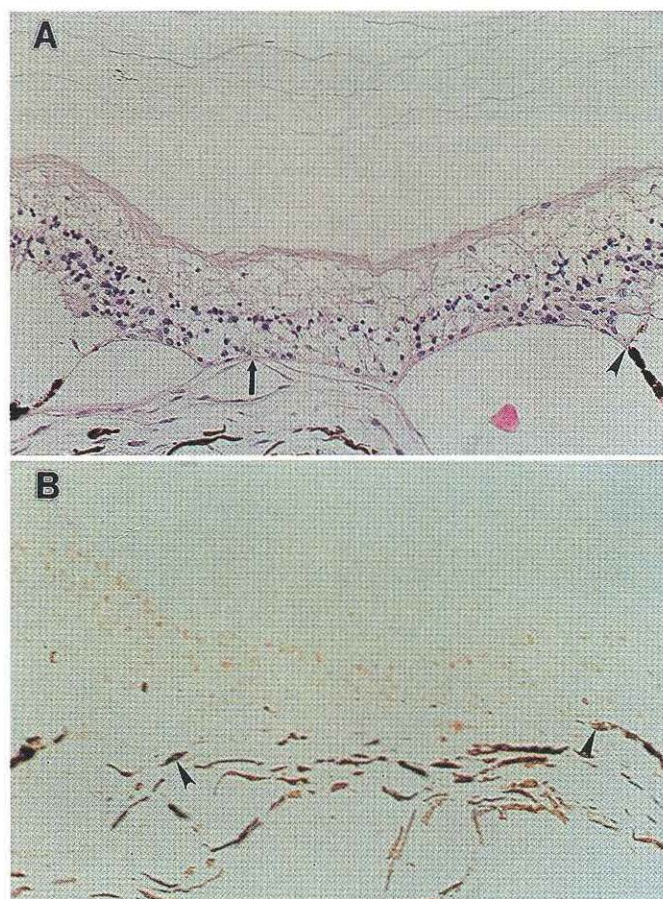


Figure 10. Paving stone degeneration in peripheral retina.

- A. The RPE ended (arrowheads) abruptly in the area of degeneration, where there was absence of choriocapillaris and retinal pigment epithelium (arrow). The overlying retina exhibit extensive atrophy, especially in the outer nuclear layer. (H&E, x200)
 B. None of retinal cells was labelled by the TUNEL technique. (x200)

Discussion

In this study, we examined 37 human eyes with various types of retinal degenerations with TUNEL labelling technique for evidence of apoptosis. Labelled photoreceptor cells were noted in 2 of the 4 eyes with pathologic myopia, and 4 of the 16 eyes with ARMD. Gavrieli and co-workers showed that the TUNEL technique labels the 3' end of the DNA fragments of the apoptotic nuclei, and internucleosomal DNA fragmentation is a hallmark of apoptosis. Therefore, we conclude that apoptosis is one of the important mechanisms of photoreceptor cell death in pathologic myopia and ARMD.

In 4 of 7 eyes with serous retinal detachment secondary to malignant melanoma of choroid, few photoreceptor nuclei were labelled. In contrast, traumatic retinal detachment in humans had many labelled photoreceptor cells. Apoptosis might not be a prominent mechanism in this secondary serous retinal detachment.

TUNEL technique failed to demonstrate positive labelling of retinal cells in 6 eyes with paving stone degeneration. Choroidal vascular insufficiency is believed to be responsible for the development of paving stone degeneration.¹⁴ Curtin reported increased prevalence in patients with age over 40 and in eyes with long axial length.¹⁵ Similar retinal lesions had also been reported in patients with unilateral hypertensive retinopathy.¹⁶ Because ischemia is reported to induce apoptosis in neurons, we speculated that the apoptotic process might be involved in the retinal cell death in retinal paving stone degeneration but failed to demonstrate labelled cells. However, we might not have studied these lesions in the active degenerative phase. The TUNEL

technique also failed to show positive labelling in photoreceptor cells in eyes with lattice retinal degeneration. The pathogenesis of lattice degeneration remains unknown. Hypotheses of the pathogenesis of lattice degeneration include (1) vitreous traction,¹⁷ (2) retina ischemia,¹⁸ and (3) a primary defect in the internal limiting membrane of the retina.¹⁹ Indeed, breaks in this membrane might stimulate proliferation of preretinal glial membranes overlying the retinal lesions.¹⁸ Growth factors such as basic fibroblast growth factor (bFGF) induced preretinal glial membrane proliferation, and might inhibit the apoptotic process.

These chronic degenerations of the photoreceptor cells are a life-long process, but the short-lived apoptotic process, which is usually completed in 24 hours, might only be detected in certain periods of these degenerative diseases. In addition, there might be certain periods when the apoptotic process was active. For example, in experimental traumatic retinal detachment, the first apoptotic peak is detected on the third day after detachment, and the second apoptotic peak is detected around day 14 after retinal detachment.²⁰ The apoptotic process might appear in several periods of the chronic retinal degenerative process. This might be one of the reasons why apoptosis was not observed in the peripheral paving stone or lattice degeneration.

In the eyes with pathologic myopia, ARMD and serous retinal degeneration, there was absence of inflammatory response and abundant cellular debris in the retinas, even though the eyes were in advanced-stage of the diseases. This observation was consistent with cell death by apoptosis, an energy-requiring process of self-elimination of cells without production of cellular debris that attract inflammatory cells. In sharp contrast to cell death by necrosis, inflammatory reaction is inevitably seen.²¹⁻²² Two of the 4 eyes of pathologic myopia failed to show positive labelling with TUNEL technique. One of the

patients underwent cataract extraction 1 year ago and had cystoid macular edema after surgery. Recent studies showed a high level of bFGF in human and animal aqueous humor after cataract surgery.²³ bFGF was believed to be one of the inhibitors of apoptosis^{24,25} and had been demonstrated to delay photoreceptor degeneration in retina dystrophy in rats.²⁶ bFGF might have inhibited the apoptotic process of photoreceptor cells in this patient.

In this study, TUNEL labelled apoptotic photoreceptor cells were observed in 2 out of 4 eyes with exudative ARMD and sub-retinal neovascular membrane. On the other hand, 2 out of 12 eyes with atrophic ARMD without sub-retinal neovascular membranes had apoptotic photoreceptor cells. Sub-retinal neovascular membrane might be a strong stimulus that triggered apoptosis of photoreceptor cells. The endothelial cells in the neovascular network lacked blood-retinal barrier and leaked lipo-proteinaceous fluid into the sub-RPE or sub-retinal space. In addition, these fragile new vessels were prone to hemorrhage. Lipid peroxidation, which resulted from exudation and hemorrhage, might trigger apoptosis of photoreceptor cells in ARMD with sub-retinal neovascular membrane. Recently, Tso and associates reported that apoptosis was a primary mechanism of photoreceptor cell degeneration in inherited retinal dystrophy in the RCS rat.¹⁰ Studies of mouse models of retinitis pigmentosa also showed that apoptosis was a final common pathway of photoreceptor cell death.¹¹ In other studies of acquired retinal degeneration, apoptotic photoreceptor cells were observed in experimental retinal detachment²⁷⁻²⁸ and experimental photic retinopathy.^{7,29-30} Furthermore, Chang and associates also demonstrated that apoptosis appears to be a primary mechanism of human photoreceptor cell death following traumatic retinal detachment. His study additionally demonstrated apoptosis in human myopic macular degeneration and age-related macular degeneration. $\odot$

References

1. Alan CB. Retinal photoreceptor dystrophies. *Am J Ophthalmol* 1995; 119:543-52.
2. Tso MOM. Pathogenetic factors of ageing macular degeneration. *Ophthalmology* 1985; 92:628-35.
3. Tso MOM. *Retina Disease: Biomedical Foundations in Clinical Management*. Philadelphia, JB Lippincott, 1988.
4. Tomei LD, Cope FO. *Apoptosis: The Molecular Basis of Cell Death*. NY, Cold Spring Harbor Lab Press, 1991.
5. Gavrieli Y, Sherman Y, Ben-Sasson. Identification of programmed cell death in situ via specific labeling of nuclear DNA fragmentation. *J Cell Biol* 1992; 119:493-501.
6. Gregory CY, Bird AC. Cell loss in retinal dystrophies by apoptosis death by informed consent. *Br J Ophthalmol* 1994; 232: 635-45.
7. Abler AS, Chang CJ, Fu J, Tso MOM. Photic injury triggers apoptosis of photoreceptor cells. (ARVO, abstract.) *Invest Ophthalmol Vis Sci* 1994; 35:1517.
8. Buchi ER, Bernauer W, Daicker B. Cell death and disposal in retinoblastoma: an electron microscopic study. *Graefes Arch Clin Exp Ophthalmol* 1994; 232: 635-45.
9. Portera-Cailliau C, Sung CH, Nathans T, et al. Apoptotic cell death in mouse models of retinitis pigmentosa. *Proc Natl Acad Sci* 1994; 91:974-8.
10. Tso MOM, Zhang C and Abler AS, et al. Apoptosis leads to photoreceptor degeneration in inherited retinal dystrophy of RCS rats. *Invest Ophthalmol Vis Sci* 1994; 35:2693-99.
11. Chang GO, Hao Y, Wong F. Apoptosis: Final common pathway of photoreceptor death in rd, rds, and rhodopsin mutant mice. *Neuron* 1993; 11:595-605.
12. Szczesny PJ. The early stages of photoreceptor degeneration in various forms of retinitis pigmentosa in man suggest apoptosis as a common pathway (ARVO, abstract.) *Invest Ophthalmol Vis Sci* 1995; 36:s919.
13. Chang CJ, Lai WW, Tso MOM. Apoptotic photoreceptor cell death after traumatic retinal detachment in human. *Arch Ophthalmol* 1995; 113: 880-6.
14. Karlin DB, Curtin BJ. Peripheral Chorioretinal lesions and axial length of the myopic eye. *Am J Ophthalmol* 1976 81: 625-35.
15. Curtin BJ. *The myopias: basic science and clinical management*. Philadelphia, Harper & Row, Publishers, Inc, 1985.
16. Michelson PE, Knox DL, Green WR. Ischemic ocular inflammation. A clinicopathologic case report. *Arch Ophthalmol* 1971; 86:274-80.
17. Foos RY, Simons KB. Vitreous in lattice degeneration of retina. *Ophthalmology* 1984; 91:452-57.
18. Robinson MR, Steeten BW. The surface morphology of retinal break and lattice retinal degeneration: A scanning electron microscopic study. *Ophthalmology* 1986; 93:237-46.
19. Streeten BW, Bert M. The retinal surface in lattice degeneration of the retina. *Am J Ophthalmol*. 1972; 74:1201-9.
20. Cook B, Lewis GP, Fisher SK, et al. Apoptotic photoreceptor degeneration in experimental retinal detachment. *Invest Ophthalmol Vis Sci* 1995; 36:990-6.
21. Wyllie AH. Glucocorticoid induced thymocytes apoptosis is associated with endogenous endonuclease activation. *Nature* 1980; 284:555-6.
22. Kerr JFR, Harmon BV. *Apoptosis: The Molecular Biology of Cell Death*. New York Cold Spring Harbor Press, 1991; pp5-30.
23. Namiki M. Quantification of basic fibroblast growth factor (bFGF) and transforming growth factor (TGF alpha) in rabbit aqueous humor after intraocular lens implantation. *Nippon Ganka Gakkai Zasshi* 1994; 98:334-9.
24. Fuks Z, Persaud RS, Alfieri A, et al. Basic fibroblast growth factor protects endothelial cells against radiation-induced programmed cell death in vitro and in vivo. *Cancer Res* 1994; 54:2582-90.
25. Haimovitz-Friedman A, Balaban N, McLoughlin M, et al. Protein kinase C mediates basic fibroblast growth factor protection of endothelial cells against radiation-induced apoptosis. *Cancer Res* 1994; 54:2591-7.
26. Faktorovich EG, Steinberg RH, Yasumura D, et al. Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor. *Nature* 1990; 347:83-6.
27. Cook B, Lewis GP, Adler R, et al. Photoreceptor degeneration in experimental retinal detachment: Evidence for an apoptotic mechanism. (ARVO, abstract.) *Invest Ophthalmol Vis Sci* 1994; 1833.
28. Wilson DJ, Cuthbertson RA and Kijavini I. Apoptosis as the mechanism of photoreceptor cell death in experiment retinal detachment. (ARVO, abstract.) *Invest Ophthalmol Vis Sci* 1995; 36:s64.
29. Hafezi F, Weller M, Munz K, et al. Light-induced apoptosis in the rat retina in vivo: Threshold, time course and potential regulators. *Invest Ophthalmol Vis Sci* (ARVO, abstract.) 1995; 36:s917.
30. Lai WW, Chang CJ, Abler AS, et al. A comparative study of apoptosis of photoreceptor cells following light injury to four strains of inbred albino rats. (ARVO, abstract.) *Invest Ophthalmol Vis Sci* 1995; 36:s63.