

Mechanisms of Photoreceptor Death in Retinal Degenerations: From the Cell Biology of the 1990s to the Ophthalmology of the 21st Century?

In the inaugural review article for the Mechanisms of Ophthalmologic Disease section in the January 1996 issue of the ARCHIVES, Dr Adler¹ begins with the statement, "There is still no effective treatment for retinal degenerative diseases such as retinitis pigmentosa (RP), in which the loss of photoreceptor cells causes visual loss and eventually blindness." It is surprising that no mention is made of "A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa," an article by Berson et al² published in the June 1993 issue of the ARCHIVES. Also in 1993, the National Eye Institute issued a report of this trial's results and recommended that patients with RP take vitamin A palmitate (C. Kupfer, MD, written communication, June 14, 1993).

This treatment trial was initiated prior to the discovery that RP may involve "genes by the dozen, mutations by the score."¹ No evidence was found that the beneficial effect of vitamin A was confined to one or another genetic type. Since we now know that this trial must have included patients from many different pedigrees with numerous genetic abnormalities, it could be inferred that if the treatment provided a beneficial effect for the group, then some phenotypes might benefit more from treatment than others. The clinician often has no way of determining which phenotype or genetic mutation a given patient has, let alone whether the patient will respond to treatment.

Dr Adler's informative article outlines some theoretically possible future treatments for RP such as neurotrophic growth factors, or pharmacological intervention on metabolic genetic pathways, which may come to fruition in the 21st century. Until researchers have developed future treatments, ophthalmologists are left with vitamin A palmitate. While this treatment is not without controversy,³ it would seem prudent for ophthalmologists to offer vitamin A palmitate to patients with RP.

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1. Adler R. Mechanisms of photoreceptor death in retinal degenerations: from the cell biology of the 1990s to the ophthalmology of the 21st century? *Arch Ophthalmol.* 1996;114:79-83.
2. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol.* 1993; 111:761-772.
3. Berson EL, Bird AC. Retinal photoreceptor dystrophies: LI Edward Jackson Memorial Lecture. *Am J Ophthalmol.* 1995;120:683-684.

In reply

The goals of my contribution to the Mechanisms of Ophthalmic Disease series were to review recent advances in our understanding of cellular and molecular mechanisms of retinal degenerations and to discuss possible avenues for research into new therapeutic strategies for these devastating disorders. It would have been beyond the scope and space limitations of the article to review the literature on previously described or proposed therapeutic approaches, such as the use of vitamin A in RP or antioxidant treatments for macular degeneration. The opening sentence of my article was actually meant to indicate that no cure is currently available for these diseases, but Dr Crane's comments suggest that the wording of that statement was ambiguous. I would like to thank Dr Crane very much for pointing this out, and for the opportunity to clarify such possible misunderstanding.

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Apoptotic Photoreceptor Cell Death After Traumatic Retinal Detachment in Humans

In a recent article in the ARCHIVES, Chang et al¹ ascribed photoreceptor cell degeneration in patients with traumatic retinal detachment as being due to apoptosis. They based this claim on terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick end labeling (TUNEL)-positive labeling of photoreceptor nuclei in 7 (46.7%) of 15 eyes that were enucleated within 2 days after trauma. Furthermore, they found nicked nuclear DNA as early as 8 hours after trauma. This is of great interest since apoptosis is thought to represent genetically programmed cell death, which may be triggered by a variety of biochemical and other physiological factors. If apoptosis is found to be an important mechanism of photoreceptor cell degeneration soon after traumatic retinal detachment in humans, then it may be impossible to reverse the consequent degeneration. This may serve as an indication for the need for very early intervention in trauma. Such information might have an impact on how soon to operate on primary retinal detachments.

However, greater caution should be exercised prior to such judgments. While the 2 features described above are characteristic of apoptosis, their presence may not always be specific to this mechanism. This is important, since, in the purest sense, apoptosis connotes a preprogrammed mode of cell degeneration and a state of irre-

versibility, perhaps even inevitability. Yet, a variety of causes can lead to an end stage that looks like apoptosis.

That some of these cellular mechanisms might be amenable to reversibility has serious clinical implications. For example, if true apoptosis were the single operative mechanism, it would be difficult to explain the clinical course observed following primary retinal detachment. It is well known that peripheral visual field loss resulting from the retinal detachment often resolves with time. Furthermore, central vision often recovers remarkably following reattachment of the macula if this is accomplished early, a finding that is consistent with studies of human subretinal fluid² that identified increasing degeneration during the first 2 weeks and a plateau thereafter. These improvements would not be anticipated if true apoptosis had taken place within the first few hours after retinal detachment. It would seem more likely that ischemia and the attendant glutamate-mediated neuroexcitotoxicity³ cycle might underlie much of neuronal cell death in retinal detachment, and would not be an irreversible phenomenon such as apoptosis. Psychophysical measures of patients with retinal detachment⁴ further implicate that, following retinal reattachment, there may be successful reversal of biochemical phenomena such as the glutamate/N-methyl-N-aspartate receptor cycle of neuroexcitotoxicity. Further studies are needed to elucidate the biochemical events³ underlying the histological effects of retinal detachment, so that treatment may be developed to improve post-operative visual rehabilitation. We question whether true apoptosis plays a role.

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2. Sebag J, Tuyen W, Faune JP, et al. Retinal s-antigen in human subretinal fluid. *Invest Ophthalmol Vis Sci*. 1987;28:2038-2041.
3. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic-ischemic brain damage. *Ann Neurol*. 1986;19:105-111.
4. Preston D, Sebag J, Sadun AA. The effects of retinal detachment on brightness sense. *Invest Ophthalmol Vis Sci*. 1991;32:1143.

In reply

I agree with Drs Sebag and Sadun on the importance of early therapeutic intervention in traumatic retinal detachment. They rightly point out that the loss of peripheral visual field in retinal detachment might resolve and some recovery of central vision might also occur following retinal reattachment. Indeed, both clinical observations are consistent with our thesis that apoptosis is 1 of the major pathogenetic mechanisms of photoreceptor cell loss in traumatic retinal detachment.

One of the characteristics of the apoptotic process is the scattering of the apoptotic cells in the involved organ in contrast with localized massive destruction of cells in tissue necrosis. In the detached retina, scattered apoptotic photoreceptor cells were noted and if the retina is reattached, the remaining photoreceptor cells would be able to recover their functions and provide vision. It has been

noted that after loss of more than half the cone cells in the macula, a visual acuity of 20/40 might still be attained.¹

Drs Sebag and Sadun propose that ischemia and glutamate mediated neuroexcitotoxicity might underlie the cause of neuronal cell death in retinal detachment. Indeed, Roberts-Lewis et al² showed that excitotoxicity induces apoptosis of neurons. As pointed out by Rothman and Olney,³ neuroexcitotoxicity brings about an increase of intracellular calcium, which is also known to induce apoptosis. However, mechanical separation of the neuroretina from the retinal pigment epithelium is unlikely to be the primary inducing factor for apoptosis.

In a separate study,⁴ we examined serous retinal detachment secondary to malignant melanoma and observed very few apoptotic photoreceptor cells in the detached retina. Therefore, the pathogenetic mechanisms of photoreceptor cell loss in traumatic retinal detachment is complicated.

Drs Sebag and Sadun used the term true apoptosis in their letter. Even though they did not provide a definition of their term, they seemed to imply that apoptosis is "a pre-programmed mode of cell degeneration." Apoptosis is observed in embryogenesis, morphogenesis, and histogenesis. In these situations, it is indeed a form of preprogrammed cell elimination. However, in most disease states, apoptosis occurs mostly as a signal-induced cell death.⁵ A great variety of signals including radiation, light exposure, ischemia, hormonal changes, growth factors, viral and other infection, an increase in intracellular calcium, and many other factors induce apoptosis. Furthermore, in various tissues and in different disease states, apoptosis expresses different cellular markers. It is difficult to develop a simple definition for apoptosis. Therefore, the term true apoptosis should not and has not been used in the literature. However, it appears that 2 of the most important markers that characterize apoptosis include (1) the ladder pattern in DNA gel electrophoresis and (2) TUNEL labeling, to mark the fragmented nuclear DNA. Indeed, we observed a ladder pattern in DNA gel electrophoresis in experimental traumatic retinal detachment in rats.⁶ The TUNEL labeling of photoreceptor cells was also observed in experimental retinal detachment in rats and traumatic retinal detachment in human patients. Therefore, we have concluded that apoptosis is one of the primary pathogenetic mechanisms of photoreceptor cell loss in traumatic retinal detachment.

I would like to thank Drs Sebag and Sadun for their interest in our work.

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