PHOTOTOXICITY TO THE
NEWBORN PRIMATE RETINA

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Phototoxicity to the newborn primate retina.

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Newborn stump-tailed monkeys were continuously exposed to 400 fc of cool, white, fluorescent light for periods varying from 12 hr to 7 days. The right eye of each monkey was occluded by a patch of black color material to serve as a control. The protected eyes retained normal ultrastructure; the exposed eyes showed progressive damage to the retina from the 12 hr to the 7-day exposure periods. Early changes were evident in the outer nuclear layer with darkly staining pyknotic nuclei and electron-dense cytoplasmic processes that could be traced to their synaptic terminals. Late changes included marked distortion, vacuolization, and fragmentation of the rod and cone outer segments. The potential for phototoxicity to be additive to the normal aging of the retina is proposed, and we conclude that there is a sound basis for the current practice of patching the eyes of infants undergoing phototherapy.

The toxic effects of light have been demonstrated in the retina of rats, pigeons, and piglets. These studies show that the retina can suffer considerable damage after relatively brief exposure to high levels of illumination. Phototherapy with high-intensity fluorescent light of 500 to 800 foot-candles (fc) is used extensively for the treatment of hyperbilirubinemia, and it is calculated that about 90,000 infants are likely to receive phototherapy annually in the United States. One of the potential complications of exposure to this high level of illumination is damage to the retina of the newborn infant. To date, there have been no studies in newborn subhuman primates which address this question. This preliminary report describes the acute morphologic changes in the retina of newborn monkeys exposed to continuous illumination simulating clinical phototherapy as currently practiced.

Methods. Newborn stump-tailed monkeys (Macaca arctoides) weighing 450 to 500 gm were continuously exposed to 400 fc of cool, white, fluorescent light from a clinical phototherapy lamp for periods of 12 hr, 24 hr, 3 days, and 7 days. This resulted in 1,230 microwatts per square centimeter of corneal irradiance in the visible spectrum as measured by a Tektronix 116 digital photometer. The infant monkeys were maintained in standard nursery incubators heated to a mean temperature of 35°C. Rectal temperatures ranged from 37.2°C to 37.8°C. A restraining device inside the incubator maintained the monkey in a supine position facing the light source throughout the light exposure period. The monkeys were nourished by hand-feeding 5% glucose and water during the first 12 to 24 hr and infant formula reconstituted to 15 calories per ounce thereafter, which involved removal of the incubator for periods of 5 to 10 min. The eyelids of the right eye of each monkey were sutured closed, and a patch of black velour material was sutured over the eye. The left eye was uncovered, and the monkey could open and close the lid as desired. Following continuous light exposure, the animals were anesthetized with Nembutal and the eyes were enucleated and bisected. The posterior eyecups containing the retinas were fixed in 3% glutaraldehyde in 0.1M Na cacodylate buffer and postfixed overnight in 1% osmium in the same buffer. The tissues were dehydrated in a graded series of ethanols followed by propylene oxide and embedded in Epon 812. Sections (1 to 2 μ) for light microscopy were stained with methylene blue-azure II. For electron microscopy, ultrathin sections were double-stained with uranyl acetate and lead citrate and examined and photographed with an RCA EMU IV electron microscope.

Results

Control eyes. All eyes with constant occlusion by patching showed preservation of normal cytoarchitecture.

Exposed eyes

12 AND 24 HR OF EXPOSURE. The retinal pigment epithelial mitochondria showed swelling and vacuolization of their internal structure. The outer segments showed vacuolization and intercellular edema. Patchy mitochondrial damage occurred in the inner segments, characterized by swelling, vacuolization, and disruption. Some rod and cone nuclei appeared pyknotic, with electron-dense cytoplasmic processes in various stages of degeneration.

3 DAYS OF EXPOSURE. The outer segments appeared vacuolated, with early fragmentation and distortion (Fig. 1), and further degenerative changes were noted in the inner segment mitochondria. The outer nuclear layer showed an increase in darkly staining pyknotic nuclei in various stages of degeneration (Fig. 2).

7 DAYS OF EXPOSURE. Advanced degeneration
with marked swelling, distortion, and disintegration occurred in the outer segments (Fig. 3). Areas of the outer nuclear layer showed many dark pyknotic nuclei. Both rods and cones were involved, and their respective darkly staining proximal processes could be traced to the outer plexiform layer.

Discussion. Our findings suggest that the newborn nonhuman primate retina is damaged in a progressive manner when continually exposed to cool, white, fluorescent light of 300 to 400 fc. Morphologic damage at 12 hr of exposure (the shortest interval examined in the experimental protocol) consisted of mitochondrial swelling and vacuolization in the inner segments, scattered dark pyknotic rod and cone nuclei, and electron-dense cytoplasmic processes. With increasing periods of exposure, damage to the outer segments was noted with distortion, fragmentation, and vacuolization occurring by 7 days. The extensive damage seen at 1 week in this study resembled the changes that Gorn and Kuwabor4 observed in the rat retina exposed to 750 fc of fluorescent light for 3 to 4 days. They also found that separation of the outer segments from the inner segments resulted in irreversible damage. Subsequently, the remainder of the rod and cone cell bodies underwent degeneration with complete absorption. In our study, similar acute trauma to the outer segments developed in 7 days of continuous exposure to fluorescent light of 400 fc, suggesting that most of the retina would not recover from the photic injury.

Patchy destruction of rod and cone cell nuclei was evident at the 12 hr level of exposure and progressively greater by 7 days. Although damage was most evident in rods, cones also were involved, with darkly staining pyknotic nuclei and electron dense cytoplasm in the conducting fibers and synaptic terminals. Weiss and Stotzer emphasized the changes that both light and age can produce in the outer nuclear layer of the albino rat retina. They found destruction of rod and cone inner and outer segments, cell bodies of the outer...
nuclear layer, and the outer plexiform layer in a majority of animals exposed to 20 fc of fluorescent light for 12 hr daily over a 3-year period. No photic damage was observed at levels of less than 3 fc. They further noted age-related changes in the outer nuclear layer by observing a 35% loss of rod and cone nuclei at the end of 3 years.

Kowalska and Okinaka suggested that the excess of rod and cone elements compared to optic nerve fibers in primates provides a safety margin for the anticipated senescent changes in the outer nuclear layer of the retina. Thus, although a considerable number of rods and cones degenerate, enough intact cells remain to allow for apparently normal visual function. Without histologic examination, a significant loss of outer cellular elements might remain undetected. Therefore visual acuity and ophthalmic examination in a photo-damaged human infant may be normal in childhood although considerable tissue has been lost.

The electretinogram (ERG) has been used to detect acute photic trauma in the intact retina. Dobson and co-workers have reported a normal scotopic ERG and dark adaptation curves in two groups of children who had previously undergone phototherapy. However, the ERG is a mass-evoked response, and a significant decrease in amplitude requires massive destruction of retinal tissue. The finding of a normal ERG does not rule out the possibility of significant photic trauma, since diabetic patients, for example, can have most of their retina ablated by photocoagulation and still retain a normal ERG.

Since both photic trauma and aging produce loss of rod and cone cells, the effects of phototoxicity may be additive to the normal aging of the retina. This effect may not become clinically evident for many years, until there is sufficient accumulative cellular attrition with aging which, in combination with the early photic cell loss, results in visual compromise. When viewed with the above consideration, the acute cellular trauma to the retina...
of newborn primates shown in this study emphasizes the necessity of providing adequate protection to the eyes of human infants undergoing phototherapy. The long-term effects of this photic injury to the retina of the newborn primate and the potential for regeneration are currently under investigation.

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Fig. 3. Seven days of light exposure. Marked distortion occurs in the rod and cone outer segments with vacuolization and fragmentation of lamellar membranes. (×8,625.)