

Light and the developing retina

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Abstract. Retinopathy of prematurity (ROP) has increased in the United States in the past decade. Its resurgence has been attributed to advances in medical care which have increased the survival of infants less than 1000 g. Retinal immaturity and exposure to supplementary oxygen are generally accepted as the principal factors associated with ROP, however precocious exposure of the immature retina to light may also contribute. The preterm infant is routinely exposed for the duration of hospital stay to bright continuous light at levels which produce retinal damage in animals. A recent study has provided evidence implicating light in ROP. Preterm infants for whom the light levels were reduced had a lower incidence of ROP, compared to a similar group of preterms exposed to standard levels of nursery light. Given the problems of a non-randomized design, the results must be considered preliminary; however the findings are substantiated by parallel results in both hospitals studied and by an effect of exposure to light within the treatment group. Speculations regarding the mechanisms of light as a contributor to ROP include: alterations of retinal metabolism, cellular damage by phototoxicity, and the generation of free radicals. Mechanisms of phototoxicity are compatible with theories of oxygen toxicity. Light may not be necessary for ROP to occur, but it may increase the risk.

Retinopathy of prematurity has increased in the United States in the past decade. Its resurgence has been attributed to advances in medical care which have improved the survival of infants less than 1000 g. Retinal immaturity and exposure to supplementary oxygen are generally accepted as the principal factors associated with ROP, however precocious exposure of the immature retina to light may also contribute.

Retinal immaturity

Twenty-three to twenty-four weeks gestation now seems to be the lower limit of viability. The infant's fetal state is most apparent by the translucent skin and fused eyelids. At such time the eye is an embryonic organ which is

undergoing maturation and differentiation not only of the vascular system but the neural system as well. By 28 weeks gestation, a visual evoked response to bright light can be recorded from the occipital region and a momentary behavioral response to bright light can be observed; at the same time the photoreceptors are approaching the ora serrata. However, it is another 12 weeks before the retinal vascular system is in place. Retinal oxygen supply is initially obtained solely by diffusion from the choroid. Normally there is synchrony between the progressive metabolic demand of the maturing photoreceptor cells and the development of the retinal vessels which supply them. Premature birth and exposure to light inevitably involve precocious function of this developing structure and subject it to unusual stress during a potentially vulnerable period [1].

Oxygen and ROP

For three decades, human and animal data have supported the contention that elevated blood oxygen plays a significant role in ROP. However, it is also widely recognized that some infants who receive no supplementary oxygen still develop ROP; and many prematures with well documented hyperoxia do not develop the disease. This evidence does not negate the potential toxicity of oxygen for the developing the retina, but only emphasizes the need to broaden our perspective with regard to pathogenesis.

Light exposure of the preterm

The preterm infant is routinely exposed to bright continuous light 24 hours a day in the NICU. Levels are widely reported at 50–90 ftc with peak levels frequently over 220 ftc (2–6) Fig. 1A. With the sun entering the room in one nursery, the level was over 1000 ftc. Exposure time is a function of length of hospital stay. The smaller or sicker the infant the longer the length of hospitalization. The average length of stay for infants weighing less than 1000 g at birth is approximately 3 months.

In addition to ambient light, the preterm may be exposed to a number of supplementary sources such as the bili-light, the heat lamp, and the indirect ophthalmoscope. A phototherapy unit typically consists of a bank of 8–10 fluorescent tubes placed over the incubator which produce 300–400 ftc. During phototherapy, the infants' eyes are routine patched. However, in some cases the eye pads for the treated infants are inadequate or may slip off, and babies adjacent to phototherapy units are not shaded. A new

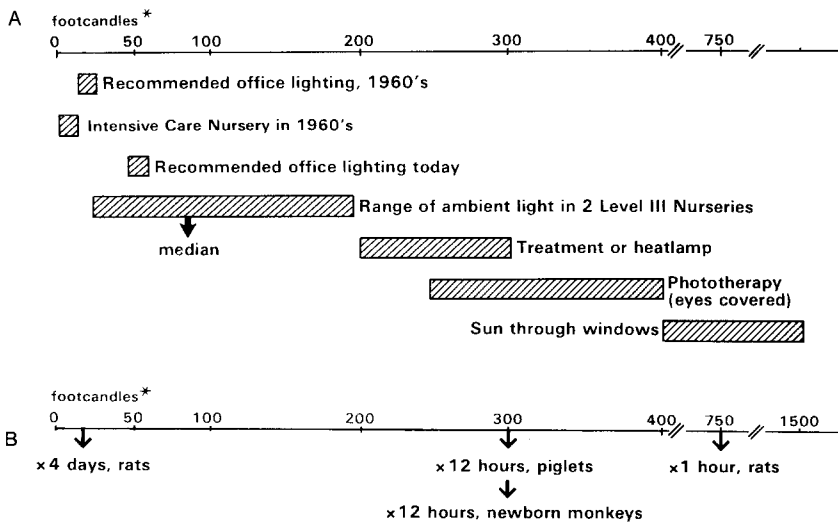


Fig. 1. A: Levels of light exposure in the intensive care nursery. B: Light exposure and retinal damage in animals. Reproduced from Glass et al. [3], with permission from the publisher.

phototherapy device called the 'Mini Bili-Lite' now produces an intense beam that is estimated at over 10,000 ftc.

A commonly used heat lamp consists of 1 or 2 infra-red bulbs which produce an intensity of over 300 ftc at an infant's face. The lamp is dual purpose, providing medical personnel caring for the infant with additional light that may be needed to perform delicate medical procedures and helping to maintain the infant's body temperature. Exposure time varies but is typically longer for younger and sicker infants. The eyes of infants are not routinely covered while under the heat lamp.

Finally, preterm infants have routine eye exams to rule out ROP prior to discharge from the ICN. Exposure to an indirect ophthalmoscope for 2 minutes (approximate time to examine for ROP) at maximum power has been estimated as equivalent to exposure at 2000 ftc for 3 hours [13]. Extra precautions for protecting the infant's dilated eyes from ambient or supplementary sources of light prior to and following the eye exam are not routine. For the smallest infants the addition of a heat lamp during the exam is often necessary to maintain the baby's temperature.

The necessity for adequate illumination in the hospital nursery is unquestionable, but there is mounting concern that both the high level and the continuous nature of the exposure may be hazards [1-11].

Phototoxicity

Retinal damage in animals exposed to excess light levels is widely recognized [11–18]. Phototoxicity occurs in the photoreceptors, the pigment epithelium, and the choroid. The rat studies are important because they demonstrate the damaging effects of continuous compared to cyclic illumination, using even the low-to-moderate light levels that were standard in the laboratory. Retinal damage in adult rats was found after 4 days of continuous low-intensity light (20 ftc) and after 1 hour exposure of high intensity light (750 ftc) [14, 15] Fig. 1B. This suggests that even levels of illumination that are thought to be safe are still potentially hazardous if the lighting is continuous rather than cyclic. Additional studies have demonstrated photoreceptor damage in piglets and monkeys exposed to 300 ftc for 12–72 hours [16, 17]. Unlike the rat, both these animals are diurnal and their eyes more closely resemble those of human (albeit fullterm) infants. It is generally accepted that increasing the length of exposure lowers the threshold for light damage. The effectiveness of light in producing retinal damage is proportional to its efficiency in bleaching rhodopsin. A level of 100 ftc bleaches rhodopsin to 80% in approximately 10 minutes.

Factors which enhance photochemical damage to the animal retina strikingly parallel the perinatal course of a preterm infant. For example, retinal damage in animals is facilitated by maintenance of the animal in constant dark prior to light exposure, by an increase in body temperature, by either hyperoxia or hypoxia, and by retinal disease. Continuous light exposure disrupts the normal regenerative process of the retina, alters retinal metabolism and retinal blood flow. These considerations suggest the possible association of light exposure and ROP.

Light and ROP

A relationship between light exposure and ROP was first suggested by Terry in 1946 [19]. Early studies which followed indicated that patching the eyes from birth to discharge did not reduce the incidence of RLF [20, 21], leading to the conclusion that light was not a factor. However, the conditions were quite different from today's nursery. Oxygen was still in liberal use at that time, and the ambient illumination was quite dim. In 1969 Riley and Slater proposed a mechanism for light as a contributing factor to oxygen-induced retinopathy of prematurity and recommended shielding the eyes of preterm infants to reduce the incidence of the disease [22].

In 1982 we began a prospective study of the effect of ambient light level in the hospital nursery on the incidence of ROP [3]. The study group

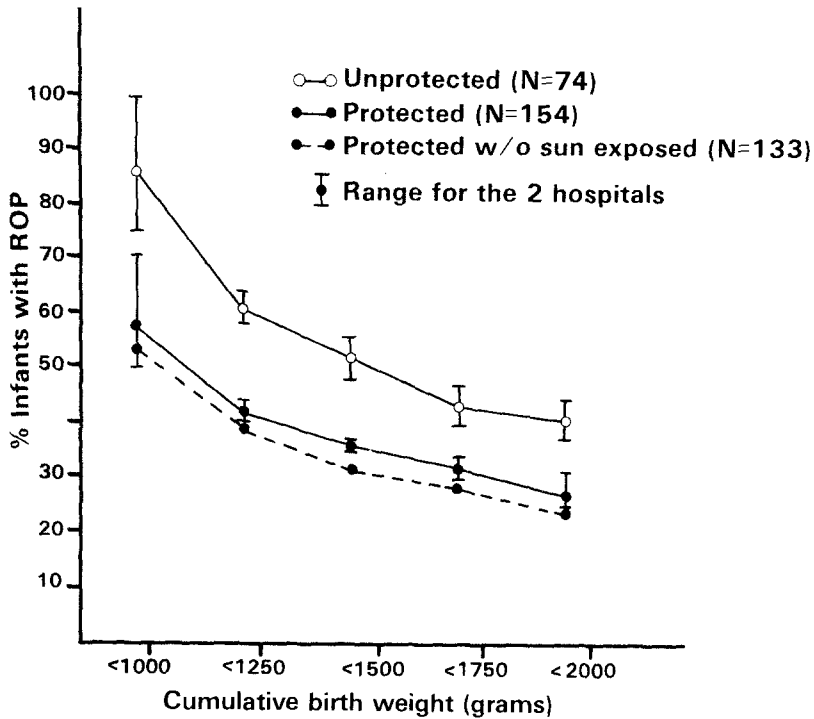


Fig. 2. Effect of light intensity on the incidence of ROP in two intensive care nurseries (cumulative birthweight function). Reproduced from Glass et al. [3], with permission of the publisher.

consisted of all infants < 2001 grams and < 35 weeks gestation who were admitted to either of 2 hospital intensive care nurseries by the 2nd day of life. Those between 1500 and 2000 grams were included only if they required oxygen in the nursery. Following the control condition of exposure to customary light levels, the treatment condition was instituted in both hospitals. By placing a neutral density filter over the incubators the amount of light reaching a baby's face was reduced from a median of 65 ftc. to below 25 ftc. The treatment began as soon as possible after admission and was maintained for the duration of the hospital stay. Infants were routinely examined near the time of discharge by pediatric ophthalmologists using the indirect ophthalmoscope. Grade I ROP was defined by a sharp demarcation between the vascular and avascular retina, or shunt formation. If the infant had more than 1 eye exam or asymmetric disease, the highest grade was used. The results combine all grades of ROP. Preterm infants for whom the light levels were reduced had a lower incidence of ROP, compared to a similar group of preterms exposed to standard levels of nursery light, Fig. 2.

An association between light level and ROP was also found for a subgroup of infants. During the treatment period, nursery renovations in one hospital resulted in the intermediate nursery having a southern exposure. On occasion, infants in the light-protected group whose beds were next to the window were observed with the sun in their faces. Since the neutral density filter had been placed over the top and back of the incubator, this meant periodic exposure to intensities in excess of 400 ftc. Of the 14 infants in the treatment group in that hospital who had ROP, 11 (79%) had been in a bed next to the window (chance was 25%). Ten of these infants could be matched for birthweight with Non-ROP infants within the same treatment group. In contrast to the infants with ROP, only one (10%) of these Non-ROP infants had been in a bed next to the window. Based on this empirical relationship between probable sun exposure and ROP (Fisher's Exact $p = 0.005$), subsequent analyses excluded from the light protected group the 21 babies whose beds had been next to the window in that intermediate nursery, whether or not they developed ROP. Returning to Figure 2, removal of this subgroup further enhanced the treatment effect.

Given the problems of a non-randomized design, the results must be considered preliminary; however the findings are substantiated by parallel results in both hospitals studied and by an effect of exposure to light within the treatment group.

Mechanisms of light toxicity and ROP

The early clinical signs for diagnosing ROP are the vascular changes in the periphery of the retina. However, vascular pathology may be accompanied by, or be secondary to, underlying retinal changes. ROP need not be a purely vascular disease. From this premise, a number of mechanisms may account for light as a contributing factor to ROP, including alteration of normal retinal metabolism, damage to non-vascular retinal structures, and the generation of free radicals [3, 23].

Light toxicity interfaces well with hypotheses of oxygen toxicity. An increase in the oxygen tension at the inner retina is generally regarded as a hyperoxic insult predisposing to the development of ROP. At least two factors could increase retinal PO_2 , which could in turn contribute to ROP. Light exposure leads to a decrease in oxygen consumption and thus an increase in retinal PO_2 [24, 25]. Photoc damage to the photoreceptor/pigment epithelial complex (the major oxygen consumer of the retina) would reduce oxygen consumption and thereby increase oxygen tension in the inner retina. Thus light exposure could lead to hyperoxic conditions in the region

of the developing retinal vasculature, whether or not an infant was receiving supplementary oxygen.

The Mueller cells form cystic spaces in the retina which are thought to provide an organizing structure for the advancing mesenchyme and developing retinal vasculature [26]. Following photoreceptor damage, the Mueller cells may respond by closing off the damaged from the undamaged portion of the retina. Alteration of this matrix could contribute to unpredictable patterns of vascularization.

Even retinal detachment may be exacerbated by light exposure [13]. The photoreceptors normally interdigitate with the pigment epithelial layer. Damage to either layer, which occurs during excess light exposure, could weaken this normal adhesion. The subretinal exudation reported in some cases of ROP may be a severe inflammatory response to excess light. Retinal edema is a consequence of excess light exposure and may alter retinal blood flow and produce an ischemia/reperfusion injury similar to the brain model.

Finally, oxygen radicals are recognized agents of oxygen toxicity, and the mechanism of free radical damage to cellular membranes has been well described by others [27]. It follows that factors which increase free radical formation would increase the potential for tissue damage. Free radicals are generated during light exposure and more expediently under bright light [28]. Thus the combination of light and oxygen could further increase the formation of free radicals and the potential for tissue damage. Animal research has shown that exposure to oxygen lowers the threshold for light damage [28, 29].

In the preterm infant, light and oxygen may act synergistically to increase the probability of ROP. Light exposure is probably not necessary for retinopathy of prematurity to occur, but its presence may be one of a number of factors which increase the risk. The role of light exposure in the pathogenesis of ROP may not be any better understood than the role of oxygen, but the levels may be easier to control.

Future directions

Even with the concern for potential retinal phototoxicity, an environment of continuous dim light may not be optimal for the preterm infant. Furthermore, the extensive literature on the effects of visual deprivation would advise against keeping a preterm infant in continuous darkness. Some evidence indicates that cycled lighting may protect against light damage [30]. We have recently initiated a study testing this hypothesis. Theoretically, cycled lighting could be especially protective against the development of

cicatricial stages of retinopathy. It may be useful to pursue this line of research. Until sufficient evidence makes it clear that current levels of exposure are safe for the preterm infant, a prudent approach would be to shade the infants' eyes from excess light [31].

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