LIGHT AND THE IMMATURE VISUAL SYSTEM

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SUMMARY

Preterm neonates are cared for in an environment which is continuously and brightly lit, and is very different to that experienced at any other time of life. The amount of light reaching the neonatal eye is governed by two groups of factors. Physical factors include intensity, spectral characteristics and duration of light exposure. Physiological factors are: Frequency of eyelid opening, transmission of light through the closed eyelid, pupil reactivity and area, transmission by the ocular tissues and retinal surface area. Retinal irradiance declines with increasing postmenstrual age. Mechanisms by which light may affect the neonatal eye and clinical conditions in which light have been implicated are considered.

Over the 24 hour period adults are generally exposed to a mixture of natural and artificial light, each with different spectral characteristics. Periods of sleep provide some respite from what would otherwise be continuous exposure to light. The fetus grows in almost complete darkness[1] whilst the environment in which preterm babies are cared for, the neonatal unit (NNU), is usually brightly and continuously lit. Thus the baby born prematurely is exposed to a pattern of lighting quite different from that experienced either *in utero* or at any other time of life.

Advances in neonatal medicine, have led to increased survival of the very low birthweight neonate,[2] and these immature babies are at risk of developing a variety of visual problems ranging from myopia and strabismus, to blindness due to retinopathy of prematurity (ROP).[3,4] Although some of these conditions such as ROP have been extensively investigated, many issues remain unresolved. That light may be a factor in ROP has been considered for over four decades.[4,5,6,7,8,9,10] Whilst there is little doubt, that in the adult, visible radiation can damage the lens, photoreceptors and retinal pigment epithelium,[11,12,13] the effect of early exposure to light on the immature visual system is unknown. Furthermore there is little information about either the lighting environment of neonatal units or the biological factors which control the amount of light entering the eye.

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This article is divided into three sections. First, the data on the neonatal light dose is summarised. Second, the mechanisms by which light may affect the eye will be considered and third, we mention clinical conditions in which light has been implicated as a factor.

NEONATAL LIGHT DOSE

The amount of light reaching the eye is governed by two groups of factors. First, physical factors: the intensity, spectral characteristics, and duration of light exposure. Second, physiological factors: the frequency of eyelid opening, transmission of light through the closed eyelid, pupil reactivity and area, transmission of light through the optic media and calculations of the retinal area on which an image is formed.

PHYSICAL FACTORS

Neonatal units are illuminated 24 hours a day, typically by a mixture of daylight and fluorescent tubes. Several studies have reported on the light intensity within NNUs but most state only illuminance.[14,15,16] Illuminance measurements are based on the ability of the optical radiation to induce a sensation of light in the eye, and are weighted by the filtering properties of the adult human eye. Illuminance surveys therefore do not completely describe the lighting conditions in NNUs, particularly at the shorter wavelengths.[17] Generally, the levels reported range from 400–1000 lux during the day, reducing in those units which have initiated a cyclic lighting regimen, to 50–100 lux at night. In addition, these studies demonstrate that light intensity varies greatly both between and within NNUs, and can be influenced greatly by seasonal factors. The illuminance (brightness) of seven NNUs in the UK has recently been measured over the 24 hour period and except for two low dependency areas, all were brightly and continuously illuminated.[15] At night when the lighting was provided solely by fluorescent tubes the mean illuminance was 348 lux: range 192–690 lux. During the day the mean illuminance was 470 lux: range 236–905 lux. The high dependency regions in four of the seven units were significantly brighter than their corresponding low dependency nurseries at all times. In two of these units there is a policy of reducing the level of artificial light in

the low dependency areas at night and under these conditions the minimum illuminance was 50 lux.

There are two studies of the spectral characteristics of NNU lighting.[17,18] In the latter study multi-point spectral irradiance curves were obtained at each cot or incubator. One conclusion apparent from both investigations was that photometric measurements of NNU lighting, are by themselves inadequate: the NNU irradiance from 400–500 nm is about 30% of the total irradiance, in contrast illuminance only accounts for 10% of its integral. Thus photometric estimates of light exposure underestimate the amount of light reaching the infant, especially at short-wavelengths. Both the irradiance and illuminance surveys showed significant and consistent differences between the high and low dependency regions (Table I), the former being associated with the highest light intensities.

In addition to general ward illumination, infants are exposed to light sources both as part of their treatment and during examinations. Premature infants are often exposed to phototherapy (2400–3000 lux) for the treatment of neonatal jaundice. During phototherapy which may last for periods exceeding 24 hours, infants will generally have their eyes shielded from the phototherapy lights by "patches", which transmit some of the light[19,20] ranging from <2–10% at 700 nm according to patch type.[21] Eyeshields securely in place will attentuate >90% of the light emitted by a phototherapy source and reduce the potential risks of photokeratitis due to UV exposure and retinal injury mediated through the blue-light photochemical mechanism. However, eyeshields are prone to slip away from the eyes (9292 of 16615 observations).[22]

Routine ophthalmoscopic examinations are performed on neonates of low gestational age to screen for ROP. Animal studies suggest that indirect ophthalmoscopy can cause retinal damage.[23,24] Kirkness[25] has evaluated the retinal hazard posed by this instrument by calculation of the temperature rise resulting from light absorption in the retina, correlating retinal irradiance values with safety guidelines and comparing these figures with threshold values for retinal damage. These results suggest that the indirect

ophthalmoscope poses no threat of retinal damage for the adult, provided that exposure duration does not exceed 23–80 seconds per eye depending on the power of the supplementary lens used. Pupils remain unresponsive to light stimuli and dilated for >18 hours post-instillation of cyclopentolate (0.5%). Perhaps therefore, the potential light hazard posed by the indirect ophthalmoscope *per se* is small compared with the effect of prolonged pupillary dilation.

The position of the baby within the unit and its head position relative to the mattress also influence the retinal light dose. The eye closer to the mattress is more likely to be closed.[22,26] Due to shielding of the lower eye, by clothing, an arm, or the mattress, the lower eye or eyelids (eye closer to the mattress) receives a mean of 25% (range 0–78%) of environment light, whereas for the upper eye or eyelids (eye away from the mattress) this mean value is 86% (range 57–100%).[27,28,29]

PHYSIOLOGICAL FACTORS

Here we will consider the following topics: frequency and patterns of eyelid opening; transmission characteristics of the closed eyelid; transmission and absorption of light through the eye; pupillary diameter and retinal factors including area and photoreceptor distribution.

Frequency and patterns of eyelid opening have been examined in 50 neonates with a gestational age range of 24–35 weeks.[22] Observations were made, over the 24 hour period to obtain a complete pattern of events. Mean eyelid closure was 74%. When babies were grouped by gestational age, differences became apparent, babies of less than 26 weeks having their eyes shut for only 55% of observations compared with 93% at 28 weeks. Trend analysis confirmed that eyelid closure reached a peak at 28 weeks. Neonates exposed to a day and night regimen opened their eyes significantly more than those exposed to continuous illumination.

When closed, the light transmission characteristics of the eyelids become important. Measurements of light transmission through the eyelid of adults,[26] and preterm infants, measured *in vivo*, suggest that the eyelid acts as a predominantly red-pass filter.[30] Peak transmission for the adult and neonatal eyelid was 18% and 22% respectively at 700 nm declining in both to <5% tranmission below 480 nm.

The passage of light through the ocular media depends on absorption, scatter and reflection by the ocular tissues. The ability of radiant energy to damage ocular tissues is largely determined by the spectral transmittance and/or absorbance properties of individual tissues. Both are probably wavelength dependent, and thus influence the spectral composition of "white" light absorbed by the photopigments. The spectral transmission properties of the ocular tissues taken as a whole were determined by Ludwigh and McCarthy[31] working on freshly enucleated eyes. Since these data were obtained from elderly eyes (average age 62 years), the authors corrected their results for age-related changes in lens absorbance using data

Table I. Mean irradiance for the two neonatal units surveyed. Measurements are given for the total irradiance in each of the wavelength bands, with standard deviations in parenthesis. Values are given separately for the high and low dependency regions of each unit.

| | Irradiance (μW/cm^2) | | |
	400–500 nm	500–175 nm	400–700 nm
Unit A			
High dependency	153.8	280.6	436.5
	(49.0)	(83.6)	(106.2)
Low dependency	36.7	101.7	134.5
	(11.9)	(28.7)	(35.8)
Unit B			
High dependency	145.3	314.1	529.2
	(28.9)	(67.3)	(134.1)
Low dependency	34.6	132.6	165.2
	(9.8)	(31.9)	(43.3)
Mean			
High dependency	149.5	297.1	482.8
	(38.9)	(74.5)	(120.2)
Low dependency	35.6	117.2	149.8
	(10.3)	(31.1)	(39.6)

obtained from isolated lenses of younger eyes. Boettner and Wolter[32] measured the spectral transmission properties of each component of the ocular media using nine eyes from subjects whose age ranged from four weeks to 75 years. These authors constructed a transmission curve light transmission through the eye of a young observer. The cornea transmits radiation from 295 nm in the ultra-violet to 2500 nm in the infra-red. Transmittance increases rapidly from 300 nm reaching about 70% at 380 nm and over 90% between 500 and 1300 nm (see [33]). The crystalline lens transmits radiation from 350 to 1900 nm. The transmissivity of the lens decreases with age especially at the short wavelengths.[33] Psychophysical determinations of lens absorption have depended largely on the study of aphakic observer responses and these investigations have shown that the visual sensitivity of an aphakic observer extends into the near UV, with little reduction in sensitivity between 400 and 320 nm. This indicates that the lens acts as a shortwave cut-off filter for the eye. Said and Weale's[34] values for the density of the lens are lower than those derived by phychophysical methods. The vitreous apparently causes some light scatter but Boettner and Wolter[32] found that less than 10% of the incident light is absorbed.

Kishto[35] produced evidence of variations in visual thresholds associated with screening by blood vessels, whilst Vos and Bouman[36] estimated that light scatter in the retina constitutes some 30% of the total light scatter in the eye.

Thus the cornea, aqueous and lens normally filter out most radiation below 400 nm.[37] The ocular media of neonates are highly transmissive especially in the blue and ultra-violet regions of the spectrum,[32,38,39] and the lens at this time transmits >90% of light ≤420 nm.[40] Finally, light does not enter the eye exclusively through the pupil, as the sclera and choroid also transmit about 14%, again predominantly at the red end of the spectrum.[41,42]

Retinal irradiance is influenced by pupil size. The time course for the development of the pupillary light reflex and its diameter before and after this event have been studied.[43] The pupillary light reflex was absent in all neonates of less than 30 weeks gestation, gradually developing from this age, and by 34 weeks was present in all. These data are broadly similar to those reported by others, who state that pupils react to light around 30[44] to 32 weeks gestational age.[45,46] Before the onset of the pupil reflex, mean horizontal pupillary diameter was 3.46 mm compared with 3.02 mm after the reflex development.[43]

Before considering the retinal irradiance, or ocular light dose, it is appropriate to consider briefly retinal growth. Cones are present at the fovea by 12–14 weeks gestation.[47] By the seventh month both rods and cones may be distinguished in the peripheral retina and there is no further increase in cell number after this time.[47,48] Retinal surface area increases two-fold between the sixth and ninth fetal months with a further 50% increase occurring before the second postnatal year.[49] Thus considerable redistribution of photoreceptors and other cellular elements must occur during this period.[50,51]

The adult human rod is some 2 μm thick and 60 μm long. Cones vary in shape and size depending on their position in the retina, becoming long and thin in the foveal region. Neonatal cone inner and outer segments are much shorter than their adult counterparts, measuring 8.7 μm compared with 32 μm respectively,[52] and it is possible, that foveal cones of the preterm neonate trap photons inefficiently.[53]

Using the aforementioned data an estimate of the retinal irradiance received by a preterm neonate has been made.[27,28] As shown in Figure 1 this declines as a function of increasing postmenstrual age. For example, the immature neonate of 29 weeks PMA receives ~350 μW/cm², a level similar to that known to cause cone damage in the macaque monkey.[54]

THE ACTION OF LIGHT ON THE EYE

Light is the essential stimulus for vision, and in addition to photoreceptor metabolism it may also affect other aspects of retinal metabolism,[55] and induce retinal damage. Light-induced free radical oxidation of rod outer segment membrane lipids has been proposed as one of the early signs of light damage.[56,57,58] Any factor, such as light, will by increasing the production of free radicals thus raise the possibility of tissue damage.[59]

In the adult exposure to light increases retinal metabolic activity[55] which shifts from aerobic to anaerobic.[60] Retinal blood flow and oxygen consumption are both higher in the dark than light in the human,[61,62] although Hill and Houseman[63] recorded increased flow in some cats but decreased in others in response to dark exposure. Raised retinal oxygen tension has been measured in the light compared to the dark in the rabbit,[64] confirming decreased metabolic activity under these conditions. Oxygen consumption across the cat retina in the light was only 60% of that in the dark.[65]
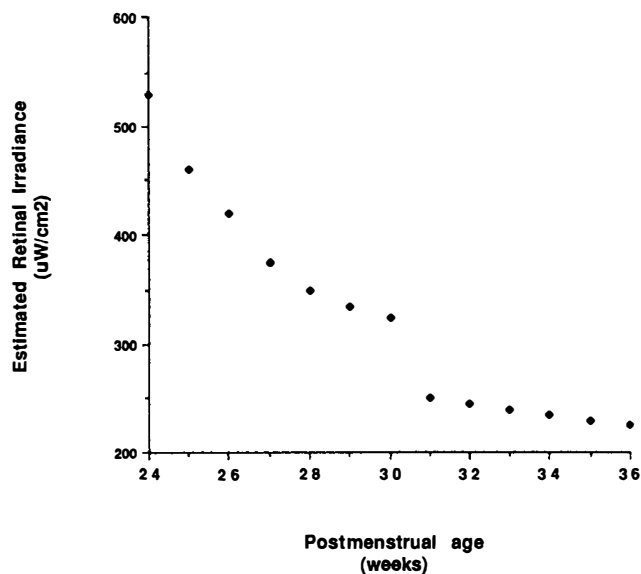

Fig 1.   *Estimated retinal irradiance (μW/cm²), as a function of postmenstrual age. The reduction at 30–31 weeks PMA may partly be explained by the onset of the pupillary light reflex and also the move from a high to low dependency nursery. The latter are associated with lower luminance.*

Recently, Dorey and associates[66] demonstrated that blue light inhibits the growth of retinal endothelial cells. These authors stated that since light or oxygen act synergistically with Dopa to inhibit endothelial cell growth; exposure to light or oxygen could exacerbate the potential for vascular damage. The levels of dopamine in the immature retina are about 1/20th of those in the adult;[67] Hollyfield and associates,[68] have suggested that the low dopamine concentrations at birth could be partly due to very low light levels *in utero*.

In the adult, under normal conditions, the intracellular content of both superoxide dismutase and peroxidases are sufficient to remove superoxide radicals and peroxides generated by oxidative metabolism.[69] Slater and Riley[59] suggested that the oxidant-antioxidant balance in the retina of a preterm neonate was critical because of the potential for light-induced auto-oxidative damage to the lipid membranes. In the following sub-sections we will consider some factors which may be involved in free radical scavenging in the immature human retina.[70] We can find no information about the levels or activity of superoxide dismutase in the retina of the preterm neonate.

Vitamin C may aid Vitamin E regeneration[69] and its level in the preterm retina exceeds adult levels by 35–50%.[71] In contrast retinal Vitamin E levels in the preterm neonate are low (5–12% of levels in mature tissue) particularly in the avascular regions.[71] Vitamin E supplementation increases retinal tissue levels, particularly in those neonates of >27 weeks gestational age.[71]

Preterm infants are deficient in selenium.[72] This trace element is an essential component of both glutathione-S-transferase and glutathione peroxidase, and both enzymes play a role in the prevention of autoxidative damage.[70] No age-related changes in glutathione S-transferase activity have been detected;[71,73] however the specific activity of glutathione peroxidase is higher in preterm than mature retinae.[71]

Paralleling photoreceptor differentiation, a space develops between the retinal pigment epithelium, photoreceptors and Müller cells. This sub-retinal space appears first in the central retina at 20 weeks gestational age and by 28 weeks it covers 75% of the retinal area.[74] This space contains the inter-photoreceptor matrix of which inter-photoreceptor binding protein (IRBP) is a major constituent.[75] This protein facilitates nutrient transport, including Vitamins E and A, between the retinal pigment epithelium and the neural retina.[76] Thus IRBP may have a role in protecting the retina from light damage (for example see [76]).

We will now consider physical and genetic factors which influence susceptibility to retinal light damage. In 1966, Noell and co-workers showed that light damage (photochemical) of the rat retina caused attenuation of electroretinogram (ERG) responses and photoreceptor cell degeneration.[57] Today, it is known that the severity of damage is related to both the physical properties of the light such as its intensity, wavelength and duration of exposure.[12,77] In the primate, abnormal continuous retinal illumination provided by virtually full-field fluorescent lamps can severely damage the retina.[78] Human protective, behavioural patterns (blinking, gaze aversion etc) fortunately prevent the adult from staring for minutes, hours, or even days at banks of high intensity fluorescent lamps. If these are not present, photoreceptor damage will result as shown by Calkins *et al.*, in the 1960s (discussed in [78]) and by Kitahara *et al.*[79] Another consideration is the genetic species variation in light-damage susceptibility found amongst different strains of mice and rats.[80,81,82] Retinal susceptibility to light damage increases with age in the albino rat,[83,84] as does dark rearing before light exposure.[85] Ocular melanin has a protective function, presumably by the screening and absorption of light.[57,80,86] These effects are associated with increasing rhodopsin content of the photoreceptors.[87] Although there is extensive characterisation of the factors mentioned above, little is known about the manner by which they exert their influence, partly due to an incomplete understanding of the development of metabolic function in the immature retina and the precise mechanisms of retinal light toxicity.[88]

CLINICAL ASSOCIATIONS WITH LIGHT EXPOSURE

Although the adverse or even beneficial effects of early light exposure to the developing human visual system are unknown, preterm babies are at risk of developing a variety of ocular problems in which early exposure to light has been implicated (for review see [4]).

Whether light-induced photoreceptor cone damage occurs in the human preterm infant is unknown, but cone dysfunction has been reported in children who received stray light from phototherapy as neonates,[89] and low, but normal acuity has been noted in ex-premature children[90,91] and teenagers.[92] There is no evidence, however, for significantly accelerated visual development following preterm birth.[4,93]

The role of light in the pathogenesis of ROP has been debated for nearly 50, years.[4] Unfortunately, each of these studies can be criticised on the basis of their experimental design, and this important and topical question remains unanswered. Ricci and co-workers[94] failed to demonstrate a role for light in oxygen-induced retinopathy in the rat; but their animals were exposed to 12 hour cycles of light and dark, a situation not analagous to lighting conditions in the NNU. We have recently reported an association between the location of the retinopathy at onset and the retinal light dose.[10,95] It is apparent (see previous sections) that due to large variations in the neonatal light environment, single light measurements at infrequent intervals are inadequate to estimate the total light dose received by an individual preterm baby. Therefore to investigate the relation between light exposure and ROP continuous monitoring of the light environment of each infant is required. With this aim in mind we have developed a portable monitor—the EyeLiDD—which enables light intensity (i.e. illuminance and irradiance) to be sampled at eight second intervals and an average intensity stored every ten

minutes for periods exceeding 100 days. Data obtained with the EyeLiDD can be used to estimate either a total light dose received by each neonate, or to follow the patterns of light exposure over various time-periods.

Exposure to light may also have effects remote from the visual system. Melatonin has been implicated in the regulation of various neural and endocrine processes in vertebrates which are cued by the daily change in photoperiod, including the control of circadian rhythms and the modulation of photoreceptor renewal.[96] It has been suggested that continuous exposure to bright light affects sleep states,[97] hormonal biorhythms[98] and may increase the frequency of patent ductus arteriosus.[99,100] The absence of day and night cycling in the NNU may be a factor responsible for the delayed onset of periodicities and sleeping problems in preterm neonates.[101] Exposure of human neonates to constant lighting reverses their normal diurnal variation in blood amino acid concentrations.[72]

To conclude, the baby born before term may spend days, weeks or months in an environment which is both bright and usually constantly lit. As estimates of the retinal light dose have only recently been attempted, the effects of this early exposure to light on the immature visual system and on the baby as a whole are poorly understood and require further study.

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