Oxygen-Induced Retinopathy

To the Editor:

Kremer and coworkers recently purported to show that light is not a factor in the development of oxygen-induced vasoproliferative retinopathy in newborn kittens, with the obvious implication that these findings also could hold true for retinopathy of prematurity (ROP) that affects human pre-term neonates. Indeed, the purpose of their study was to investigate the role of light in the pathogenesis of ROP. Four groups of animals were studied and all were raised under an identical oxygen regimen (80%). Each group was exposed to a different intensity and duration of light exposure as follows: condition A, continual exposure to bright light (115 foot-candles or 1237 lux); B, darkness throughout the 24 hr period; C, a 12 hr cyclic lighting pattern; and D, normal laboratory environmental lighting. Lighting condition A was chosen as it was about twice as bright as the environment of the typical neonatal intensive care unit in which pre-term neonates are nursed.

As all kittens developed vasoproliferative retinopathy, with no difference of severity between the four groups, the authors concluded that light could be eliminated as a risk factor. In fact, as the study design was fundamentally flawed in this respect, they have provided no information on light and ROP, but have shown that newborn kittens exposed to high levels of oxygen develop retinopathy. This is not news and was elegantly demonstrated by Ashton and Patz almost four decades ago.

In their study, all animals received a dose of oxygen guaranteed to produce retinopathy in all, regardless of light exposure, thereby precluding any possibility of investigating the effect of light on the development of this condition. In other words, severe ROP had been produced in the entire cohort before the effect of light could be investigated. To study the role of any factor, such as light, in an oxygen-induced ROP model, it is necessary that under control conditions, its incidence should be <100% or that not all of the animals are severely affected. This was achieved by Wosowski, Smith, and D'Amato who, in a murine model, recently demonstrated a protective effect of darkness on retinal neovascularization.

The early clinical studies did not support light as an ROP-risk factor, but as with the study of Kremer et al, the high concentrations of supplemental oxygen routinely administered to pre-term neonates in the 1940s and 1950s could have swamped any additional effect of light. Since that time, there have been many advances in neonatal management, including the introduction of blood gas monitoring. As a result, over the past four decades, the incidence of ROP-induced blindness has fallen in larger neonates of birthweight >1000 g. However, it has remained relatively constant in infants <1000 g and because they previously were unlikely to survive, the number of infants in this birthweight group who are blind because of ROP has increased. These two periods now are frequently referred to as the first and second epidemics of ROP. The first was brought to an end by oxygen restriction and is now considered largely preventable. However, the second currently is nonpreventable. The experimental model described by Kremer et al was designed specifically to produce ROP by administering high doses of oxygen and therefore reflects the first epidemic. The current clinical situation is extremely complex, as the infants most at risk are extremely immature, are often ill, and require supplemental oxygen for prolonged periods. Although oxygen administration is monitored, and great care is taken to maintain PaO2 levels within the recommended range of 50-80 mmHg, this often is not possible, as Flynn et al recently demonstrated.

Unfortunately, there is more to ROP than oxygen. Its cause generally is considered to be multifactorial, because despite meticulous control of O2, some infants still develop severe ROP. The finding that the neonate most at risk for developing severe ROP receives the greatest retinal irradiance has provided added impetus to investigate whether light exposure is a risk factor for this condition. Unfortunately, for the reasons already stated, the study of Kremer et al has not advanced our knowledge on this topic. To date, clinical
studies are conflicting, and further clinical and basic studies need to be undertaken to unravel this issue, for there is at least one modality that can be easily and immediately controlled.

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References


REPLY

To the Editor:

Regarding the comments made by Dr. Fielder and Dr. Robinson in their letter to the editor, I would like to point out the fact, which was discussed in our previous paper, that oxygen-induced retinopathy in the newborn kitten is a different disease than retinopathy of prematurity (ROP), both histologically and clinically. Therefore, it is incorrect to call this disease severe ROP, as was done by these two authors. Because of this, one should be very careful when trying to draw any conclusions from oxygen experiments done with kittens and other animal newborns, with regard to hu- man ROP.

The retinopathy seen in our kitten model is actu- ally an ischemic vasoproliferative retinopathy developing after retinal vascular obliteration caused by high levels of oxygen. There is no ridge, and the new ves- sells develop in a diffuse pattern from the revascular- ized posterior pole. It is not accurate to state that the neovascular response found in our kittens treated by 80% oxygen for three days was a maximal response. According to our experience with these kittens, when they breath 92% oxygen for five days, the vasoprolifer- ative response is more extensive, extending to the reti- nal periphery and the retrolental area. This probably is related to the greater extent of damage caused to the kittens’ retinal and optic nerve vasculature, with subsequent larger areas of capillary nonfusion of the retina. In addition, the neovascular response of the kittens’ retinas is not identical to all the 80% oxygen- treated animals, and there is a certain degree of inter- animal variation in the extent of pre-retinal new ves- sels. Therefore, our four groups of kittens had to be compared by an image analyzer. We, therefore, disagree with the two authors’ views that our model is inappropriate for studying the effect of light on oxy- gen-induced retinopathy. Our aim simply was to compare the severity of pre-retinal neovascularization in 80% oxygen-treated kittens that were being raised in complete darkness, with the severity of this retinopa- thy in other kittens raised in different levels of illumi- nation and treated by the same concentration of oxygen.

After the evaluation of the results of our study, we do not mean to say that light is not an important factor in the pathogenesis of human ROP, but we con- clude that fluorescent light of 115 foot-candle intens- ity is not a required factor for the development of oxygen-induced retinopathy in kittens, being a different entitiy from ROP. Besides, we point out in our recent report that phenotypically identical animals