# Retinopathy of Prematurity and the Peripheral Retina

Preservation of visual acuity in advanced, acute-phase retinopathy of prematurity (ROP) usually requires retinal ablation (destruction) of the peripheral retina. The avascular peripheral retina in ROP likely produces vascular endothelial growth factor, which in turn induces pathological angiogenesis at the advancing margin of developing retinal blood vessels. To treat severe ROP, surgeons use a destructive procedure on the peripheral retina to effect regression of neovascularization. The goal is to preserve the macula, which subserves the ability to discriminate fine detail (eg, read). In fact, without this destructive procedure, the peripheral retina also would be lost, because most cases of adverse outcome in advanced ROP result in retinal detachment that involves the entire retina.

What is the effect of destruction of the peripheral retina? In the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study, peripheral retinal ablation was found to reduce visual fields somewhat but, surprisingly, not much more than was reduced by the acute-phase ROP per se.[1] (Recall that in the CRYO-ROP Study, control eyes did not receive treatment and thus were available for comparison with treated eyes.[1]) In other words, peripheral retinal functioning is adversely affected by the ROP disease process. Untreated control eyes in the CRYO-ROP Study had *advanced* disease, as we emphasize later in this editorial.

In 2008, the effect of ROP on peripheral retinal function is more important than ever. Following the CRYO-ROP Study, the National Eye Institute funded a study to evaluate the effect of earlier treatment for ROP at high-risk prethreshold disease (the Early Treatment for ROP [ETROP] Study). Advances in neonatal care have led to improved survival rates for more immature infants, but concerns remain regarding eyes with zone I disease (ie, very posterior ROP with extensive areas of avascular retina), as well as persistently high retinal detachment rates in eyes with zone II (advanced) disease. Zone I ROP occurs most commonly in very low birth weight infants, in whom retinal vessel development is quite immature. The ETROP Study demonstrated a significant benefit of earlier treatment on high-risk prethreshold disease.[2] Surprisingly, approximately 40% of the eyes randomized in the ETROP Study had zone I disease. The reasons for this finding have been debated,[2] and although some eyes might have been diagnosed as zone I when only 1 clock hour of ROP was present in zone I (with the other clock hours of disease located more anterior), there can be little doubt that zone I ROP is more common today than 15 years ago.

Many very low birth weight infants have ROP disease that is present for a time in zone I and regresses without treatment or is treated in zone I. The ETROP Study included infants with zone I eyes in whom 1 eye was treated at prethreshold disease and the other (control) eye was either treated at conventional threshold disease or simply observed as the disease regressed spontaneously.[2] The significance of posterior ROP and its effects on visual field and rod (and cone) function remains unclear; this is one reason why the cohort from the ETROP Study will be followed to age 6 years. At that time, randomized children in this cohort will undergo visual field measurement in part to identify the effects of regressed versus treated posterior disease.

This is one reason why the study reported by Hamilton et al in this issue of *The Journal* is so timely.[3] The authors report that rod sensitivity is slowed but maturation of responsivity is accelerated by preterm birth. Untreated ROP reduces sensitivity, but treatment of ROP results in reduced sensitivity and responsivity. As the authors point out, a likely explanation for this finding is that postphotoreceptor gain is altered in prematurity with or without ROP and increased due to extrauterine visual experience. This effect seems to occur even in mild ROP. On the other hand, conditions that alter the photoreceptor cells themselves will reduce sensitivity. This appears to be the case in infants with both ROP and treated ROP.

The article has additional significance as well. The study design included comparisons of full-term infants and preterm infants without ROP. A nature–nurture experiment emerges in which the effects of extrauterine time and visual experience can be compared between preterm and term infants. The authors find that extravisual experience influences retinal neuronal behavior. This finding is consistent with the findings of other studies comparing extrauterine experience in

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| CRYO-ROP | Cryotherapy for Retinopathy of Prematurity Study |
| ETROP | Early Treatment for Rentinopathy of Prematurity Study |
| ROP | Retiniopathy of prematurity |

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preterm infants and full-term matched infants. For example, Mirabella et al[4] found that preterm infants with no other known complications of prematurity (eg, no intraventricular hemorrhage or ROP) exhibited higher signal amplitudes on steady-state visual evoked potentials compared with full-term infants. Although the study of Mirabella et al evaluated cortical responses, not simply retinal responses, the findings were similar to those of Hamilton et al. Some factor associated with preterm birth influences neuronal development and architecture at the levels of both the retina and the visual cortex.

The peripheral retina, with its population of rod photoreceptor cells, is a readily accessible area for studying the effects of preterm birth on neuronal development. Although the findings of Hamilton et al are tempered somewhat by the small sample size, the authors clearly demonstrate the feasibility of studies of even very small infants. Future studies should continue to use groups of infants tightly controlled for postconceptual age and other factors. For example, such factors as neonatal jaundice and sex could influence results. Longer follow-up is desirable to investigate whether population differences resolve over time. Whether mild ROP has the same effect on rod functioning as more advanced but untreated ROP merits study as well.

Meanwhile, studying the effects of preterm birth and advanced ROP on the developing retina has assumed an even higher priority, because of changes in the demographics of preterm infants. Teasing apart the effects of laser treatment versus the disease itself has become particularly important, considering that more infants are now treated with greater amounts of retinal ablation. Visual acuity outcomes in the CRYO-ROP Study, even with preserved structural outcome, were often less than desirable, indicating that the cone cell population of photoreceptor cells likely is also affected by the disease process or its treatment.[5] New tools and methods for measuring electrophysiological changes are needed. In some areas of the world, growth factor inhibitors are being evaluated for the management of neovascularization in ROP. We need to know how these cytokines may affect other aspects of retina and vision development.

ROP is truly a panocular problem. Clinicians treating it understandably emphasize preventing retinal detachment and preserving posterior retina and cone cell function. But other effects of ROP on the eye are very important as well, even when the retinal structure appears normal. Effects of ROP are not always visible on ophthalmoscopy. Hamilton et al are to be congratulated for directing our attention to aspects of visual development that may prove very important to the health and vision status of very low birth weight infants.

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## REFERENCES

**1.** Cryotherapy for Retinopathy of Prematurity Cooperative Group. Effect of retinal ablative therapy for threshold retinopathy of prematurity: results of Goldmann perimetry at the age of 10 years. Arch Ophthalmol 2001;119:1120-5.
**2.** The Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity trial. Arch Ophthalmol 2003;121:1684-96.
**3.** Hamilton R, Bradnam MS, Dudgeon J, Mactier H. Maturation of rod function in preterm infants with and without retinopathy of prematurity. J Pediatr 2008;153:605-11.
**4.** Mirabella G, Kjaer PK, Norcia AM, Good WV, Madan A. Visual development in very low birth weight infants. Pediatr Res 2006;60:435-9.
**5.** Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of Cryotherapy for Retinopathy of Prematurity. Arch Ophthalmol 2005;123:311-8.

# Time to Step Up to the Plate: Adopting the WHO 2006 Growth Curves for US Infants

The Centers for Disease Control and Prevention's (CDC) 2000 growth curves for infants, children, and adolescents are used by the vast majority of pediatric health care providers in the United States and in many other parts of the world as well.[1] These charts, a growth reference, describe how children and adolescents in the United States actually grow across a wide range of social, ethnic, and economic conditions. But since the publication of the World Health Organization's (WHO) 2006 growth standard curves, which describe how infants should grow under ideal conditions not subject to economic restraints,[2] there has been much discussion about adopting the WHO's curves for US infants and children.[3,4] At a meeting held June 28-29, 2006 at the National Center for Health Statistics in Hyattsville, Maryland, representatives from the CDC, National Institutes of Health, and American Academy of Pediatrics discussed how the WHO curves might be used by clinicians in the United States, and how these curves interface with the CDC 2000 growth curves for infants, children, and adolescents. The article by Mei et al in this issue of *The Journal* summarizes the data presented at that meeting and compares the

CDC Centers for Disease Control and Prevention
WHO World Health Organization

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