Retinopathy of Prematurity:
History, Classification, and Pathophysiology

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Objectives
After completing this article, readers should be able to:

1. Describe the onset of retinopathy of prematurity (ROP).
2. Explain the role of oxygen in ROP.
3. Compare and contrast zones I, II, and III disease.
4. Describe the stages of ROP.
5. Characterize "plus" disease.
6. Describe the infants in whom severe ROP leading to the need for surgery is common.
7. Describe the timeframe at which ROP is visible in the eye.

History

The First ROP

In 1942, Terry described the first infant who had grey, blood vessel-covered membranes behind the pupil. As more cases were described, the name retrolental fibroplasia (RLF) was coined (Fig. 1). Distressingly, it became common around the world in special units for preterm infants. Pathologic specimens were rare (Fig. 2), but serial examinations of preterm infants following birth revealed that infants were not born with RLF; they developed it after birth. By the end of the 1940s, many innovations in the new preterm infant nurseries had been implicated, some were exonerated, and it was time to examine the role of oxygen.

The Oxygen Link and First Cooperative Trial

The first multicenter, randomized, controlled trial in neonatology provided telegraph randomization of infants weighing less than 1,500 g who survived for 48 hours. Routine care at the time was to administer oxygen for approximately 4 weeks because of its beneficial effect on apnea of prematurity. Normally, it was delivered at approximately 8 L/min, which provided about 50% oxygen in the newer incubators. For this trial, oxygen analyzers were provided to each participating unit, with oxygen maintained at a target of 0.50 Fio_2 for 28 days in the control group. For infants in the experimental group, the oxygen was reduced to room air unless the infant became cyanotic, in which case it was increased sufficiently to relieve the cyanosis, but not more than 50% (Fig. 3). Infants randomized to receive the curtailed oxygen had less RLF of all degrees of severity, but surprisingly, many infants had no RLF (Table 1). At this time, no intravenous fluids, no ventilators, and no laboratory blood tests were available in preterm infant units, so many infants in this study may have been small for gestational age and at less risk for their weight. None of the survivors was ill with severe respiratory distress syndrome.

Following the publication of this study, oxygen use was restricted in nurseries. When RLF occurred, most people assumed that the infant had received too much and unnecessary oxygen. Although true in a few cases, the explanation was not quite that simple.

The Fall and the Rise of Retinopathy of Prematurity (ROP)

During the late 1950s and into the 1960s, RLF disappeared. Students rarely were taught about the disease, which was considered a sad, closed chapter in early neonatology. The hallowed "40% rule" emerged in some locations, stating that 40% oxygen was safe for eyes and more than 40% was dangerous. Unfortunately, there was indirect evidence that both infants who received 40% oxygen but needed more to relieve cyanosis from respiratory

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Figure 1. End-stage ROP. The white pupils (leukocoria) of stage 5 ROP result from total retinal detachment, with the mass of fibrous neovascularization and the retina pushing up against the lens from behind. This is the source of the historical name retrolental fibroplasia. Photograph courtesy of A. Patz, MD, used with permission. Reprinted with permission from *Pediatrics.* 1957;19:502–504.

distress and healthy preterm infants who received weeks of 40% oxygen suffered (cerebral palsy and RLF, respectively).

As intravenous fluids, exchange transfusions, the ability to measure serum electrolyte levels, and eventually ventilators were added to units, they were renamed neonatal intensive care units (NICUs). With improved survival of preterm infants in the mid-1970s, RLF re-emerged at alarming rates, and the blame could not be laid on poor control of oxygen administration. The pathophysiology of this disorder, studied in animal models, suggested that the degree of prematurity of the eye at birth was the critical and necessary risk factor for the

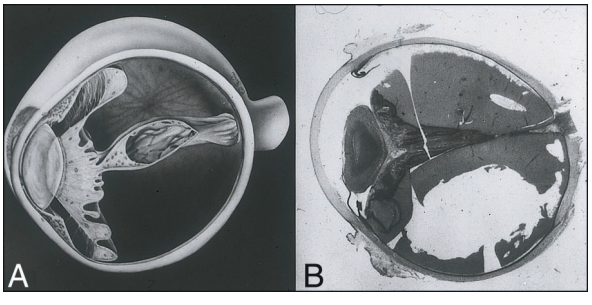


Figure 2. A. Artist's rendering of stage 5 retinal detachment. B. Pathologic specimen of an eye with stage 5 ROP. In this cross section, the lens is displaced into the anterior chamber by the mass of tissue in the vitreous composed of the detached retina and the large number of extraretinal vessels and accompanying scar tissue (fibroplasia). The retina remains attached at the posterior pole at the optic disc and around the rim of the most anterior edge of the retina, the ora serrata. The white gaps in the subretinal fluid are artifacts. Figure 2A reprinted with permission from *Arch Ophthalmol.* 1987;105: 906–912. Copyrighted 1987, American Medical Association.

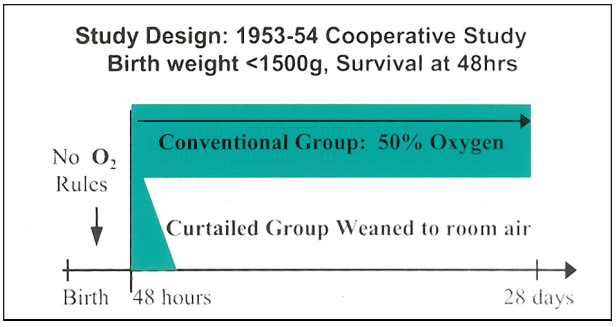


Figure 3. Study design in which the experimental group of infants was reduced to room air after 48 hours of age, as long as cyanosis did not develop. If it did develop, only the least amount of oxygen could be used to relieve it, and not more than 50%.

disorder. RLF was renamed retinopathy of prematurity (ROP), and research progressed with the understanding that the primary cause of ROP was prematurity (immaturity of the eye), and the condition only secondarily occurred after birth.

New epidemiologic studies of ROP were needed to determine its incidence and severity in NICUs. The new technology of the indirect ophthalmoscope permitted a better view into the infant's eye (Fig. 4). Several publications revealed that the lower the gestational age (or birthweight) of the infant, the greater the risk of ROP and that ROP was more common than previously believed (Fig. 5). In addition, severity of illness and number of complications in the neonatal period were related to the development of ROP at a given gestational age. Duration of oxygen administration remained strongly correlated with ROP risk and with other medical complications. To date, it still has not been determined whether this effect is only an association or a cause of ROP.

Table 1. Results of the Trial of Oxygen Control for Retinopathy of Prematurity (ROP)

	Percentages of Infants			
	Survival	ROP	Stages 3 to 5	Blind
Conventional oxygen	22%	72%	23%	11%
Curtailed oxygen	25%	33%	6%	2%

Data from Kinsey VE et al. *Arch Ophthalmol.* 1956;56:481–547.

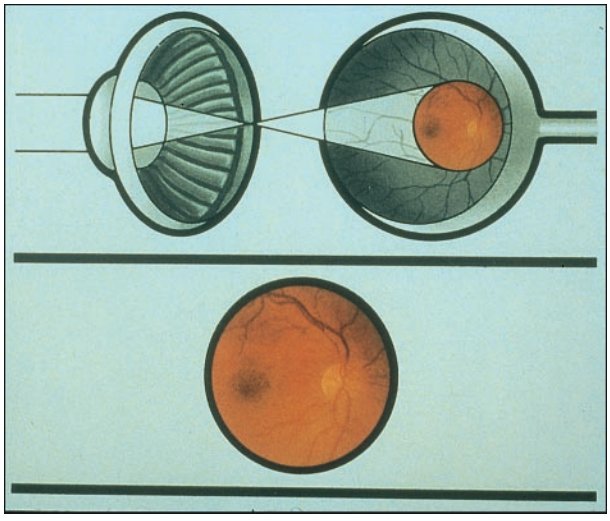


Figure 4. In the viewing area seen most commonly using a direct ophthalmoscope, the visible circle of retina can shift from left to right by about the circle's width. The indirect ophthalmoscope allows a wider view of about half the retina at one time. With some extra effort, the view extends to the front edge of the retina (the ora serrata). Reprinted with permission from Paton D, Hyman BN, Justice J Jr. *Introduction to Ophthalmoscopy.* Kalamazoo, Mich: The Upjohn Company; 1976.

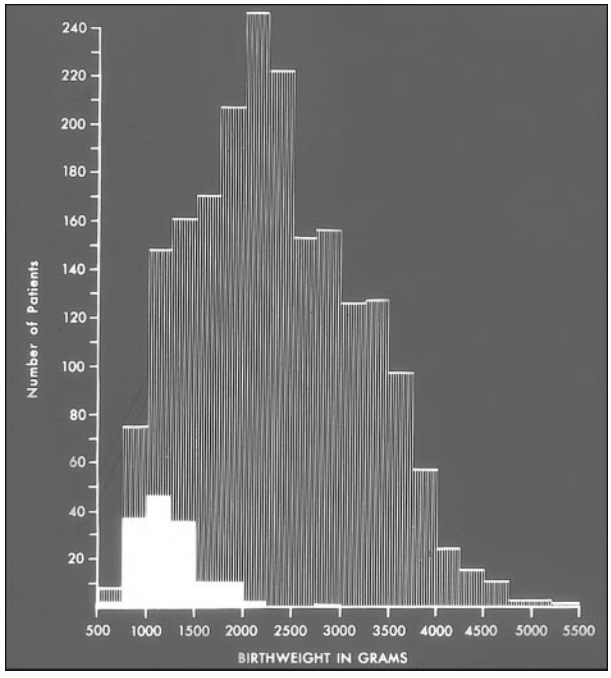


Figure 5. Using the indirect ophthalmoscope in a population in whom oxygen administration was carefully controlled, ROP was shown to be related to the infant's gestational age. The solid bars are the ROP cases, and the lined bars are all admissions. Reproduced from McCormick AQ. *Curr Probl Pediatr.* 1977;7:1–28 with permission from Mosby, Inc.

Developing a New Classification

In the 1980s, ophthalmologists grew increasingly frustrated with the old classification of RLF based on direct ophthalmoscopic findings. There was no agreed-upon, effective method of describing the progression of ROP, its severity, or points in its course at which to attempt interventions. It was impossible to design an interventional clinical trial because enrollment criteria could not be specified. In 1981, at the Ross Conference on ROP, ophthalmologists from around the world joined neonatal colleagues to debate the essentials of a new classification, returning home to evaluate new concepts. One year later, a second conference was held, and the group finalized the classification in 1983 at the National Eye Institute. The classification was published simultaneously in the pediatric and ophthalmic literature in 1984.

The International Classification of ROP (ICROP)

The ICROP describes vascularization of the retina; characterizes ROP by its position (zone), severity (stage), and extent (clock hours); and delineates whether the "plus disease" component is present. These features permit documentation of the deterioration or healing of ROP, classification of degrees of severity for surgical interventions, and accurate communication among investigators for enrollment into clinical trials.

Zones

The ICROP describes three zones in the retina (Fig. 6). Vessels growing from the optic disk initially cross zone I, then zone II, and finally reach the ora serrata as they complete crossing zone III on the temporal side. Zone III disappears on the nasal side because the optic disk is situated asymmetrically in the eye, and the distance from the disk to the ora is much shorter on the nasal side than the temporal side. Thus, vessels on the nasal side become "mature" (reach the ora serrata) as they finish crossing zone II. Because the blood vessels that supply the inner retina begin growing from the optic disk at about 16 weeks, the more immature an infant is at birth, the less progress the vessels will have made from the disk toward the outer edge of the retina (the ora serrata). ROP seen initially in zone I has a much worse prognosis than ROP observed first in zone II. ROP in zone III generally is mild and recovers fully.

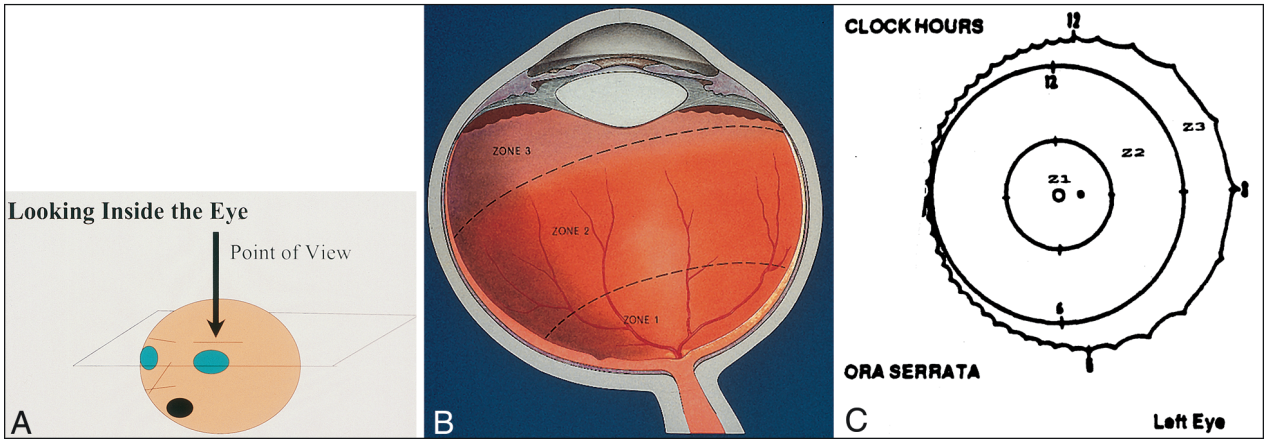


Figure 6. ICROP Zones. A. Orientation of the eye. B. Hemisection looking down into the left eye with the temporal side to the left and the nasal side to the right. The thin retina lining the back of the eye receives an enlarging network of differentiating blood vessels between 16 and 42 weeks of gestation. Theoretical lines have been superimposed on these retinal diagrams to indicate the zones used in ICROP (which, unfortunately, do not appear in reality, making the assignment of zone sometimes challenging). In this diagram, the vessels have progressed into zone II, but not yet into zone III, and there is no ROP. C. Retinal diagram used in ICROP to depict the three zones. Figure 6B modified from EA Palmer with permission.

Stages

Stages of ROP are based on the number and overproduction of vessels at the transition between the vascularized and avascular retina. Higher stage indicates greater severity. Examining the growing front edge of the vessels reveals the presence and severity of the ROP. If the vessels imperceptibly fade from vascularized retina into avascular retina, no ROP is present. Stage 1 is characterized by a distinct line (usually white or yellowish) demarcating the transition from vascularized to avascular retina

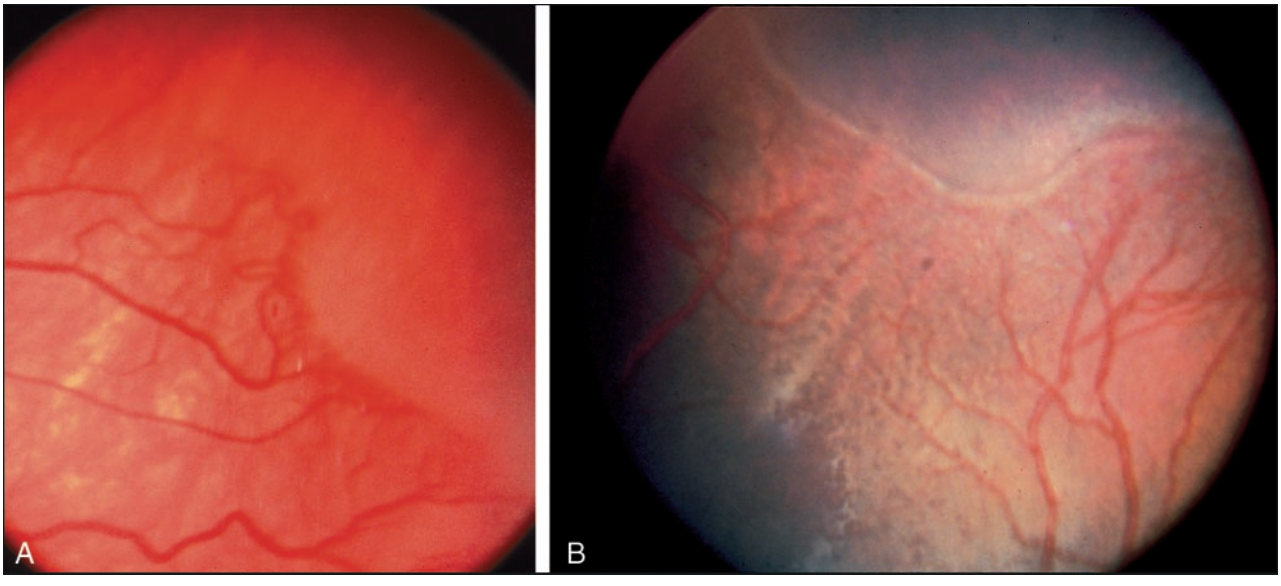


Figure 7. Photographs of ROP show only small sections of the retina. A. Stage1 ROP is the most mild and is characterized by a thin white line of demarcation between the vascular and avascular retina (right portion of retina). In many eyes, this stage lies next to areas of no ROP (left portion of retina); there is only a gentle transition of vessels coming to the furthest extent of their present growth. B. Stage 2 ROP in which the demarcation line has thickness, both in height and width, forming an actual ridge of tissue that gives the impression of being a barrier to further growth of the retinal vessels. From the *CRYO-ROP Study Atlas*, with permission from E Palmer, Oregon Health Sciences University.

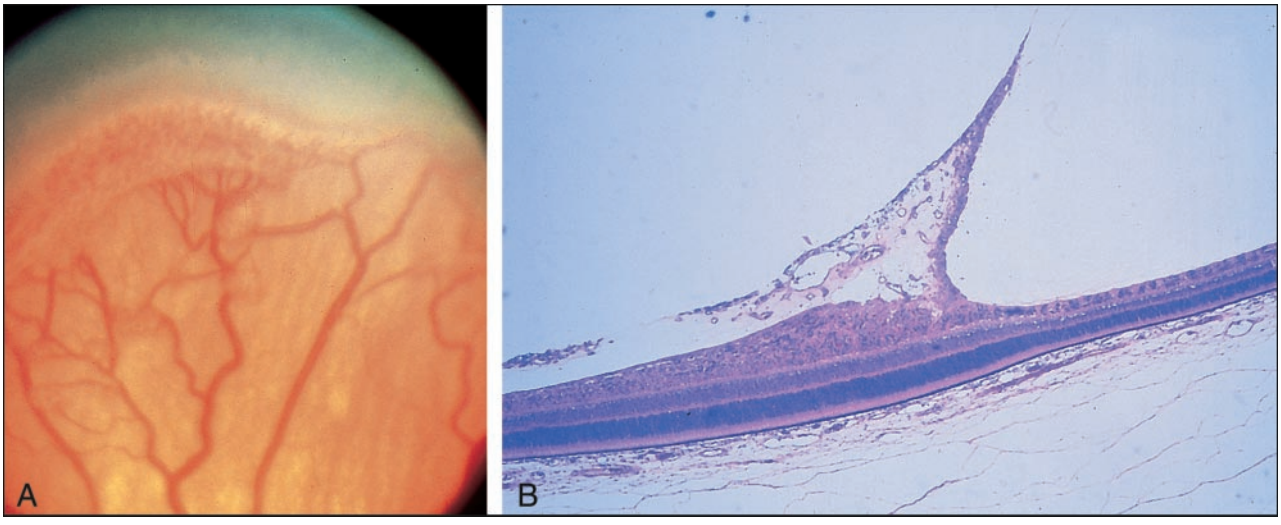


Figure 8. Stage 3 ROP. A. Retinal vessels emerging from the retinal surface and growing into the vitreous, acquiring the appearance of a shaggy ridge. B. A histologic cross section showing the vertical extent of moderate stage 3 ROP and how these vessels can appear to apply upward traction on the retina below. From the *CRYO-ROP Study Atlas*, with permission from E Palmer, Oregon Health Sciences University.

(Fig. 7A). If the line develops thickness in height and width, it is called a ridge and becomes Stage 2. Stage 2 ROP is believed to be a mass of growing immature vascular elements, but they are still contained within the retina (Fig. 7B). When vessels break through the retina into the vitreous space, they become extraretinal neovascularization, which describes Stage 3 (Fig. 8). At stage 4, the retina begins to detach, lifted or pulled off the choroidal bed, and if the detachment becomes complete, disease has reached stage 5.

Clock Hours

The position (zone) and stage of ROP are still insufficient to describe the degree of ROP present in an infant's eye. Figure 9 shows an ICROP diagram with stage 3 in both eyes, but it is obvious that the prognosis must be very different for the two eyes. This difference can be captured by describing the number of clock hours of the zone that contains the stage of ROP identified. Thus, the more complete description of ROP includes the zone where the vessels end and the number of clock hours of the worst stage of ROP.

"Plus Disease"

"Plus disease" is a critical and final component in describing ROP. It is determined solely by the findings in zone I near the optic disk and, thus, can be seen even with a direct ophthalmoscope (Fig. 10). As the ROP in the periphery becomes more severe, the posterior pole veins become dilated, and the arteries become tortuous. This is indicated in the retinal sketch in Figure 9 by the "waviness" of the retinal vessels near the optic disk in the right eye. It is believed that the progressive, severe type of ROP leading to retinal detachment always advances through plus disease before retinal detachment.

When plus disease is present, hidden in the back of the eye, the iris may reveal its presence. Examination of the iris with a bright light reveals similar dilation of the normally invisible vessels that circulate over the iris body (Fig. 11). This finding may be seen transiently in the hours immediately following birth, but when seen weeks later in a preterm infant, it indicates that ROP is very

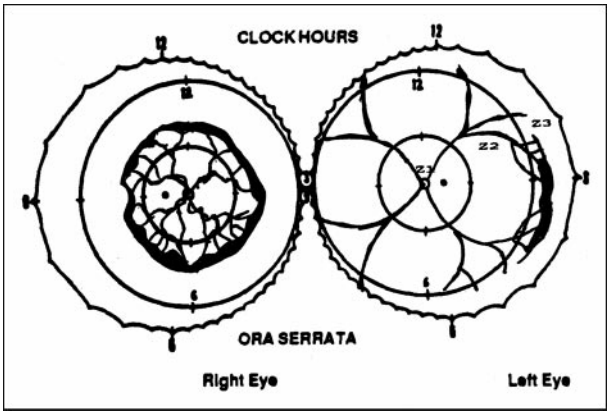


Figure 9. In the right eye, ROP is present in zone II for 12 clock hours of stage 3, with plus disease. In the left eye, ROP is present in zone III for 2 clock hours of stage 3.

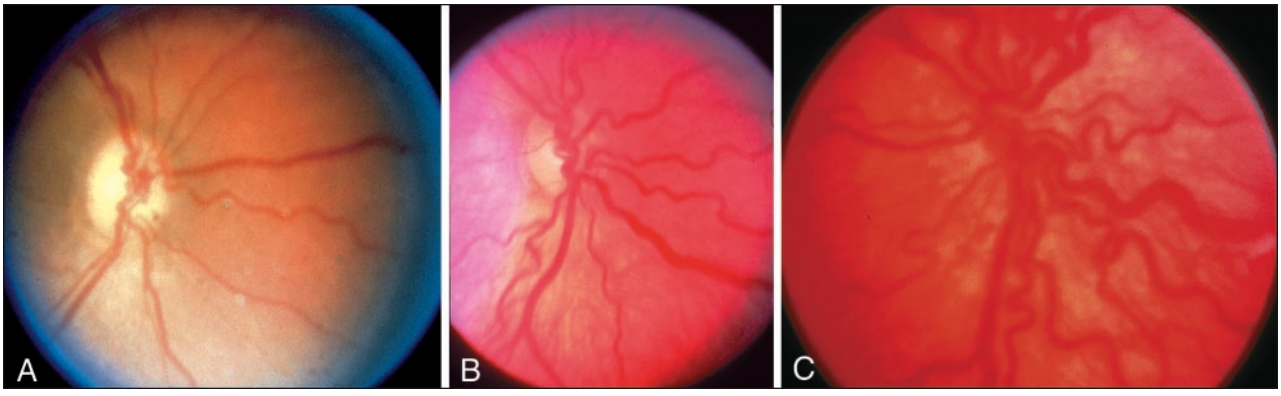


Figure 10. Posterior pole fundus photographs. A. A normal posterior pole. B. Moderate dilation of the veins and arterial tortuosity of plus disease. C. Severe dilation and tortuosity of severe plus disease. Plus disease is determined by the findings only in zone I near the optic disk. Figure 10A is from the *CRYO-ROP Slide Atlas*, B is courtesy of EA Palmer, and C is from an IRIS Medical brochure.

active in the eye, and an ophthalmologist should be involved.

When ROP develops in zone I and is accompanied by severe plus disease (Fig. 12), it has been termed "rush disease" because it progresses very rapidly to total retinal detachment.

Composite Categories of ROP

In the clinical trial to test the efficacy of cryotherapy to prevent vision loss from ROP, two composite definitions of certain degrees of ROP severity were developed. Initially developed as research tools, they proved extremely useful and are commonly used in practice today.

"Threshold ROP" is defined as the presence of ROP in either zone I or zone II, at least 5 continuous (right eye) or 8 composite (left eye) clock hours of stage 3, and plus disease (Fig. 13). Untreated threshold ROP progresses to retinal detachment in approximately 50% of cases.

"Prethreshold ROP" is less severe and is used as a marker to identify infants who require more frequent ROP examinations to discern threshold ROP as soon as it occurs (Fig. 14). Any ROP (less than threshold) in zone I is considered prethreshold. In zone II, ROP that is stage 2 with plus disease or stage 3 without plus disease is

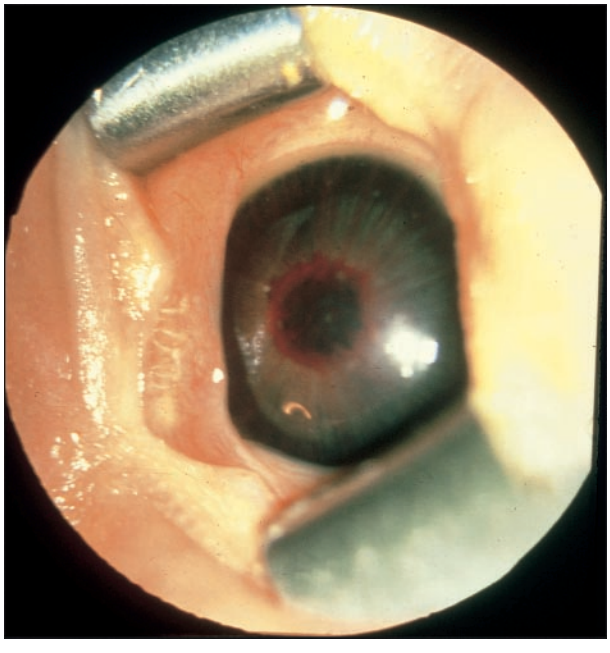


Figure 11. Iris vessel dilation and engorgement in the undilated pupil when plus disease is present in the back of the eye. From D Schaffer with permission for the *CRYO-ROP Slide Atlas*.

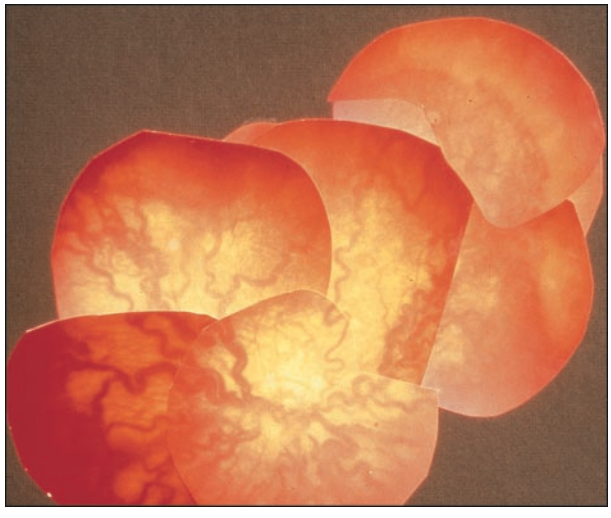


Figure 12. "Rush disease" is severe stage 3, zone I ROP with plus disease and carries a particularly poor prognosis. From EA Palmer with permission for the *CRYO-ROP Slide Atlas*.

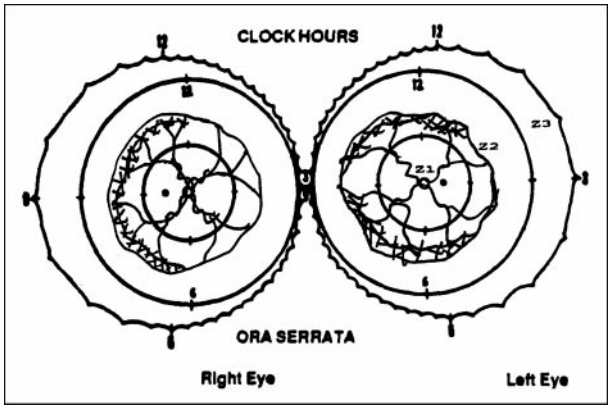


Figure 13. Minimum threshold ROP must be in zone I or II with plus disease. In the right eye, stage 3 ROP is present for just over 5 contiguous clock hours. In the left eye, stage 3 ROP is present for 8 composite clock hours.

prethreshold. Zone II, stage 3+ ROP without enough clock hours to meet threshold criteria also is considered prethreshold.

"No ROP" is a category with potential disaster if it is erroneously interpreted to mean that the retina is mature and no longer at risk for developing ROP. "No ROP" is an incomplete description; it always must be followed by the zone of the immature retinal vessels or notation that the retina is fully vascularized (mature) (Fig. 15). In Figure 15, it would not be appropriate to call the mature eye zone III because the vessels have completed their traverse of zone III. The immature zone I left eye is at high risk for developing severe ROP, even though it does not presently have ROP.

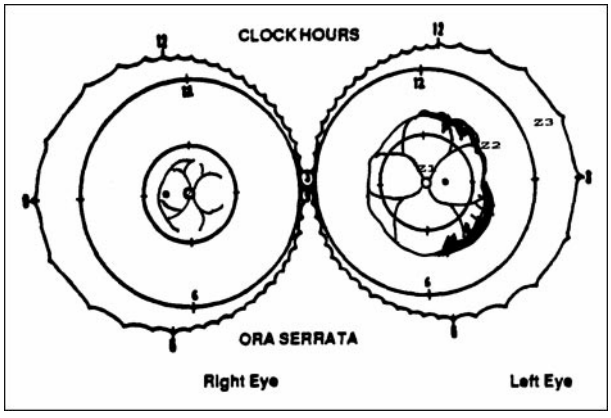


Figure 14. Two common variations of "prethreshold ROP," showing some stage 1 ROP in zone I in the right eye and stage 3 ROP in zone II without plus disease in the left eye.

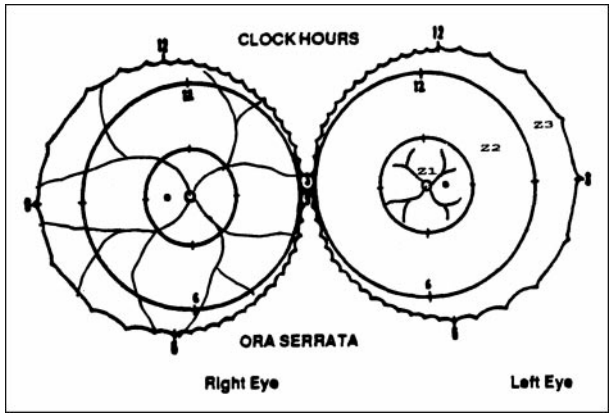


Figure 15. "No ROP" in two eyes with very different prognoses for ROP outcomes. The right eye shows "no ROP" with mature vasculature; the left eye shows no ROP, zone I immature.

Classifying Retinal Detachments

ROP can cause vision loss by progressing to retinal detachment, and the ICROP classification uses stages 4 and 5 to describe degrees of detachment. Stage 4 is a partial retinal detachment (Fig. 16) and is subdivided into stage 4a in which the detachment spares the fovea and stage 4b in which the fovea is involved. Stage 5 is total retinal detachment. Partial retinal detachments may be stable, but most often progress from stage 4 to stage 5.

Pathophysiology of ROP

Current understanding of the pathophysiology of ROP comes from data collected in animal models and human studies. The inner retina (next to the vitreous) becomes hypoxic as its metabolic needs increase with maturation. When the retina is inactive, sufficient nutrients and oxygen diffuse from the choroid below the retina, but with differentiation and increasing function, a second supply line is needed. At approximately 16 weeks' gestation, the primitive capillaries begin to grow into the inner retina, proceeding outward and toward the ora serrata. Growth is symmetric from the optic disk and reaches the nasal ora serrata at about 35 to 40 weeks' gestation and the temporal ora at about 38 to 44 weeks' gestation (Fig. 17).

Michaelson proposed that a "growth factor X" would be produced by the avascular retina in front (anterior) of the advancing vessels, leading them to areas with an oxygen deficit. A family of such angiogenic growth factors is now being described and studied in the eye as well as many other tissues. Vascular endothelial growth factor (VEGF) typifies these factors, and Figure 18 demon-

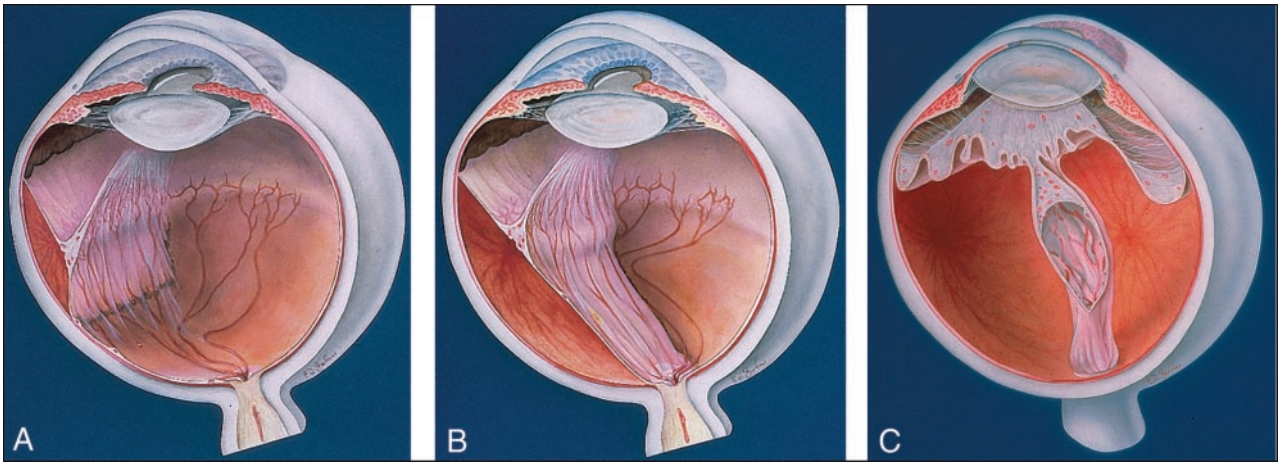


Figure 16. A. Early partial retinal detachment (stage 4a) that spares the fovea. B. Stage 4b retinal detachment involves the fovea. C. Final progression to stage 5 total retinal detachment. Reprinted with permission from *Arch Ophthalmol*. 1987;105:906–912. Copyrighted 1987, American Medical Association.

strates the striking increase in messenger RNA for VEGF in the avascular retina compared with the vascularized retina in the kitten model of oxygen-induced retinopathy. These findings have been confirmed in a human infant's eye.

When infants are born preterm, the delicate growing retinal capillaries are subjected to many injurious changes. Prolonged (days) hyperoxia injures them (confirmed in animal models), and stresses such as intraventricular hemorrhage, pneumothorax, hypovolemic shock, and sepsis greatly increase the chance of ROP. Animal models suggest that such injuries result in severe pruning back of the growing vessels. There follows a variable pause in vascular growth, then at approximately 30 to 34 weeks' gestation (in the human), the vessels begin to grow again, but with an abnormal "catch-up" pattern that involves excessive numbers of vessels, im-

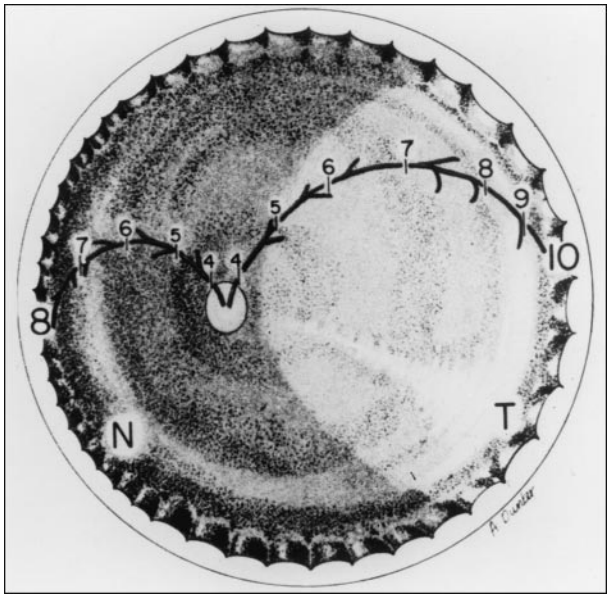


Figure 17. Schematic diagram of the progression of retinal vessel growth in the healthy infant from 16 to 44 weeks' gestation. Reprinted with permission from Palmer EA, et al. In: Ryan SJ, ed. *Retina*. Vol 2. 2nd ed. St. Louis, Mo: Mosby; 1994:1473.

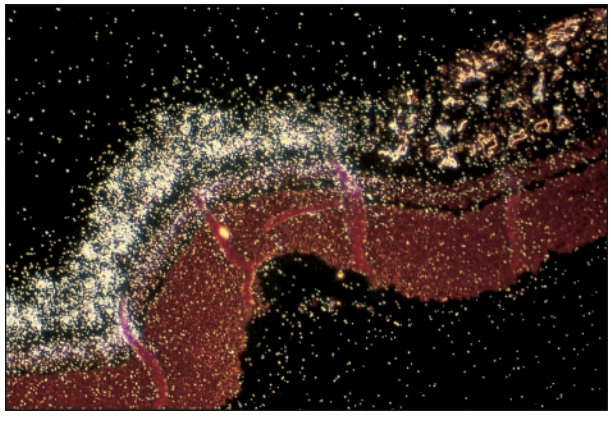


Figure 18. The avascular retina to the left is filled with mRNA for the growth factor VEGF in the retina of a 2-week-old kitten that has oxygen-induced retinopathy. The in situ hybridization reveals the message as very fine, speckled, pale dots in this phase contrast photomicrograph. (The vitreous is up in this field, with the optic disk out of the field to the right.) The line of demarcation between vascular and avascular retina is in the center, and the avascular retina is to the left. The striking overexpression of the message for VEGF disappears as the vessels grow into the retina.

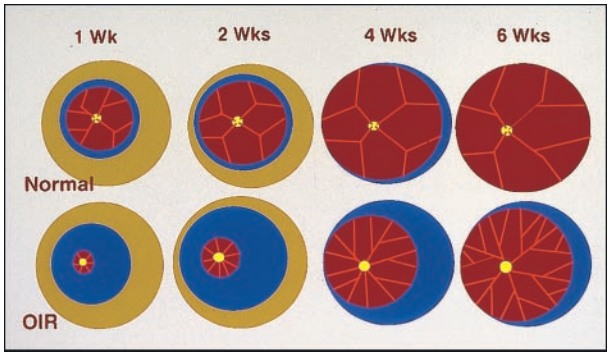


Figure 19. Schematic of the normal progression of retinal vasculature (upper) and the pattern seen in ROP (lower) in the animal model of oxygen-induced retinopathy. The red area represents the vascularized retina, the mustard area is the avascular retina, and the blue area is the putative region of hypoxic retina that probably is producing excess angiogenic growth factors.

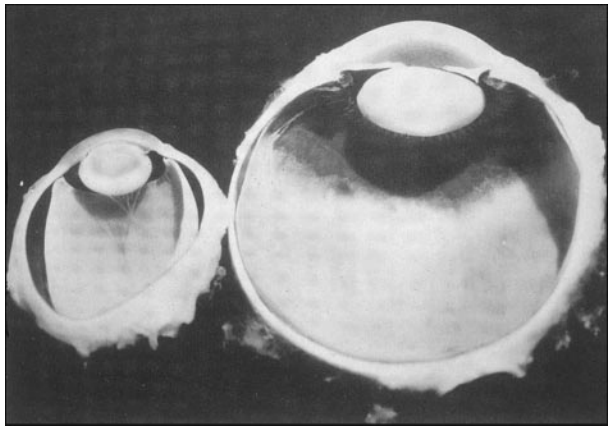


Figure 21. Eye of a 26-week-old infant (left) and an adult (right). Although the cornea and lens are fairly similar in size, there is substantial retinal growth yet to occur in the 26-week-old eye. The retinal vessels will not only be growing into an avascular retina, but into one that is enlarging. Courtesy of Foos R. In: Isenberg SJ, ed. *The Eye in Infancy*. 2nd ed. St. Louis, Mo: Mosby; 1994:39.

paired capillary progress, and sometimes vascular escape from the retina into the vitreous (Figs. 19 and 20).

Vessel regrowth (neovascularization) is the visible ROP that ophthalmologists see (Figs. 7 and 8). It is likely that excessive tissue hypoxia leads to overproduction of growth factors and, thus, excessive new vessel growth. ROP is a repair process that proceeds successfully in about 80% of cases. Although vessels take longer than normal to forge their way to the ora serrata, they do reach that point, supplying the retina with a capillary bed and making it functional. Figure 21 shows the relative size of the eyes of a preterm infant and an adult, demonstrating the great distance the retinal vessels must cover.

When ROP reaches stage 3 before healing, residual scars may remain in the eye, even when there is recovery without retinal detachment (Fig. 22). These can be the site of future retinal thinning, retinal holes, and late retinal detachments in adolescence or young adulthood.

Very little is known about why most infants heal (the ROP regresses), but some develop severe stage 3, plus

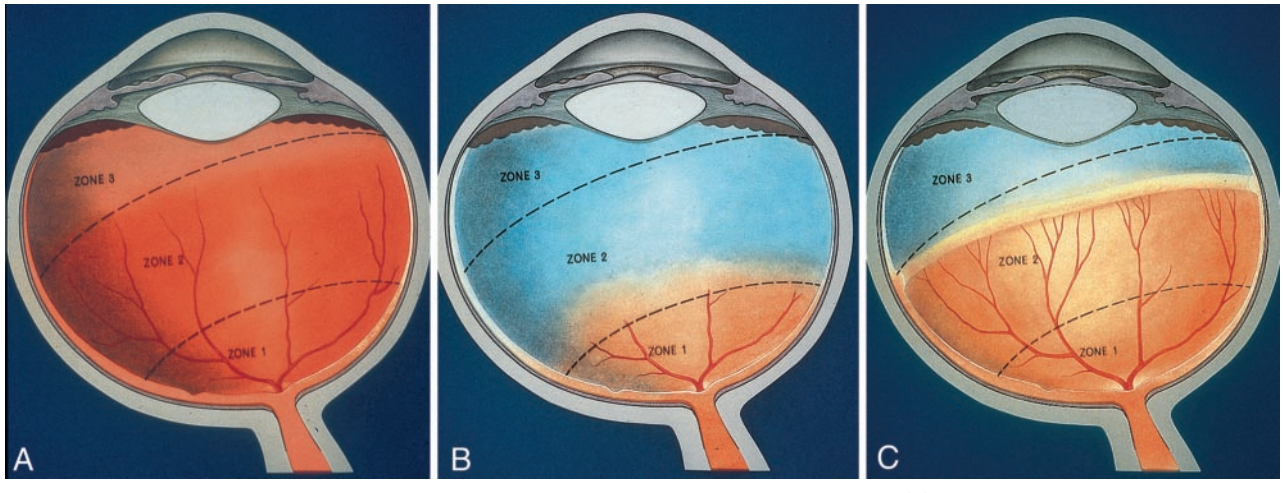


Figure 20. Artist's rendition of the development of ROP from the immature normal retina (A) to the pruned-back, injured retina following the first unstable days after preterm delivery (B) to the active ROP seen as the retina begins to repair by growing a new set of retinal vessels (C). The orientation of all the drawings is with the nasal side to the right, the temporal side to the left, and looking down into the eye. The artificial zones of ICROP are also indicated. Figure 20A modified from EA Palmer with permission.

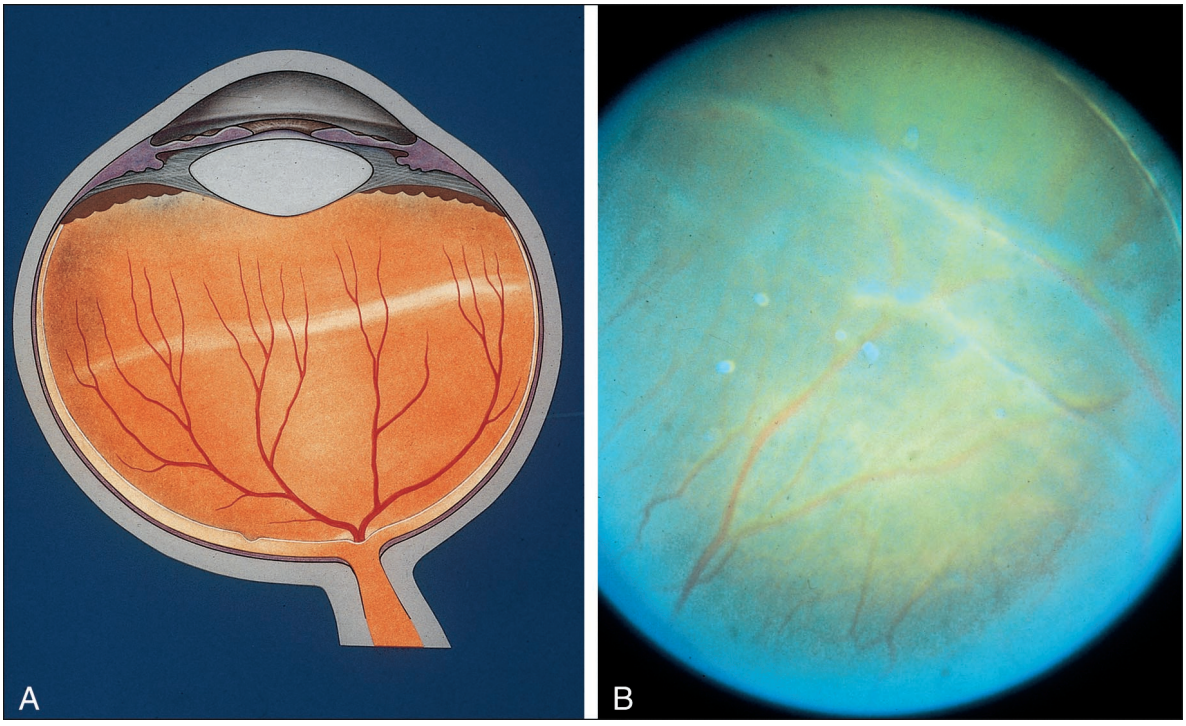


Figure 22. Retinal scars may remain after ROP, particularly when stage 3 disease heals (regresses). A. Artist's depiction of the eye with a residual scar. B. A fundus photograph showing portion of such a scar (actually a double scar) in an approximately 5-year-old child. From JT Flynn with permission for the *CRYO-ROP Slide Atlas*.

disease and develop retinal detachments. The greater the area of avascular retina, the more likely this is to occur, which is why zone I ROP is so prognostically worrisome. Therapeutic efforts have been aimed at prevention (attempts to protect the growing retinal capillaries) and intervention (attempts to prevent the retinal detachment). These are discussed in the clinical trials section of this issue.

Natural History of ROP

Incidence

Following the development of the ICROP, a cohort of 4,099 infants whose birthweights were less than 1,251 g was followed prospectively in 23 centers across the United States to determine the incidence and worst severity of ROP in this population (CRYO-ROP Study Group supported by the National Eye Institute). Figure 23 shows the incidence and severity of ROP data according to gestational age at birth and the worst ROP composite category reached. Clearly, lower gestational age was associated with a greater chance of some ROP and of more severe ROP. Almost all infants who were younger than 27 weeks' gestation had ROP.

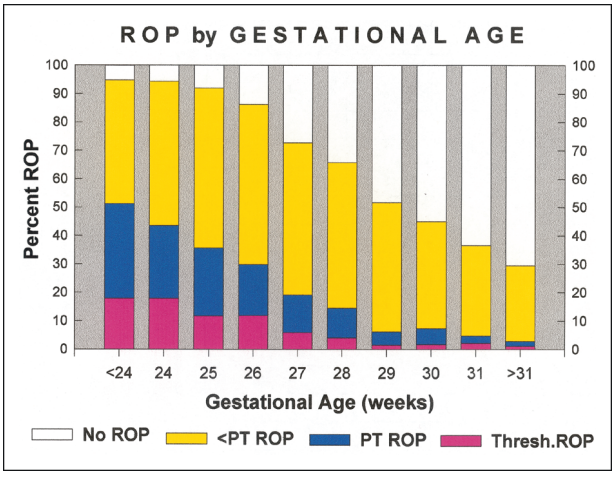


Figure 23. The incidence of any ROP, prethreshold ROP (PT ROP), and threshold ROP by gestational age at birth among 4,099 infants whose birthweights were less than 1,251g born in 1986 through 1988 and examined sequentially by study-certified ophthalmologists who conducted the first examination at 4 to 6 weeks after birth. Reprinted with permission from Phelps DL on behalf of the CRYO-ROP study. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 7th ed. St. Louis, Mo: Mosby-YearBook; 2001.

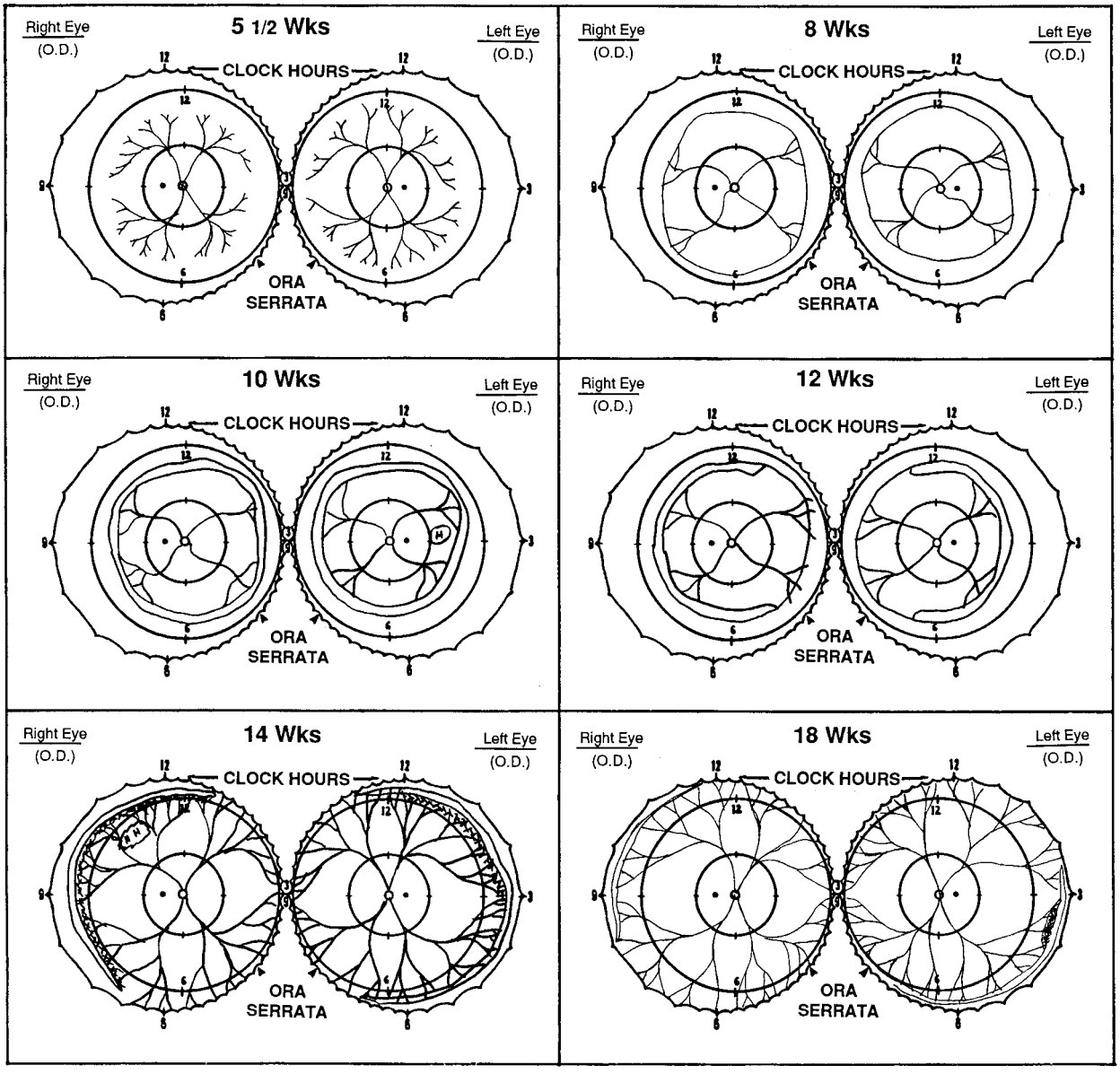


Figure 24. Examination results of an infant born at 25 weeks' gestation who began eye examinations at 5.5 weeks after birth. Initial zone II, immature vessels at the time of first examination progressed to stage 2 by 10 weeks, grew into zone III while advancing to stage 3 at 14 weeks, and then had nearly full regression by 18 weeks. Stage 1 ROP is indicated by a single heavy line at the end of the branching vessels, stage 2 by a double line, and stage 3 as a double line with crosshatching. Reproduced from Phelps DL. *Curr Probl Pediatr.* 1992;22;349–370, with permission from Mosby, Inc.

Although these data are from a cohort of infants born in 1986 through 1988, it is interesting that infants of the same birthweight enrolled in the LIGHT-ROP study a decade later had very similar rates of any ROP and prethreshold ROP.

Course

ROP rarely becomes visible until at least 4 weeks after delivery. This occurs even later in the infants of lowest gestational ages. Accordingly, ROP rarely is seen before 31 weeks postmenstrual age (the gestational age at birth

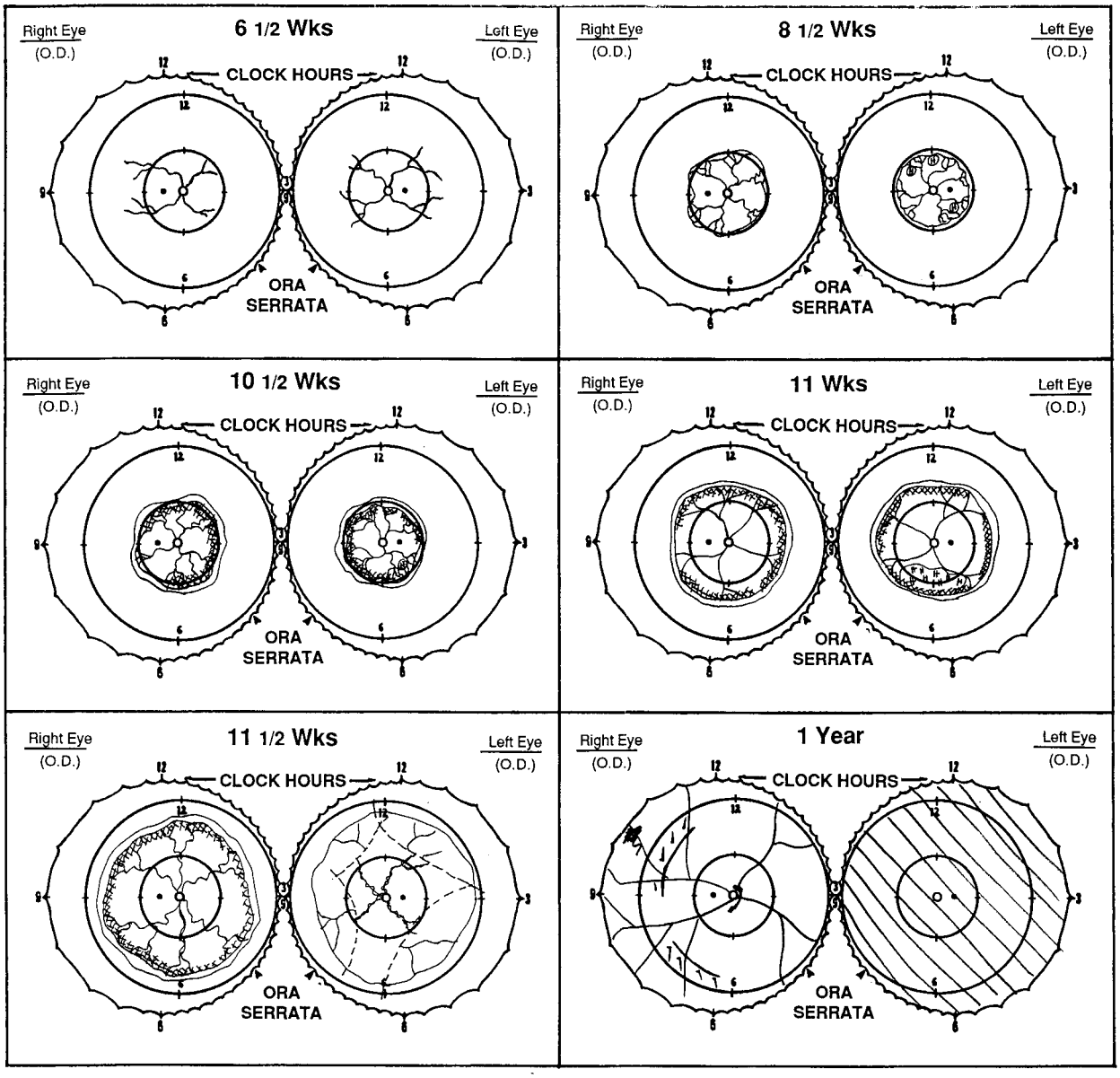


Figure 25. Examination results of an infant born at 24 weeks' gestation who began eye examinations at 6.5 weeks after birth. The vessels were in zone I/II at the time of first examination and rapidly progressed to stage 3 for 12 clock hours with plus disease by 10 weeks. The right eye eventually regressed, leaving a residual circumferential scar in zone II. In the left eye, a partial retinal detachment developed at 11.5 weeks, which progressed to stage 5 total detachment. Retinal detachment is indicated by the diagonal parallel lines. Reproduced from Phelps DL. *Curr Probl Pediatr.* 1992;22:349–370, with permission from Mosby, Inc.

plus the age in weeks following delivery). Once it begins, it is usually in just a few clock hours and at stage 1 or 2. Over time, the number of clock hours and the stage of disease advance until a maximum is reached for that particular infant. The zone where ROP is seen initially usually does not change during this process. In infants who have reached the peak and begin to improve (the ROP is regressing), the vessels pass through the ridge/line and grow toward the ora. As this happens, the vessels grow out of the zone where ROP initially was observed (usually zone II) into zone III, finally reaching the ora serrata.

If the ROP progresses, stage 2 advances to stage 3 plus disease that develops in the posterior pole (near the disk),

Table 2. Probability of Reaching Threshold ROP According to Postmenstrual Age and Eye Findings

	Postmenstrual Age** in Weeks					
	≤32	33 to 34	35 to 36	37 to 38	39 to 40	41 to 42
Zone I						
Incomplete ZI	33%	37%	7%	36%	*	*
Stage 1−+	18%	33%	*	*	*	*
all others	*	*	*	*	*	*
Zone II						
Incomplete ZII	9%	6%	3%	1%	2%	0%
Stage 1−+	8%	6%	4%	2%	1%	1%
Stage 2−	4%	6%	4%	2%	1%	1%
Stage 3−	*	16%	13%	8%	2%	0%
Stage 1++	*	83%	42%	*	*	*
Stage 2+	*	44%	34%	25%	17%	0%
Stage 3+	*	77%	61%	34%	31%	14%

*means not calculated due to small number.
†"+" means with plus disease, "−" means without plus disease.
**Postmenstrual age = gestational age at birth plus chronologic age in weeks since birth.
Data modified and reprinted from Schaffer DB, et al. *Ophthalmology.* 1993; 100:230–237 with permission from Elsevier Science.

and the risk of retinal detachment increases. ROP that progresses to threshold and retinal detachment usually is rapidly progressive, moving from the first observation of prethreshold ROP to threshold in 1 week. An infant in whom many repeat examinations reveal zone II, stage 2 disease with no changes is experiencing an indolent course and has a better prognosis. The findings that most predict progression to threshold are zone I disease at first ROP, plus disease, rapid progression of disease, and having 9 to 12 clock hours of stage 3 ROP. Although black and nonblack infants develop some ROP at similar rates, black infants are less likely to progress to threshold.

Table 2 shows the rates of reaching threshold in the natural history evaluation of the CRYO-ROP study. Entering the table across the top at the infant's postmenstrual age at the time of the most recent eye examination, find the zone of the ROP and worse stage of ROP recorded to the left, being careful to note that "−" indicates no plus disease and "+" indicates the presence of plus disease. The intersection of the column and row describes the percentage of infants in that category who eventually reached threshold and needed surgery.

AN EXERCISE ON THE SEQUENCE AND PACE OF EVENTS OF ROP

Figures 24 and 25 are examples of the course of significant ROP. Using each eye examination, look up the risk of progressing to threshold in Table 2. The gestational age and age in weeks after birth are indicated. How you would counsel the parents after each examination?

Suggested Reading

International Committee for Classification of ROP. An international classification of retinopathy of prematurity. *Pediatrics.* 1984;74:127–133

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Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology.* 1991;98: 1628–1640

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Silverman WA. Retrolental fibroplasia: a modern parable. In: Oliver TK, ed. *Monographs in Neonatology.* New York, NY: Grune & Stratton; 1980

Silverman WA, Flynn JT. Retinopathy of prematurity. In: Finer NM, Chiswick ML, eds. *Contemporary Issues in Fetal and Neonatal Medicine 2.* Boston, Mass: Blackwell Scientific Publications; 1985

NeoReviews Quiz

1. The ROP in the right eye in the Figure is *best* described as:

   A. Zone I, stage 1, 3 clock hours, plus disease.
   B. Zone II, stage 1, 2 clock hours, no plus disease.
   C. Zone II, stage 2, 6 clock hours, plus disease.
   D. Zone II, stage 3, 12 clock hours, no plus disease.
   E. Zone III, stage 3, 2 clock hours, no plus disease.

2. The ROP in the left eye in the Figure is *best* described as:

   A. Zone I, stage 1, 3 clock hours, no plus disease.
   B. Zone II, stage 2, 6 clock hours, plus disease.
   C. Zone II, stage 3, 12 clock hours, plus disease.
   D. Zone III, stage 3, 6 clock hours, no plus disease.
   E. Zone III, stage 3, 12 clock hours, no plus disease.

3. The eyes in the Figure represent:

   A. Less than threshold ROP in the left, less than threshold in the right.
   B. Less than threshold ROP in the left, threshold ROP in the right.
   C. Neither threshold nor less than threshold ROP in either eye.
   D. Threshold ROP in the left, less than threshold in the right.
   E. Threshold ROP in the left, threshold ROP in the right.

