Retinopathy of Prematurity

Major MFP Griffiths,
FRCS, DO, RAMC, Senior Specialist in Ophthalmology
Queen Elizabeth Military Hospital, Woolwich, London SE18

SUMMARY: This paper briefly reviews Retinopathy of Prematurity. It outlines the present incidence and risk factors, summarises the ophthalmic pathology and suggests a scheme of ophthalmic examination and management.

Historical Background

Retro Lental Fibroplasia (RLF), now known as Retinopathy of Prematurity (ROP), was first described by Terry in 1942¹. It is estimated that during the peak years of incidence in the nineteen forties and early fifties, some 700 children were rendered blind from the condition each year in the USA². Following the implication of oxygen by Kinsey in 1956³, the incidence fell, only to rise again in recent years, probably due to the improved survival of very low birthweight infants. American figures^{2,4}, suggest that the present incidence of visual deficit and blindness may be approaching the peak of forty years ago.

Present Incidence

Although the perceived incidence of the disease depends somewhat on the method and time of examination⁵, birthweight seems to be the single most important factor and most studies present their figures in this way. A consensus would seem to be that the incidence of acute ROP is 30 to 40% for birthweights less than 1000 gms, falling to 10% for the 1000 to 1500 gm group and 0 to 5% for those with birthweights over 1500 gms^{2,5,6,7}.

More important perhaps is the proportion of babies with acute ROP that subsequently develop cicatricial disease. Here estimates vary, but about 25% would be reasonable. Of these, roughly a further quarter will progress to blindness^{2,5,8,9}.

Risk Factors

Over 80% of infants with retinopathy of prematurity have birthweights less than 1500 gms, and although some 200 cases of ROP unassociated with prematurity and oxygen administration have been reported in the literature, this may be an overestimate since, particularly in the USA, reports of spontaneous cases weaken prosecutions made on the grounds of excess oxygen administration¹⁰. However, other reviewers^{11,12}, suggest that the role of oxygen in the modern epidemic may be overstated, and feel that other factors need to be carefully considered (Table 1).

Some 80% of babies with acute ROP have Chronic Lung Disease (CLD)², and about 40% of those with CLD will progress to cicatricial ROP¹³. Animal experiments suggest that high levels of oxygen combined with a subsequent period of relative anoxia, may be

more dangerous than oxygen alone¹⁴. Animal experiments again suggest that high levels of carbon dioxide may be harmful in that protective vascular spasm on exposure to high levels of oxygen is prevented¹⁵. Two large human series however have conflicting conclusions^{13,16}. Transfusion with packed cells and adult blood, results in levels of oxygen being delivered to the retina, which are inappropriately high relative to its developmental stage¹⁰. Wolbarsht gives a good review¹⁷. Ischemia, hypothermia and lactic acidosis, together with free oxygen radicals released by macrophages and polymorphonuclear leukocytes in response to sepsis, are all thought to be mediators of ROP, and these may explain the occurrence of ROP in full-term babies. They may also be considered to have an effect in premature babies^{11,12}, although this is overshadowed in most studies by the association with birthweight and gestational age.

The Examination

1. When?

The optimal timing for the initial examination is the 7th to 9th week. Palmer¹⁸ found that examination before this time led to many cases being missed. Retinal detachment is very rarely seen prior to the 8th week. The frequency of subsequent examinations should depend on the severity of disease found at this time.

Table 1
Risk Factors in Retinopathy of Prematurity

Lower birthweight
Younger gestational age
Chronic lung disease
Longer mechanical ventilation
Prolonged oxygen administration
Higher peak oxygen levels
Wider swings in oxygen levels
Carbon dioxide levels (conflicting data)
Ischemia
Lactic acidosis
Hypothermia
Intra-ventricular haemorrhage
Seizures
Septicaemia
Vitamin E deficiency

Earlier handling can be quite hazardous in small, sick infants and about 30% have a significant slowing of the pulse from the oculocardiac reflex¹⁹.

2. Why?

Quite apart from the advantages of liaison with parents and paediatric colleagues, any increase in the incidence of ROP in a unit due to faulty equipment, new management regimes or drugs can be detected earlier. There is a possibility that prophylactic cryopexy performed under topical anaesthesia at the bedside, may be of benefit in selected cases¹⁰. In addition, detachment surgery gives better results if performed early²⁰.

3. How?

The premature pupil is difficult to dilate as it is miotic. The dilator of the iris develops late, and in advanced ROP, the iris may be splinted by new vessels. Tropicamide (0.5 or 1%) is the safest mydriatic because it has no recorded side effects. The alpha adrenergic agonist effects of even 2.5% Phenylephrine cause a significant rise in diastolic blood pressure and bradycardia²¹. Cyclopentolate (0.5%) protects against the bradycardia, but not against the rise in BP, and can cause ileus and problems with temperature regulation. Needless to say the minims of 10% Phenylephrine should not be used undiluted. A Bowmans premature baby lid speculum is used for lid retraction, and a drop of Benoxinate (0.4%) is placed on the cornea. There have been no recorded problems with this concentration; it is, however, possible that a lower concentration may be equally effective²².

Both eyes are examined by binocular indirect ophthalmoscopy using a 28 or 30 dioptre lens. Indentation of the peripheries is mandatory, a disposable plastic ointment spatula or a filed down and rounded meibomian cyst curette may be used. After examination, a small quantity of Chloromycetin ointment is placed on the eye. The naso lacrimal ducts are not patent until some three months after birth so there can be no systemic absorption of the drug from the nasopharynx.

Findings

The lids of the babies of less than seven months gestation may occasionally be closed, since these normally open between the fifth and seventh month of development. The problems of mydriasis have already been mentioned. Visualisation may be further impeded by the presence of the tunica vasculosa lentis which is complete at 27 weeks, and breaks down progressively, normally disappearing by 34 weeks. Lens and vitreous opacities are common.

The normal premature fundus has several specific features. The optic disc is unmyelinated and has a greyish hue; there is little uveal pigment, giving the fundus an albinoid appearance. The macula is not developed and thus poorly defined, although in the same

relationship to the disc as in adults. Other landmarks such as the long ciliary arteries and nerves are also poorly defined. It is normal to see a distinct boundary between the posterior vascular retina and the anterior unvascularised zone.

Pathology

Retinal vascularisation normally commences from the optic disc at 16 weeks gestation, and reaches the nasal ora serrata by the 36th week and the temporal ora by term. The normally distinct vascularising boundary consists of spindle shaped mesenchymal cells which form an advancing network into which capillaries grow. During or after exposure to oxygen (and possibly other factors), anterograde migration stops, gap junctions form between cells and a barrier is formed to further vascularisation. Local vascular arcading then occurs, with fibrovascular proliferation occurring some 8 to 10 weeks later^{10,23,24}.

Abnormal Findings

The anterior segment of the eye may show a vascularised iris with a shallow anterior chamber pushed forward by a retrolental mass, and cataract.

The posterior segment changes are summarised Table 2.

Table 2

Vitreous:	Haze
	Haemorrhage
	New vessels
	Membranes (especially temporal periphery)
Optic Disc:	Pallor
	Traction/distortion
	New vessels
Retinal Vessels:	Abnormally tortuous
	Abnormally straight (traction)
	New vessels elsewhere in the retina
Macula:	Displaced
	Distorted
	Home formation
	Oedema
	Detachment
	Vessels crossing foveal avascular zone ²⁵
Periphery:	Falciform folds (especially temporal)
	Retinoschisis (splitting of the retina)
	Patchy pigmentary change
	Degenerations: Lattice

Classification

A new international classification has been agreed^{26,27}. The earliest detectable sign of acute ROP is an indistinctness of the normal red/grey demarcation line between vascularised and non-vascularised retina.

In Grade 1 disease, a white demarcation line forms at the border, and some abnormal vascular arcading may be seen posterior to this line.

In Grade 2 disease the line is pinkish in colour, slightly raised and vessels are seen growing onto it.

With progression to Grade 3, fibrovascular tissue may be seen growing into the vitreous, or posterior to the ridge, either connected to it or separate. Grade 3 disease is further subdivided into mild, moderate and severe.

Grade 4 ROP is present when the above changes are accompanied by retinal detachment, either exudative or tractional.

When the posterior pole arterioles are tortuous and the veins engorged, an addition "plus" is made to the retinal record to denote this complication which is thought to be an important predictor of prognosis⁹.

Other findings to be commented on and recorded are iris vessel dilatation, pupil rigidity, vitreous haze and haemorrhages. The classification of cicatricial disease after Reese remains²⁸.

Example record sheets were printed in several journals in 1984^{26,27} (Table 3).

Management

While it is not the intention of this paper to comment on the paediatric management of the premature baby as it relates to ROP, the role of vitamin E and some aspects of ophthalmic treatment will be discussed.

Several good studies have shown apparent benefit from routine vitamin E administration in the management of ROP^{4,10,24,29,30,31}. Nevertheless there remains much scepticism about its effectiveness and concern about possible serious side effects. It is interesting to note, however, that while the initial study implicating oxygen in the pathogenesis of ROP included only 53 babies³, this stopped the routine administration of oxygen in neonatal units until the results were confirmed by a larger series. The response to studies on vitamin E effects has been much more cautious.

The premature baby has low serum levels of vitamin E due to a 4:1 placental concentration barrier and relatively smaller fat stores (0.3 mg% as compared with 1 to 3 mg% in the adult). It is thought that vitamin E acts as a natural anti-oxidant, conserving infant antioxidant enzymes such as superoxide dismutase, reducing harmful lipid peroxidases produced after high oxygen exposures and indirectly inhibiting platelet aggregation by encouraging prostacyclin (PG12) regeneration³⁰. High serum levels of vitamin E have been shown to be associated with an increased incidence of septicaemia and necrotising enterocolitis. None of the above studies however showed any increased incidence of these complications in the treated groups when serum levels

were monitored and not allowed to rise above 3.5 mg%. The safety of vitamin E however would have to be conclusively proved before its routine use could be recommended because in routine administration the majority of premature babies receiving it would not in fact need it³², and at present there is no way of identifying those babies who will develop ROP.

Other Ophthalmic Treatment

Both cryopexy and photocoagulation have been advocated in the treatment of ROP. The latter is often impractical, however, due to the frequency of lens and vitreal opacities in premature babies. Cryopexy to the avascular retina anterior to the fibrovascular ridge is therefore favoured^{33,34,35,36}. The purpose of treatment is to destroy the activated spindle cells which are thought to be the precursors of the neovascular process. Cryopexy to the ridge itself may result in an increased incidence of complications such as vitreous haemorrhage and retinal detachment. Timing of treatment is also important because if it is carried out too late, i.e. after the neovascular process is complete, it has no therapeutic effect and may actually exacerbate cicatrization.

Detachment surgery has a greater chance of success carried out early. One study²⁰, compared results of early (open detachment funnel) and late (closed funnel) surgery for advanced cicatricial disease. Surgery consisted of lensectomy with vitrectomy, retinal membrane peeling and scleral buckling. Results were significantly better in the early treatment group. Early treatment depends, of course, on early diagnosis, and this in turn depends on early and possibly frequent examination of at-risk neonates.

Prognosis

Low grade ROP (1&2) has a good prognosis with no greater incidence of squint³⁷, and only a slightly greater incidence of anisometropia³⁸ than the general population. Cicatricial disease (Grades 3 and greater) is frequently accompanied by visual deficit short of the blindness previously mentioned. High myopia is much more common (50% as compared with 16% in a control group in one study³⁹), and complications resulting from retinal degenerations may continue into adulthood.

Studies on the late psychological and learning difficulties are few and conflicting, but have been well reviewed recently⁴⁰.

Recommendations

To conclude, the following recommendations may be made concerning the ophthalmic management of babies with birth weights less than 1500 gms or gestational age (GA) less than 31 weeks:

1. If vitamin E is considered appropriate by the neonatologist, it should be commenced orally in a dose of 100mg/kg/day within 12 hours of birth and supplemented with intramuscular vitamin E if the baby is "nil

Table 3
ROP Eye Examination

NAME:
DOB (DD/MM/YY):
SEX (M = 1, F = 2):
BIRTH WEIGHT (Gms):
GESTATIONAL AGE (Wks):
MULTIPLE BIRTHS (Single = 1, Twin = 2 etc):

HOSPITAL NO:
EXAMINER:
DATE OF EXAM'N:
MYDRIATIC:

BLANK = NORMAL
1 = DEMARCATION LINE
2 = RIDGE

MARK HIGHEST
STAGE AT EACH
CLOCK HOUR

3 = 2 + EXTRA RETINAL PROLIF
4 = 3 + RETINAL DETACHMENT
9 = NOT EXAMINED

Z3 []	Z2 []	Z1 []	[x]	[]	Z1	[]	Z2	[]	Z3
12 []	12 []	12 []		[]	12	[]	12	[]	12
11 []	11 []	11 []		[]	11	[]	11	[]	11
10 []	10 []	10 []		[]	10	[]	10	[]	10
9 []	9 []	9 []		[]	9	[]	9	[]	9
8 []	8 []	8 []		[]	8	[]	8	[]	8
7 []	7 []	7 []		[]	7	[]	7	[]	7
6 []	6 []	6 []		[]	6	[]	6	[]	6
5 []	5 []	5 []		[]	5	[]	5	[]	5
4 []	4 []	4 []		[]	4	[]	4	[]	4
3 []	3 []	3 []		[]	3	[]	3	[]	3
2 []	2 []	2 []		[]	2	[]	2	[]	2
1 []	1 []	1 []		[]	1	[]	1	[]	1

RE

IF STAGE 3

LE

1 = MILD
3 = SEVERE

2 = MODERATE
9 = NOT EXAM'D

IF STAGE 4

1 = EXUDATIVE
3 = COMBINED

2 = TRACTIONAL
9 = NOT EXAM'D

OTHER FINDINGS [x]

[]	DILATED/TORTUOUS POSTERIOR VESSELS	[]
[]	IRIS VESSEL DILATATION	[]
[]	PUPIL RIGIDITY	[]
[]	VITREOUS HAZE	[]
[]	VITREOUS HAEMORRHAGE	[]

by mouth" for more than three days. Serum vitamin E levels should not be allowed to exceed 3.5 mg%.

2. The retinae should be examined at 8 weeks and thereafter depending on the severity of ROP found at this first examination.

3. In severe ROP in babies of 27 weeks gestation or less at birth, cryopexy to the peripheral avascular retina should be considered as near to the 8th week of life as possible.

4. If detachment surgery is contemplated, it should be carried out early and not postponed.

5. All groups should be followed carefully by an ophthalmologist using refraction and fundoscopy to detect refractive error and late retinal complications.

REFERENCES

1. TERRY T L. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind the crystalline lens. 1. Preliminary report. *Am J Ophthalmol* 1942; **25**: 203-4.
2. CAMPBELL P B et al. Incidence of retinopathy of prematurity in a tertiary newborn intensive care unit. *Arch Ophthalmol* 1983; **101**: 1686-8.
3. KINSEY V E. Retrolental fibroplasia. Cooperative study of retrolental fibroplasia and the use of oxygen. *Arch Ophthalmol* 1956; **56**: 481-543.
4. HITNER H M et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N Engl J Med* 1981; **305**: 1365-7.
5. KEITH C J and KITCHEN W H. Retinopathy of prematurity in extremely low birthweight infants. *Med J Aust* 1984; **141**: 225-227.
6. FEMAN S S, PODGORSKI S F and COTTON R. Changing patterns in retinopathy of prematurity. *Annals of Ophthalmol* 1984; **16**: 1056-8.
7. KALINA R E and KARR D J. Retrolental fibroplasia: experience over two decades in one institution. *Ophthalmology* 1982; **89**: 91-95.
8. PHELPS D L. Retinopathy of prematurity: an estimate of vision loss in the United States - 1979. *Pediatrics* 1981; **67**: 924-5.
9. TASMAN W. The natural history of active retinopathy of prematurity. *Ophthalmology* 1984; **91**: 1499-1503.
10. HITNER H M, RUDOLPH A J and KRETZER F L. Suppression of severe retinopathy of prematurity with vitamin E supplementation. Ultrastructural mechanism of clinical efficacy. *Ophthalmology* 1984; **91**: 1512-23.
11. LUCEY J F, HORBAR J D and ORISHI M J. Cerebral and retinal hypoperfusion as a possible cause of retrolental fibroplasia: Hypothesis to explain non-oxygen related RFL, abstracted. *Pediatr Res* 1981; **15**: 670.
12. LUCEY J F and DANGMAN B. A re-examination of the role of oxygen in retrolental fibroplasia. *Pediatrics* 1984; **73**: 1: 82-96.
13. BIGLAN A W et al. Risk factors associated with retrolental fibroplasia. *Ophthalmology* 1984; **91**: 1504-11.
14. PHELPS D L and ROSENBAUM A L. Effects on marginal hypoxemia on recovery from oxygen-induced retinopathy in the kitten model. *Pediatrics* 1984; **73**: 1: 1-6.
15. FLOWER R W et al. Prostaglandins as mediators of vasotonia in the immature retina. *Pediatrics* 1984; **73**: 440-444.
16. BOSSI E et al. Retinopathy of prematurity: a risk factor analysis with univariate and multivariate statistics. *Helv Paediatr Acta* 1984; **39**: 307-317.
17. WOLBARSH T M L et al. Retinopathy of prematurity: A new look at an old disease. *Ophthalmic Surg* 1983; **14**: 11: 919-924.
18. PALMER E A. Optimal timing of examination for acute retrolental fibroplasia. *Ophthalmology* 1981; **88**: 662-8.
19. CLARKE W N et al. The oculocardiac reflex during ophthalmoscopy in premature infants. *Am J Ophthalmol* 1985; **99**: 6: 649-51.
20. TRESE M T. Surgical results of stage V retrolental fibroplasia and timing of surgical repair. *Ophthalmology* 1984; **91**: 461-66.
21. DUANE T D. Clinical Ophthalmology. Philadelphia. Harper and Row. 1984. Vol 5; Ch 39: p11.
22. MAURICE D M and SINGH T. The absence of corneal toxicity with low-level topical anaesthesia. *Am J Ophthalmol* 1985; **99**: 6: 691-6.
23. KRETZER F L et al. Vitamin E protects against retinopathy of prematurity through action on spindle cells. *Nature* 1984; **309**: 793-5.
24. HITNER H M et al. Retrolental fibroplasia: Further clinical evidence and ultrastructural support for efficacy of vitamin E in the preterm infant. *Pediatrics* 1983; **72**: 423-432.
25. IBAYASHI H, NISHIMURA M and YAMANA T. Avascular zone in the macula in cicatricial retinopathy of prematurity. *Am J Ophthalmol* 1985; **99**: 3: 235-239.
26. An international classification of retinopathy of prematurity. *Br J Ophthalmol* 1984; **68**: 690-97.
27. An international classification of retinopathy of prematurity. *Pediatrics* 1984; **79**: 1: 127-133.
28. REESE A B, KING M J and OWENS W C. A classification of retrolental fibroplasia. *Am J Ophthalmol* 1983; **36**: 1333-35.
29. HITNER H M et al. Retrolental fibroplasia and vitamin E in the preterm infant-comparison of oral versus intramuscular: oral administration. *Pediatrics* 1984; **73**: 238-249.
30. FINER N N et al. Effect of intramuscular vitamin E on frequency and severity of retrolental fibroplasia. A controlled trial. *Lancet* 1982; **1**: 1087-1091.
31. FINER N N et al. Vitamin E and retrolental fibroplasia. Improved visual outcome with early vitamin E. *Ophthalmology* 1983; **90**: 428-435.
32. ROSENBAUM A L and PHELPS D L. Discussion following reference 10. *Ophthalmology* 1984; **91**: 1522-1523.
33. HINDLE N W and LEYTOIN J. Prevention of cicatricial retrolental fibroplasia by cryotherapy. *Can J Ophthalmol* 1978; **13**: 277-282.
34. MOUSEL D K and HOYT C S. Cryotherapy for retinopathy of prematurity. *Ophthalmology* 1980; **87**: 1121-1127.
35. BEN-SIRA I et al. Treatment of acute retrolental fibroplasia by cryopexy. *Br J Ophthalmol* 1980; **64**: 758-762.
36. NISSENKORN I et al. A clinicopathological case of retinopathy of prematurity (ROP) treated by peripheral cryopexy. *Br J Ophthalmol* 1984; **68**: 36-41.
37. HAMMER H M et al. Ophthalmic findings in very low birthweight children. *Trans Ophthalmol Soc UK* 1985; **104**: 3: 329-31.

38. SCHAFER D B, QUINN G E and JOHNSON L. Sequelae of arrested mild retinopathy of prematurity. *Arch Ophthalmol* 1984; **102**:373-376.
39. NISSENKORN I et al. Myopia in premature babies with and without retinopathy of prematurity. *Br J Ophthalmol* 1983; **67**:170-173.

40. SCHARF L S AND ADAMS K M. Long-term neuropsychological impact of retrolental fibroplasia; review and implications. *J Pediatr Psychol* 1984; **9**:303-316.

JOURNALS/PUBLICATIONS RECEIVED

The following Journals/Publications have been received and are available in the Royal Army Medical College Library.

JOURNALS

Acta Medicinalia Militaria Belgica; Annales Chirurgiae et Gynaecologiae; Annals of Clinical Research; Archives of Surgery; Australian & New Zealand Journal of Surgery.

Boletín de la Oficina Sanitaria Panamericana; British Medical Journal + Index; Bulletin of the Academy of Military Medical Sciences, China; Bulletin of the Pan American Health Organization; Bulletin of the World Health Organization.

Central African Journal; Gazette, The (QARANC); Giornale di Medicina Militare; Hellenic Armed Forces Medical Review; Indian Journal of Medical Research, The; Journal of the Oslo City Hospitals; Journal of the Royal Army Chaplains' Dept; Journal of the Royal Society of Health + Newsletter; Journal of the Royal Society of Medicine.

Lancet, The + Index; Medecine Tropicale; Medical Journal of Australia, The; Medicina Militar; Military Medicine, Military Review; National Defense Medical Journal, Tokyo; Quarterly Journal of Medicine; Revista del Servicio de Sanidad de las Fuerzas Armadas; Revista Sanitaria Militar; Revue Internationale des Services de Sante des Armed Forces Armees; Royal Army Pay Corp Journal; Royal Engineers Journal, The; Royal Pioneer, The.

Scottish Medical Journal; South African Medical Journal + Supplement; Transactions & Studies of the College of Physicians of Philadelphia; Tropical Diseases Bulletin; Ulster Medical Journal; Wehr-Medizinische Monatsschrift; World Health Forum, WHO; WHO Chronicle.

PUBLICATIONS

AMSUS - Assocn of Military Surgeons of the United States, 93rd Annual Meeting Program, 1987. Appropriate Use of Fluorides for Human Health - WHO; Basic Principles for Control of Acute Respiratory Infections in Children in Developing Countries - WHO; UNICEF; BASICS - Monographs on Immediate Care for the Sick - No: 3 - Rescue from Remote Places: etc; Basic Tests for Pharmaceutical Substances - WHO; Bulletin of the International Civil Defence Organisation No's: 366-375; Chemotherapy of Malaria - Rev. 2nd Edn - WHO; Clinics in Tropical Medicine and Communicable Diseases, Ed. G T Strickland; Control of Schistosomiasis, The Report of a WHO Expert Committee - WHO; Doctor at Dunkirk, with the 6th Field Ambulance at War by I Samuel; Environmental Health Criteria - No's: 54, 57, 59-60, 66-67; Law and the Treatment of Drug and Alcohol-Dependent Persons - WHO; NAAFI News; Prevention and Control of Yellow Fever in Africa - WHO; SSAFA News; Single Surgical Procedures - 33 A Colour Atlas of Gastric Revision Operations by J A Williams; To the Kwai and Back - War Drawings 1939-45 by R Searle; Tropical Disease Research - WHO; WHO Chronicle Vols 39 & 40 - WHO; WHO Joint/UNICEF Statement - Maternal Care for the Reduction of Perinatal & Neonatal Mortality - WHO/UNICEF; WHO - Public Health Papers - 82 - Leadership for Primary Health Care - WHO; WHO - Technical Report Series No's: 730-731, 733-734, 736 & 740 - WHO.