RETINOPATHY OF PREMATURITY

SOME EPIDEMIOLOGICAL

AND

PAEDIATRIC ASPECTS

YIN KHOW NG

BSc., M.B.B.S. (LONDON),

D.R.C.O.G., D.C.H. (LONDON), M.R.C.P. (U.K.)

Submitted in fulfilment of the requirements for the degree of
Doctor of Medicine, the University of Leicester, November 1996

UMI Number: U078977

UMI U078977

ABSTRACT:
Retinopathy of prematurity: Some epidemiological and paediatric aspects
Yin Khow Ng

With the development of modern neonatal intensive care and the increase in
the survival of very low birthweight babies, it was reported from a number
of centres around the world that the incidence of retinopathy of
prematurity (ROP) seemed to be once again on the increase. Since there was
very little information regarding this condition in the United Kingdom
after the early 1950s, a grant was awarded by the Medical Research Council
in 1985 to enable further investigation.

This thesis presents some of the results of this prospective survey of ROP.
The epidemiological part of the study showed that in the geographically-
defined population which we studied, acute ROP is common, being seen in
49.1% of infants weighing 1700 gm or less at birth. Most of these
developed at worst, stage 1 or 2 disease (44.9%) and in all these 277
babies there was complete resolution. Of the 21 infants who developed more
severe disease (stage 3 or 4), five (nine eyes) progressed to the
cicatricial stages. However none of these infants was blind. There was no
sex difference found but it was observed that there was a significant
relationship between the stage of ROP and the race of the infant, Asian
infants being found to have a greater tendency to develop stage 3 or 4
disease.

In the paediatric factors part of the study, several variables describing
neonatal events and treatments were subjected to univariate analysis to
find those which could be used in a multivariate analysis. Only a few of
these variables are considered and discussed here. A significant
association was found between the stage of acute ROP and cranial ultrasound
findings of haemorrhage and periventricular leucomalacia, the presence of a
persistent ductus arteriosus, a longer duration of assisted ventilation and
oxygen treatment, bradycardias, apnoeas, cyanotic episodes and blood
transfusions. Some of the difficulties in such a study are described.

CONTENTS

INTRODUCTION

When the Medical Research Council initiated an investigation into retrolental fibroplasia, now known as retinopathy of prematurity, (ROP), in the United Kingdom in October 1951 there was a great deal of interest in and research into this relatively new condition. A few years later as the "epidemic" of children blinded by this condition waned in relation to restriction of oxygen use in neonatal nurseries, so the interest in retrolental fibroplasia faded. Since then however there have been many developments in the care of the newborn and there has been a resurgence of interest in ROP with reports from several centres caring for neonates around the developed world that the numbers of preterm infants affected with this eye condition are once more on the increase.

With this renewed interest in ROP it became clear that there was very little information about this condition in the United Kingdom (UK) since the 1950's. In 1985 the Medical Research Council made a grant available to Mr Alastair Fielder, Reader in the Department of Ophthalmology and Dr Malcolm Levene, Senior Lecturer in the Department of Child Health at the University of Leicester to study ROP in the East Midlands area of the UK. The study had three main aims: firstly to investigate the incidence of ROP in a geographically-defined population in this country and to describe some of the epidemiology of the condition, secondly to observe and describe the natural history, and thirdly to investigate paediatric factors, including cranial ultrasound appearances, which might be associated with the occurrence of ROP.

I was the Clinical Research Fellow employed with this grant to assist in the setting up of the survey and in the collecting of paediatric data. In this thesis I will present the results of the epidemiological study and some of the results

of the study of paediatric factors associated with the occurrence and severity of ROP.

CHAPTER 1 - REVIEW OF THE LITERATURE

Retinopathy of prematurity (ROP) was first described in 1942 (Terry, 1942).
Following the original description the condition came to be called "retrolental
fibroplasia" (RLF), literally "scar tissue behind the lens of the eye", because of
the presence of an opaque grey-white membrane behind the lens. In 1984 the
international committee which agreed the classification of this disease
recommended that ROP should be the term used for this condition (Committee
for the classification of ROP, 1984) since this name describes the pathological
changes to the developing retinal blood vessels that occur in this disease. It
was thought that the term RLF was inappropriate because it described only the
cicatricial changes which are a later development in the eyes of the most
severely affected infants.

CLASSIFICATION

The history of the early research into this condition has been well-
documented (Silverman, 1980). One of the main difficulties which beset
earlier workers was the differences in the classification of the disease
(Committee for the classification of ROP, 1984). The lack of an agreed
classification made it very difficult to compare previous surveys with each
other, let alone with more modern studies. In particular, epidemiological
studies and comparisons of different treatment methods were very difficult
since it was not certain that like was being compared with like. Up to 1984, the
most commonly used classification was that devised by Reese, King and Owens
(Reese et al, 1953). However there were also several other systems in use (Patz,
1969, Kingham, 1977, McCormick, 1977, Keith, 1979, Schaffer et al, 1979).

In 1984 the International Classification of ROP (ICROP) for the acute stages of
the disease was introduced (Committee for the classification of ROP, 1984). As

well as grading the retinopathy in an agreed manner, this system required a description of the location (site) of the changes using 3 zones of involvement centred on the optic disc, and of the extent of the disease, using the 12 hours of the clock (see chapter 2). This system was used in our study which commenced in 1985. At this time the ICROP did not include a complete classification of all the changes seen in cicatricial disease, and it was recommended that the Reese classification should continue to be used for those retinal changes that were beyond those described in the new system.

Another reason which has made it difficult to compare earlier studies and more recent work has been the development and introduction of the indirect ophthalmoscope to visualise the preterm infant's fundus. With this instrument and the aid of an eyelid speculum and scleral indentor to rotate the eye, the peripheral retina can be examined, even while the infant lies within an incubator on mechanical ventilatory support. Thus any changes in these sites are now more easily seen than previously (Mushin, 1974, McCormick, 1977).

EPIDEMIOLOGY

Interest in ROP was rekindled in the 1970's by reports from the USA, Canada and Finland that the incidence of the condition seemed to be on the increase (McCormick, 1977, Bauer, 1978, Gunn et al, 1978 and 1980, Tarkkanen et al, 1978). In the late 1940s and the early 1950s the incidence of RLF reached high proportions and many survivors of preterm birth had a visual handicap as a consequence of this condition. In the late 1950s and early 1960s there was a decline in the incidence of RLF (Sorsby, 1966) and this was thought to be related to the restriction in the use of supplemental oxygen in the treatment of premature infants (Forrester et al, 1954, Cross, 1973, Silverman, 1980). However during this same period of time, developments in antenatal care and

in the intensive care of the newborn were having effects on survival of infants born prematurely, with an increase in the number of infants surviving preterm birth in all birthweight groups, even those in the very low birthweight group, that is those weighing less than 1500 gm. (Pharoah et al, 1981, Cross, 1973, Hack et al , 1979). Phelps estimated from 1979 figures that there could be 546 children blinded by ROP in that year, and that 2100 infants could be affected by cicatricial disease annually in the USA (Phelps, 1981). Subsequent reports of comparisons of ROP over a period of years within a number of centres agreed with the trend reported by Phelps (Kalina et al, 1982, Feman et al, 1984).

In the light of these reports from other countries, and with the increased survival of very low birthweight infants (Pharoah et al, 1981) it might be expected that there would be an increase in the incidence of ROP in the United Kingdom (UK). However there is little published data on the incidence of ROP in this country since the 1950's.

In a retrospective survey of children born between 1960-1979 in the North of England who had been diagnosed as having retrolental fibroplasia (Hey et al, 1980), between 6% and 9% of infants weighing less than 1000 gm, and who survived the neonatal period between 1964 and 1979 appeared to have retrolental fibroplasia, as did 1% of babies weighing between 1000 and 1500 gm. All the individuals identified had severe permanent visual damage. Information for the survey was obtained from a number of sources, including the figures for registration of blindness or partial sight in children in England and Wales. These latter figures would only be reliable for the most severely affected children, and would show incidence figures for the year of registration which may be several years after the diagnosis was made. A number of children who are partially-sighted are never registered so that

figures from the registers would be likely to be an underestimate of the incidence. This paper described several of the difficulties experienced in undertaking a retrospective survey of this condition in a defined community, not least in the ascertainment of affected individuals and in the reliability of the diagnosis.

Mushin's series of patients were examined by him in the five years up to 1974 in two London neonatal units (Mushin, 1974) and were a more selected group (hospital-based) than the children surveyed by Hey and Jarvis (community-based). 50% of Mushin's patients who weighed less than 1500 gm at birth showed some signs of ROP and 7% had signs of "fibrosis', presumably cicatricial disease. None of this latter group of infants was blind but they all had some degree of visual deficit.

In the early 1950s, a large survey of retrolental fibroplasia in the UK was undertaken by the Medical Research Council of all infants weighing less than 1800 gm who were born between October 1951 and May 1953 and who were admitted to one of 17 hospital premature baby units (A report to the Medical Research Council by their council on retrolental fibroplasia, 1955). In the same period, the Ministry of Health initiated a retrospective community-based survey of the incidence of RLF in premature infants born in 1951 in England and Wales and weighing less than 2000 gm (Boyd et al, 1955). For the reasons mentioned above neither of these surveys can be directly compared with the results of more recent studies.

From the earliest descriptions of the disease, an association with prematurity had been made. In Terry's original descriptions short gestational age as well as low birthweight were noted in all the affected infants. In many studies of ROP since that time, it has been a constant finding that the frequency of

retinal changes occurring is inversely related to birthweight and/or gestational age (King, 1950, Silverman et al, 1952, Medical Research Council report, 1955, Boyd et al, 1955, McCormick, 1977, Gunn et al, 1980, Kalina et al, 1982, Campbell et al, 1983, Flynn, 1983, Bossi et al, 1984, Reisner et al, 1985, Yu et al, 1982, Hammer et al, 1986, Hungerford et al, 1986). The severity of the changes has also been reported to be inversely related to birthweight and/or gestational age, with cicatricial disease occurring more frequently in infants of very low birthweight (Patz, 1957, Phelps, 1981, Kalina et al, 1982, Shohat et al, 1983, Feman et al, 1984, Keith et al, 1984, Reisner et al, 1985) although there have also been studies which have shown that severity of the disease is not related to birthweight or gestational age (Silverman et al, 1952, Yu et al, 1982). Even though various classification systems were used in all these studies which were carried out before the ICROP was agreed so that precise comparisons are not possible, it does appear that there is a relationship between preterm birth and the occurrence of ROP.

Some early studies reported that there was a sex difference in the incidence of ROP. It seemed that more males than females were affected by the disease (King, 1950, Silverman et al, 1952, Medical Research Council report, 1955, Boyd et al, 1955). Later studies have shown no sex difference in the occurrence of ROP (Yu et al, 1982, Shohat et al, 1983). A study carried out in England and Wales in 1951 (Boyd et al, 1955) showed that there was a greater number of girls than boys in all birthweight groups in their survey and they pointed out that for a given gestation, girls tend to weigh less than boys, that is girls would tend to be more mature at any given birthweight and boys less so. When they corrected for this, they found an equal sex incidence.

PATHOGENESIS

The pathological basis of ROP is that there is a proliferation of retinal vessels in the immature retina which may progress to exudates, haemorrhages, retinal detachment and formation of fibrous tissue (Garner 1985). In the developing human retina, vascularisation begins at about the 16th week of gestation. It progresses peripherally from the area adjacent to the optic disc, with the development of an advancing network of primitive capillaries, reaching the ora serrata by about the 8th month of gestation and the anterior temporal retinal periphery, furthest from the optic disc, at about full term. These capillaries differentiate into arterioles or venules by a process of selective hypertrophy of some capillaries and atrophy of others. The factors which affect this process are mainly metabolic and haemodynamic ones, a particularly significant one being oxygen (Garner, 1985).

Pathology (Garner, 1985)

Stage 1 ROP (demarcation line) is characterised microscopically by an anterior vanguard zone consisting of a hyperplastic mass of spindle-shaped cells which are the precursors of the vascular endothelium. Clinically this zone appears white as it is devoid of functioning capillaries. Behind these proliferating spindle cells is a rearguard zone of nascent capillaries within a compact knot of differentiating endothelium. It is from this rearguard zone that subsequent vasoproliferation occurs.

Stage 2 ROP (ridge) is progression of the demarcation line such that there is extension beyond the surface of the retina. The area of maximum activity is seen to be in the rearguard zone with clusters of proliferating endothelium and organisation into vascular channels. The pink colour of the ridge seen clinically is due to these new capillaries. In addition there may be small, isolated tufts of capillaries on the retinal surface, a liitle behind the ridge.

Stage 3 ROP (ridge with extraretinal fibrovascular proliferation) is the progression from thickening of the inner retina to surface proliferation. Although the proliferative activity starts in the rearguard capillaries, it is in this stage that growth can occur anteriorly or posteriorly.

Stage 4 ROP (retinal detachment) occurs as a result of traction or serous exudation following the growth of fibrovascular tissue.

ROP And Other Proliferative Retinopathies

There are similarities between ROP and other proliferative retinopathies (Garner, 1985). For example, branched loops of vessels can be seen at the margins of avascular foci in diabetic retinopathy, which has been explained by redistribution of blood flow following obliteration of some of the capillary bed. Similar appearances can be seen in early acute ROP, as mentioned above. One effect of capillary obliteration is that blood is redirected from the arterial to the venous side through channels at the edge of the residual vasculature, forming hyperemic and often leaky shunts. Increased blood flow in diabetic retinopathy also causes an increase in the size and tortuosity of the more proximal vessels. Similar appearances are found in early acute ROP.

There is evidence that circulatory disruption resulting in tissue hypoxia is the factor common to most of the proliferative retinopathies (Garner, 1985) and that hypoxia and tissue damage are associated with the production of angiogenic factors. Angiogenic factors have been detected in diabetic retinopathy and in the eyes of animals with experimentally induced ROP.

Timing

One of the most interesting observations about ROP is that it is only seen when the retinal vessels are immature. Once the retinal vessels have reached the temporal periphery i.e. the retina is fully vascularised, the infant is no longer

10

in danger of developing ROP. The age of onset of acute ROP occurs within a
relatively narrow range (Fielder et al, 1986). 86% of the infants reported in
that study (n=143) developed ROP between 32.5 and 38.5 weeks post-menstrual
age. It was noted that infants of < 28 weeks gestational age developed ROP at a
lower postmenstrual age (median age of onset 33.7 weeks) than those who were
≥ 28 weeks gestation (median age of onset 35.7 weeks). These authors suggested
that a certain developmental stage, probably at retinal level, had to be reached
for the response to occur. These clinical observations would fit those from the
laboratory that retinal maturity is important in determining the susceptibility
to ROP (Garner, 1985).

ASSOCIATED PAEDIATRIC FACTORS

Terry's original description and later reports showed that there was an
association between premature birth and the occurrence of ROP (see above).
Preterm birth has remained the most constant association, measured either as
low birthweight or as short gestation.

From the earliest days a great deal of effort and thought has been spent in
investigating the aetiology of the condition, and many possible factors were
suggested as being either directly responsible or contributing to the
development of the disease (Zacharias, 1952, Silverman, 1980). Maternal and
infant factors, antenatal, perinatal and postnatal events were considered.
Some of the early suggestions included exposure to light (Terry, 1943),
deficiencies in various substances such as deficiency of vitamin E (Owens et al,
1949), alterations in blood pressure such as might occur in the presence of a
persistent ductus arteriosus (Terry, 1943), exposure to oxygen (Campbell K,
1951, Crosse, 1951) and lack of oxygen at retinal tissue level (Campbell FW,
1951).

THE OXYGEN FACTOR

Oxygen Concentration And Duration Of Oxygen Therapy

Two papers published in 1951 (Campbell K, 1951, Crosse,1951) noted that there
seemed to be an increase in the number of infants affected by ROP in hospitals
where high concentrations of oxygen were used. However ROP did also occur
where oxygen was used in smaller amounts (Houlton, 1951) and there were
infants who did not develop the disease although placed in high oxygen
environments (Exline et al, 1951). Other studies (Medical Research Council
report, 1955, Kinsey, 1956) showed that there was a relationship between
oxygen treatment and the frequency of ROP. The MRC survey demonstrated
that RLF occurred more commonly in those infants who were given oxygen
for longer periods, and in those nurseries where there was increased use of
oxygen. The cooperative study between 18 hospitals in the USA (Kinsey, 1956)
suggested that the incidences of both acute and cicatricial RLF increased
rapidly with increasing duration of exposure to oxygen, the most rapid
increase occurring for durations of only one or two days. However in this
study the incidence of cicatricial disease was not dependent on the
concentration of oxygen given. It therefore seemed to confirm the theory
that the use of high concentrations of oxygen was the cause of ROP.

The events following the publication of the results of the cooperative study
have been described clearly (Silverman, 1980). The amount of oxygen given to
preterm infants was restricted, so that it was only given if clinically indicated
and in most units it was generally accepted that the maximum "safe" level of
oxygen was 40% (FiO_2 = 0.4). In the cooperative study (Kinsey, 1956) the
"routine oxygen" group was given oxygen at concentrations over 50% ($FiO_2 \geq$
0.5) for 28 days whereas the "curtailed oxygen" group was given oxygen only
for as long as was indicated on clinical grounds, and in concentrations not
exceeding 50% ($FiO_2 \leq 0.5$). Another study published at about the same time

(Guy et al, 1956) reported that no cicatricial RLF had been seen in the group of babies given restricted oxygen at a mean concentration of 30% (FiO_2 = 0.3), whereas 22% of infants given high concentrations, mean 69% (FiO_2 = 0.69), developed severe disease.

Ashton's experimental work on developing retinal blood vessels, particularly in kittens (Ashton et al, 1953, Ashton, 1966) had demonstrated that vasoconstriction occurred with total obliteration of the vessels when the animals were placed in oxygen and that this effect was related to the maturity of the vessels, the duration of exposure to and the concentration given of oxygen. Concentrations of oxygen below 35% (FiO_2 < 0.35) seemed to have little or no effect on the kittens' retinas in the most sensitive age group. This evidence seemed to give further support to the theory that giving infants oxygen concentrations of 40% or less (FiO_2 ≤ 0.4) would decrease the incidence of ROP.

However there were concerns that restricting oxygen treatment could have serious consequences on the mortality of preterm infants. The cooperative study (Kinsey, 1956) addressed this by including survival in the study design and their results showed there to be little difference in mortality between the "routine oxygen" group and the "curtailed oxygen" group. It was subsequently pointed out (Gordon, 1957) that infants were only admitted to the cooperative study if they survived the first 48 hours, the period of highest risk of death, and it was misleading to conclude that oxygen restriction as carried out in the study had no harmful effect. Later work has shown that oxygen restriction did reduce the incidence of ROP but that mortality and morbidity in preterm infants did increase (Avery et al, 1960, McDonald, 1962, Cross, 1973).

Role of Oxygen: Hyperoxia or Hypoxia?

As well as the theory of hyperoxia being the cause of ROP, there was an opposite theory which proposed that hypoxia was the underlying cause (Szewczyk, 1952, Rubinstein, 1952). Szewczyk reported that the vasodilation of the retinal vessels seen in the early stages of retrolental fibroplasia could be reversed by increasing the oxygen concentration of the infant's environment. He also reported that withdrawing infants rapidly from an oxygen-enriched environment seemed to be associated with progressive dilatation of their retinal blood vessels which was reversed when they were returned to oxygen. The hypothesis put forward by Rubinstein, an ophthalmologist in Sheffield, was based on clinical, embryological and histological evidence as known at that time. He suggested that the blood supply of the developing retina was precarious and following premature birth, disruption of the normal sequence of vascular growth would result in local anoxia and oedema. This in turn would cause local metabolites to accumulate and these would stimulate vasodilation and vascular proliferation. If adequate circulation was restored then there would be regression of the vascular changes, but if not, then the process would continue and lead eventually to the final stages of retrolental fibroplasia.

In support of hypoxia having a role in the production of ROP, there have been case reports of infants in whom hypoxic events had occurred who were found to have the retinal changes of ROP, such as the child born at 29 weeks gestation with cyanotic congenital heart disease whose measured PaO_2 levels never exceeded 91 mm Hg (Naiman et al, 1979). Intrauterine hypoxia has been suggested as a possible factor, for instance the child whose eyes showed the appearances of ROP who received no extra oxygen after birth but whose mother was very anaemic at delivery (Bruckner, 1968), and the description of

ROP-like changes in the eyes of some anencephalic infants (Addison et al, 1972).

Experimental work on the young of animals such as the cat, dog and rat (Ashton et al, 1953, Patz, 1957) showed that placing these animals in high concentrations of oxygen resulted in retinal vessel changes similar to those seen in early ROP. Ashton and coworkers showed that in kittens, if the exposure to oxygen was short, the vasoconstriction was reversible but if exposure was more prolonged, vaso-obliteration occurred followed by vasoproliferation in a disorganised way. This blood vessel proliferation could result from vasoconstriction causing ischaemia and hypoxia. As the immature retina differentiates and thickens, its metabolic requirements increase and diffusion from the choroid becomes inadequate. During the phase of ROP in which vaso-obliteration occurs, there is disruption to the developing vascular network and consequently there is an increase in the amount of avascular tissue. The stimulus for angiogenesis is thus increased. In later studies Ashton and coworkers showed that the proliferative effect could be produced by occluding the retinal vessels with glass ballotini (Ashton et al, 1965, Ashton, 1966), that is vasoproliferation was not solely an oxygen effect and local hypoxia could be one of the factors involved. It is thought that the hypoxic/ischaemic retina produces an angiogenic factor which stimulates the growth of abnormal vessels (see section on ROP and other proliferative retinopathies). An experiment in which kittens were exposed to 80% oxygen for 65 hours and then recovered in either 21% oxygen (normoxic) or 13% oxygen (hypoxic) environments (Phelps et al, 1984) showed that there was more severe retinal vessel changes in those animals subjected to hypoxic recovery. Factors which are related to the metabolic consequences of hypoxia and circulatory disturbance such as acidosis (Bossi et al 1984, Koerner et al,

1986, Prendiville et al, 1988) and hypercapnia (Flower, 1985, Bauer et al, 1981) are also likely to contribute to the development of this condition.

Oxygen diffuses into the retina from the choroidal vessels as well as through the developing retinal circulation. In hyperoxic states oxygen may therefore diffuse through all the layers of the retina. Experimental detachment of the retina in kittens prevented the vaso-obliterative effect of hyperoxia (Ashton et al, 1954).

In addition, there is some evidence which suggests that oxygen-induced vasoconstriction could be an autoregulatory mechanism which protects downstream capillaries from overperfusion (Dollery et al, 1964, Flower, 1985). However autoregulation could be harmful by causing stagnation and thrombosis (Garner, 1985), thus resulting in ischaemia./hypoxia. Even if autoregulation is occurring retinal oxygenation may reach harmful levels in hyperoxic states by diffusion from the choroidal circulation (Flower, 1985).

It is well-recognised that excessive oxygen is toxic to living tissues (Balentine, 1982). Tissue culture studies have shown that hyperoxia is damaging to growing vascular endothelium from rabbit retina (Tripathi et al, 1974). There is some evidence that damage by hyperoxia is caused by free radicals (Slater et al, 1970, Dormandy, 1978, McCord, 1985, Crowe et al 1986). The response to tissue injury may include the release of factors which may in themselves stimulate new vessel proliferation (Garner et al, 1987).

Monitoring of Oxygenation In Blood
It is well-recognised that ROP may occur in infants who have never had supplemental oxygen, both pre-term and full term (Lucey et al, 1984). At the same time it has been reported that preterm low birthweight infants who have

had periods of sustained hyperoxaemia have not developed ROP (Aranda et al, 1974).

It was realised early on that the level of oxygen in arterial blood was more important than the concentration of oxygen in the inspired air in determining the oxygenation of the tissues (Ashton as cited by Tizard, 1964). With the development of methods of measuring arterial oxygenation, it has gradually become standard practice in neonatal units everywhere to monitor an individual infant's oxygen status. Sampling from the umbilical artery or a peripheral artery provides a measure of arterial oxygenation at a given point in time. More recently, technological advances have introduced methods of monitoring oxygenation more continuously, for instance with an indwelling arterial oxygen-sensitive probe, or with a transcutaneous or saturation monitor. With the ability to measure arterial oxygen levels came the question of whether there was a safe level of oxygen and what that might be (Baum et al, 1970, Tizard, 1971, James et al, 1976).

In a study of 70 infants which attempted to show a correlation between peak arterial O_2 tension (peak PaO_2) and retinal vessel calibre, 16 infants showed retinal vasoconstriction and 2 had early signs of retrolental fibroplasia, which was graded using Patz's modification of the Reese classification (Aranda et al, 1971). In all the survivors, the retinal changes resolved. All the 18 infants had peak PaO_2 between 102 and 398 mm Hg and these authors recommended that a preterm infant's PaO_2 should be maintained below 100 mm Hg (13.3 kPa). A number of other workers (McCormick, 1977, Cantolino et al, 1971, Kingham, 1977) pointed out that it was exceptional to be able to evaluate hyperoxygenation using changes in retinal vessel calibre, and that there was no clear relationship between retinal vessel size and a PaO_2 level measured at the same time. Similarly the 1977 cooperative study of PaO_2 levels and the

occurrence of retrolental fibroplasia (Kinsey et al, 1977) attempted to study the feasibility of relating PaO_2 levels and retinal vessel calibre but this part of the survey was abandoned early on when it became apparent that this procedure was only possible in larger more mature infants because their ocular media were clear.

This second cooperative study (Kinsey et al, 1977) was designed with the main aim of establishing guidelines on the administration of oxygen to preterm infants, with particular attention to PaO_2 levels and the occurrence of ROP. The data were collected between 1969 and 1972 and included the results of arterial blood gas samples obtained from infants who were treated with supplemental oxygen in a number of neonatal centres in the USA. Of the total of 709 infants studied, 66 developed ROP. The analyses of the oxygen data, especially of the PaO_2 values, were very much summarised and it was not possible to use the results to make any recommendations concerning PaO_2 levels and prevention of ROP. In fact, Kinsey et al concluded that the occurrence of ROP was unrelated to PaO_2 levels.

The 1977 cooperative study illustrates the difficulties of interpreting data obtained by intermittent sampling of a variable which in fact is continuously changing. Another difficulty with using the results of samples from umbilical arterial catheters is that the PaO_2 of a sample from a catheter placed in the descending aorta will reflect the postductal oxygen tension and not the preductal level which is more closely related to the oxygenation of the eye and retina. In the absence of an umbilical catheter, arterial blood gas samples become more difficult to obtain and also to interpret, since it is well-recognised that peripheral arterial sampling causes distress and crying which in turn affect the blood oxygenation level. Similarly other procedures carried

out on infants in the neonatal unit have been shown to affect their
oxygenation levels (Long et al, 1980).

Developments in continuous monitoring of oxygenation in neonates together
with developments in microprocessor technology which enable these
continuous data to be handled have been used in a study reported by Bancalari
and Flynn (Bancalari et al, 1987). In this study transcutaneous monitors were
used and infants were placed in either a continuously monitored group or in a
standard care group. The infants in the latter group were monitored whilst
being given $FiO_2 > 0.4$ or when their clinical state indicated. These workers
found that ROP was reduced in infants with birthweight >1000 gm who were
continuously monitored compared to those of similar birthweight who had
standard monitoring. However there was no difference in the occurrence of
ROP in infants weighing <1000 gm at birth whether they were continuously
monitored or not.

It has been pointed out by a number of workers that the PaO_2 in a fetus is
considerably less than that measured after birth, and that breathing air may
cause some susceptible preterm infants to experience relative
hyperoxygenation (MacMahon et al, 1986). These workers described an infant
who developed ROP in spite of continuous monitoring of PaO_2 and a maximum
recorded level of 95 mm Hg (12.7 kPa). As a possible means of preventing ROP
they considered the use of low inspired oxygen concentrations to maintain the
PaO_2 levels below 80 mm Hg and yet be sufficient to prevent the occurrence of
respiratory acidosis. They described the results of treating four preterm
infants in this way, using an oxygen/nitrogen mixture. The mean duration of
low oxygen treatment was 56 hours. None of the four developed ROP. However
they observed that even during this treatment there were a number of
occasions recorded when PaO_2 exceeded 80 mm Hg.

Animal models of ROP

The use of animal models in the study of this condition has been reviewed
(Gole, 1985). Animals studied have been the kitten, puppy, and the young of
rats, mice and rabbits.

Kitten

The most studied has been the kitten, whose retinal vasculature at birth is at a
stage of development which is roughly equivalent to that of a 28-week
gestation human. The oxygen-induced retinopathy produced in the kitten was
the basis of most of the earliest laboratory work into the pathogenesis of ROP.
As described in earlier pages, oxygen causes vasoconstriction in the
developing vessels of the kitten retina and obliteration of capillaries if the
exposure is prolonged. If the animals are removed from the oxygen-enriched
environment, proliferation of new vessels occurs within the retina and into
the vitreous, sometimes with the occurrence of arteriovenous shunting and
haemorrhages. During the proliferative stage, iris vascular engorgement and
pupillary rigidity identical to that seen in the human disease may also occur.
The effect of oxygen on kitten retinal vessels continues only until the
vasculature is mature. However the major difference between the kitten
model and the human disease is that retinal detachment does not develop in the
kitten. Although the retinal vascular pattern is never completely normal,
regression of the neovascularisation occurs over a period of months in the
kitten.

Rat

Unlike most other experimental mammals, the rat shows little or no retinal
vessel development until or shortly before birth. Although the immature
retinal vessels of the rat show vaso-obliteration in response to 80% oxygen
they do not show abnormal proliferation. Retinal detachment does not occur.
This model is therefore useful for studying the effects of hyperoxia on
immature vessels but not for the study of proliferative retinopathy.

Mouse

The developing retinal circulation in the mouse is similar to that of the rat. The retinal vascular maturity of the mouse at birth is equivalent to that of a 4-month gestation human. Exposure of newborn mice to 98%-100% oxygen for several days produces obliteration of the posterior capillary bed. When the animals are returned to room air, dense vasoproliferation occurs with overgrowth into the vitreous. In some of the animals there is also engorgement of the tunica vasculosa lentis, haemorrhages into the vitreous and the anterior chamber, and retinal folding. These oxygen-induced appearances are similar to those seen in ROP. However, similarly to the rat and the kitten models, retinal detachment does not occur in the mouse.

Rabbit

Although the retinal vascular pattern in the rabbit differs from that of other mammals, the developing retinal vessels can be obliterated by oxygen. After oxygen exposure, a distorted growth of new vessels occurs which ultimately regresses, but never becomes normal. One of the advantages of the rabbit model is that the growing vascular complex can be easily removed intact from the eye and cultured, so that in-vitro studies on the effects of oxygen have been possible. The rabbit model is also one of the few models in which oxygen causes damage to the visual cells. Like the other animal models, retinal detachment has not been shown to occur in the rabbit.

Dog

Similar to the kitten model, exposure of puppies to extra oxygen has produced vasoconstriction of retinal vessels, followed by dilation and tortuosity of the vessels, retinal haemorrhages and oedema, and vitreous opacities, and some have developed retinal detachments. Dogs are known to develop spontaneous retinal detachments, so it is possible that the puppy eye could be a suitable model for the more severe forms of ROP. It has been reported that beagle puppies treated with aspirin and exposure to 95% -100% oxygen showed more

severe retinal changes including the presence of falciform retinal folds than untreated animals.

As described above, none of these models are entirely satisfactory as they do not reproduce the progression of acute to cicatricial ROP.

NEONATAL EVENTS AND ROP

There have been many reports in the literature of various events in the neonatal period and their association with ROP (Lucey et al, 1984). Only a few of these events will be considered here, in relation to this thesis.

Cranial Ultrasound Appearances

Since the retinal and cerebral circulations and the development of both the brain and the eyes are so closely related, it is not surprising that several studies of ROP have included consideration of cerebral events. Intraventricular haemorrhage (IVH) has been reported to be associated with ROP by several workers (Procianoy et al, 1981, Flynn, 1983, Biglan et al, 1984, Purohit et al, 1985, Hammer et al, 1986, Hungerford et al, 1986, Brown et al, 1987, Prendiville et al, 1988, Brown et al, 1990, Darlow et al, 1992). In the earliest description (Procianoy et al, 1981), IVH was diagnosed on CT scan or on clinical criteria. In their survey, 12 infants of birthweight <1500 gm developed cicatricial ROP and 9 of them had IVH compared with 23 infants with IVH in the group without ROP (n=126). More recently the development of ultrasound techniques to visualise the brain in preterm infants has made it possible to diagnose IVH at an early stage and has also shown other abnormalities before symptoms have been manifest eg ventricular dilatation, periventricular leucomalacia (Levene et al, 1985). An association has been reported between evidence of hypoxic-ischaemic brain injury on CT scan or cranial ultrasound scan and the occurrence of ROP (Hungerford et al, 1985)

and a paper from our group (Ng et al, 1989) has described findings of severe periventricular leucomalacia and severe acute ROP in six preterm infants. Ventricular dilatation has been mentioned specifically in one study (Prendiville et al 1988) in which it was found not to be significantly associated with ROP. Otherwise there is little in the literature concerning cranial ultrasound appearances and their relationship to ROP.

Convulsions/Seizures

Seizures may be associated with intracranial events such as IVH, and it might be expected that there could be a relationship between these and ROP. Whilst some workers have described an association between ROP and the occurrence of seizures (Biglan et al, 1984, Brown et al, 1987) others have not found there to be one (Hammer et al, 1986).

Persistent Ductus Arteriosus (PDA)

Since the presence of a PDA may affect the cerebral and hence the retinal circulations, particularly if there are clinical signs of circulatory strain, it has been suggested that there may be a relationship between the development of ROP and PDA. A number of studies have suggested that there is an association (Katzman et al, 1982, Flynn, 1983, Biglan et al, 1984, Purohit et al, 1985, Hammer et al, 1986, Darlow et al, 1992). Others have reported that there is no significant association (Yu et al, 1982, Brown et al, 1987, Prendiville et al, 1988). Since the signs of cicatricial ROP are often asymmetrical although the acute disease is usually symmetrical it is tempting to speculate whether the presence of a PDA and its haemodynamic consequences bears any relationship to this difference between the acute and scarring stages of ROP. There is very little in the literature which addresses this question.

Duration of Assisted Ventilation

With the development of assisted ventilation techniques for supporting preterm infants with respiratory difficulties, particularly from respiratory distress syndrome, several studies from neonatal intensive care centres have reported an association between the duration of ventilation and ROP (Shahinian et al, 1978, Gunn et al, 1980, Flynn, 1983, Bossi et al, 1984, Hammer et al, 1986, Hungerford et al, 1986, Brown et al, 1987, Prendiville et al, 1988, Darlow et al, 1992). Ventilator treatment for more than 28 days has been reported to be significantly associated with ROP (Brown et al, 1990). Other workers have not found such an association (Yu et al, 1982, Shohat et al, 1983, Koerner et al, 1986).

Duration of Oxygen Treatment

Several studies have shown a significant association between the time spent in added oxygen and the development of ROP (Gunn et al, 1980, Sacks et al, 1981, Flynn, 1983, Bossi et al, 1984, Hammer et al, 1986, Hungerford et al, 1986, Prendiville et al, 1988, Darlow et al, 1992). Other workers have shown that there is no difference in duration of oxygen treatment in infants with or without ROP (Yu et al, 1982). In other studies when the duration of oxygen therapy has been controlled for, other factors then appear to become significant (Sacks et al, 1981, Flynn, 1983, Biglan et al, 1984, Bossi et al, 1984, Purohit et al, 1985, Hammer et al, 1986).

Apnoeas

A number of investigators have reported an association between the occurrence of apnoeas and ROP (Flynn, 1983, Purohit et al, 1985, Hungerford et al, 1986, Hammer et al, 1986, Brown et al, 1987). Others have considered only those apnoeic episodes which have required resuscitation (eg with bag and mask) and have also found an association between these and ROP (Gunn et

al, 1980, Katzman et al, 1982, Shohat et al, 1983, Darlow et al, 1992). The concentration of oxygen given during resuscitation has not been stated except in the study reported by Shohat and colleagues (Shohat et al, 1983) in which they stated that there was no difference in the oxygen concentration given with bag and mask treatment of apnoea compared with that which the infant was being given otherwise.

Bradycardias

A few studies have described an association between the occurrence of bradycardias and the development of ROP (Flynn, 1983, Brown et al, 1987). One study reported that bradycardias on their own did not have an effect on the occurrence of ROP but there was an association if linked with apnoeic spells (Purohit et al, 1985).

Blood Transfusions

Replacement or top-up transfusions are frequently given to preterm infants, especially to those who are ill. Since replacement transfusions are always of adult blood, there is a possibility that increasing the proportion of adult haemoglobin and thus the oxygen-carrying capacity will produce the effects of hyperoxaemia on tissues including the retina (Lucey et al, 1984). With the developments in neonatal intensive care, several workers have reported an association between ROP and transfusions (Gunn et al, 1980, Sacks et al, 1981, Yu et al, 1982, Flynn, 1983, Shohat et al, 1983, Biglan et al, 1984, Bossi et al, 1984, Hammer et al, 1986, Prendiville et al, 1988, Darlow et al, 1992). One study has however reported that transfusions were not significantly associated with ROP (Brown et al, 1987).

UNIVARIATE and MULTIVARIATE ANALYSIS IN ROP STUDIES

Until the last decade, analysis of the possible factors associated with ROP has been of the univariate type, i.e. considering the variable on its own in relation to the outcome. However each variable may be dependent on several others and its contribution to the outcome may in fact be dependent on the effect of these other factors (confounding variables).

To overcome these difficulties which are common to many medical and biological conditions, statisticians have devised methods of identifying independent variables, using techniques such as multivariate regression analysis. Some of the limitations of multivariate analysis have been explained clearly by Davey Smith and Phillips (Davey Smith et al, 1992).

A number of authors have used these models to attempt to identify the independent variables associated with ROP (Flynn, 1983, Bossi et al, 1984, Hammer et al, 1986, Koerner et al, 1986, Ng et al, 1988, Prendiville et al, 1988, Brown et al, 1990, Darlow et al, 1992). In almost all of these studies, either birthweight or gestational age or both appear as the most powerful independent variables.

However when it comes to other independent variables, there is much less agreement.

Flynn was the first to use multivariate analysis in the study of ROP (Flynn, 1983). He studied 639 infants of birthweight $\leq$ 1500 gm. and used paediatric data from a retrospective survey of their charts. The outcome variable was the presence of acute proliferative ROP and he used univariate analysis and then a method of multivariate analysis called logistic risk analysis. In his study Flynn stratified the infants into three birthweight groups, those weighing

< 1000 gm., those weighing 1000 - 1249 gm. and those weighing 1250 - 1500 gm. In this study, the smallest infants appeared to have the least number of independent variables associated with the risk of occurrence of ROP (race, apnoeas/bradycardias) although as Flynn pointed out they were much more likely than the larger infants to have all the medical conditions of preterm birth, such as respiratory distress syndrome, prolonged ventilation and exposure to extra oxygen, intraventricular haemorrhage and numerous blood transfusions.

For the bigger infants in the study there were several significant variables associated with the risk of ROP occurring (birthweight, female sex, apnoeas/bradycardias, duration of ventilation, gestational age). Flynn suggested that although they are less likely to suffer the medical complications of premature birth, when they do, their risk of developing ROP is increased. The variable of duration of ventilation could be considered to be a marker of such illness, since infants with conditions such as respiratory distress syndrome and apnoeas/bradycardias often require ventilation.

Bossi and coworkers (Bossi et al, 1984) analysed the data from a cohort of infants with ROP, matched with control infants for gestational age, birthweight, date of birth and hospital unit (total of 57 pairs studied). Univariate analysis to test the difference in frequency of the various variables in ROP infants compared with controls, as well as multiple linear regression analysis using a backward elimination procedure was used, with an outcome variable of severity of ROP. The same variables which were selected on pathophysiological grounds were used in both analyses. The results of the univariate analyses gave significance to a number of variables which were not demonstrated in the multiple regression analysis. Six significant variables were found on the regression analysis: acidosis (pH < 7.25), multiple birth,

PaCO$_2$ < 30 torr (negative partial correlation), high FiO$_2$ levels, total duration of ventilation, and birthweight. The variables of acidosis, low PaCO$_2$, high FiO$_2$ and duration of ventilation could be considered to be "illness" variables - measures of the metabolic consequences of and interventions of illness. The infants studied by Bossi et al had birthweights within the range of < 1500 gm. to > 2500 gm. and were selected by different criteria to those used by Flynn.

In their study, Hammer and colleagues (Hammer et al, 1986) used a stepwise logistic regression analysis. They studied 328 infants who had had ophthalmic examinations. They had wide inclusion criteria, including those infants who had extra oxygen for more than eight hours so that their cohort ranged in birthweight from 630 to 4150 gm. Like other authors, they used univariate analysis to determine possible significant variables which were then entered into the regression analysis. The outcome variable was acute ROP. Ventilator time was found to be the most highly correlated with acute ROP, followed by xanthine administration, birthweight and maternal bleeding. They noted that when ventilator time was entered into the model and its effect controlled for, then several of the highly significant covariables found on univariate analysis lost their significance (such as hours in oxygen). These workers pointed out that the stepwise procedure may have overestimated the significance of some of these factors and the results should be interpreted with caution. Once again birthweight and duration of ventilation were associated with the occurrence of ROP.

Further work by Koerner and coworkers (Koerner et al, 1986) using data from the same cohort studied previously (Bossi et al, 1984) employed linear regression analysis to examine the effect of gestational age on the predictive value of certain variables on the severity of ROP. Entering the same variables into the model for each of the two gestational age groups (those infants < 32

weeks and those of 32 - 40 weeks) they found that there was a difference in the results. In the less mature group, the significant variables were acidosis (pH < 7.25), hyperoxia (PaO_2 > 100 torr), gestational age, $PaCO_2$ fluctuations, and multiple birth. The number of low $PaCO_2$ levels showed a negative correlation. By contrast, the significant variables in the more mature group were multiple birth and acidosis. Neither high FiO_2 levels, transfusion, mechanical ventilation nor hypercapnia seemed to be significant in either group. These workers suggested that these results demonstrated that the significance of these variables in the development of ROP is affected by the maturity of the retina.

A prospective study reported from the Hammersmith Hospital, London, (Prendiville et al, 1988) considered 34 possible risk factors in the development of ROP. These workers used stepwise logistic regression analysis to determine the independent variables associated with two outcome variables, namely, the development of ROP and its progression to stage 3 or 4 disease. 117 infants of < 31 weeks gestation were studied. The variables which were found to be independently associated with the development of ROP were acidosis (number of episodes of pH < 7.2), gestational age, and the number of episodes when PaO_2 > 12 kPa. Acidosis, PaO_2 > 12 kPa, and the occurrence of pneumothorax in the period before the appearance of stage 1 ROP were independently associated with the development of advanced disease. However, after the appearance of stage 1, there was no difference in exposure to any of the risk factors between the infants with mild disease and those with advanced disease. From their results these authors thought that it was the severity of the early insult to the retina rather than prolonged or later insults which determined progression of the disease.

Another prospective study (Brown et al, 1990) used multivariate analysis, considering only birthweight, oxygen exposure (number of days), ventilator treatment (number of days) and intraventricular haemorrhage (cranial ultrasound, Papile classification). Each of these four variables was examined whilst simultaneously controlling for the other three. In this analysis it was found that ventilator time was the only significant variable which was associated with severe ROP. The authors suggest a number of possible reasons for this, and make the point that a large number of covariates can be associated with ROP when the analyses are not controlled for confounding variables.

In a prospective study carried out in New Zealand which comprised all infants born in that country in 1986 who weighed < 1500 gm., risk factors for ROP were studied using multiple logistic regression analysis (Darlow et al, 1992). These workers found three variables which made statistically significant independent contributions to the risk of developing any acute ROP. These were gestational age, principal hospital caring for the infant, and treatment with indomethacin. The risk of developing stage 2 or more ROP was associated with two independent variables, which were gestational age and hospital.

These papers demonstrate the difficulties of identifying independent variables amongst all those which could be considered since many of these variables are markers of illness and are thus interrelated. The results of such analyses also depend to some degree on which variables are chosen for inclusion in the multivariate model.

CHAPTER 2 - METHODS

At the time this study was undertaken, all the ophthalmic examinations in the five neonatal units serving Leicester, Nottingham and Derby were carried out by one ophthalmologist, Mr Fielder. Within the time available on the project grant, and taking into account the likely number of preterm births it was thought that a prospective survey of 500 infants would be possible. The project was funded by the Medical Research Council and ethical permission was obtained from the ethical committees of the Leicester, Nottingham and Derby hospitals for this work to be carried out. Between July 1st 1985 and May 31st 1987 infants admitted to each of these five units were included in the study if they had a birthweight of 1700 gm or less and survived at least three weeks, which was the age at which the first eye examination took place. Birthweight was chosen as criterion of prematurity for entry into the study because it is an objective measure. Gestational age was more difficult to be precise about, there being a number of different ways of assessing it, and therefore it was thought not to be sufficiently clearcut to be an entry criterion. In this study the gestational age recorded was that which fitted all the available information from the mother and from obstetric records. If there was a discrepancy, a clinical assessment was made using the method described by Dubowitz and colleagues (Dubowitz et al, 1970).

Ophthalmological Examinations

The protocol for these was drawn up by Mr Fielder who carried out all the examinations. The first examination was carried out at 3 weeks of age. Subsequent examinations were performed at weekly intervals while the infant was on the neonatal unit, fortnightly after discharge until the age of 12 weeks, and thereafter as clinically indicated. A final assessment was performed at 6 months corrected age (that is corrected for prematurity, therefore age is

calculated from estimated date of delivery). Retinal examination was carried

out by indirect ophthalmoscopy after pupillary dilatation with cyclopentolate

0.5% with or without phenylephrine 2.5% eyedrops. Before the age of 12

weeks, topical anaesthesia, an eyelid speculum and scleral indentor were also

used to rotate the eye and allow the peripheral retina to be examined over its

entire circumference. The findings of each examination were recorded on a

standard form (appendix 1) according to the international classification of ROP

(Committee for the classification of ROP, 1984) for the acute stages and the

Reese classification (Reese et al, 1953) for cicatricial disease (see table).

Epidemiological   Study

For this part of the project, infants who satisfied the entry criteria and whose

mothers lived within the boundaries of Leicestershire, Nottingham and

Southern Derbyshire Health Authorities were studied. Demographic

information for each infant was collected on a standard form (appendix 2). To

identify any eligible infants born during the study period who had not been

examined, health authority birth notification data (birthweight specific) were

reviewed.

Paediatric   Factors   Study

All infants who fulfilled the entry criteria and for whom paediatric data were

available were studied in this part of the survey. It was planned that

paediatric data would be collected for each infant who was entered in the

project. Unfortunately because of illness I lost some time and the infants who

were entered during this period did not have paediatric data collected.

Demographic information, details of the antenatal and intrapartum periods

and neonatal events including blood gas and biochemical results were

recorded using a standard form (appendix 2). The information was obtained

from hospital records, medical and nursing observation charts and from the

mothers of the infants (maternal questionnaire, appendix 3) . The data were collected by myself with help later on in the study from two assistants. None of us were involved in the clinical management of the infants and since this was a prospective study we were unaware of the ophthalmic status of the children. Data were collected for the duration of the infant's stay in these units, up to a maximum of 12 weeks.

Perinatal data

Information regarding the course of pregnancy was obtained from antenatal records. In particular, data regarding maternal health, evidence of pregnancy-induced hypertension, antepartum haemorrhage and maternal drug ingestion were recorded. Information about the labour and delivery was also obtained from the mother's records, for example whether fetal distress was noted (presence of persistent dips in fetal heart rate, meconium-stained liquor, fetal pH measurements if done), type of delivery, Apgar scores at 1 and 5 minutes, and whether resuscitation was given.

Neonatal Data

1)   Cranial ultrasound examinations

Cranial ultrasound scans were carried out at three of the neonatal units (Leicester Royal Infirmary, Nottingham City Hospital, Derby City Hospital). At Leicester Royal Infirmary (LRI) and Nottingham City Hospital (NCH) an ATL Mark 3 real-time sector scanner fitted with a 5 MHz and 7.5 MHz scanhead were used and at Derby City Hospital (DCH) a GE scanner with a 5 MHz scanhead was used. At NCH and at DCH the scans were performed once a week by one observer (myself) for the first four weeks and then at 4 week intervals with a final scan at discharge. At LRI where there was a major research interest in neonatal cranial ultrasound scanning, examinations were sometimes performed more frequently and there was more than one observer doing the

scans. The findings were recorded onto video tape or on Polaroid film and were graded (see table) using the method of Levene for haemorrhage and ventricular dilatation (Levene, 1981). Periventricular leucomalacia (PVL) was scored as described by Trounce (Trounce et al, 1986).

2) Ventilation

Nursing observation records were scrutinised for details about the ventilatory support given - duration and type of support (intermittent positive pressure ventilation IPPV, intermittent mandatory ventilation IMV, continuous positive airways pressure CPAP), settings of the ventilatory support as a reflection of severity of the respiratory disease, amount of oxygen requirement as expressed by the fractional inspired oxygen (FiO_2), and the duration of oxygen supplementation as well as the number of days spent at different FiO_2.

3) Oxygen

In addition to the details described in 2), I recorded the number of intubations carried out with each infant during each week that the infant was on the neonatal unit, up to the first 12 weeks after birth. At the time of this study, none of the neonatal units were yet fitted with a system which could deliver the same oxygen concentration through the resuscitation equipment as that which the infant was receiving through the ventilator. Therefore I thought it would be important to know how frequently each infant was receiving 100% oxygen during reintubations. For similar reasons, any episodes of apnoeas (lasting longer than 15 seconds), bradycardias (heart rate < 80 per minute) or cyanosis (unrelated to apnoea or bradycardia) which required oxygen were recorded, as well as the age at which these occurred. The method of monitoring the infant's oxygenation was recorded, whether continuously through an umbilical arterial catheter with oxygen probe (Searle), or semi-

continuously with a transcutaneous oxygen monitor ($TcPO_2$) or intermittently with a peripheral arterial line. All blood gas results were recorded, whenever a sample was taken, and simultaneous readouts from the continuous oxygen monitors were also noted if these were in use. An attempt was also made to record all $TcPO_2$ readings.

4) Neonatal illness

Respiratory illness was recorded by type of initial disease, for example idiopathic respiratory distress syndrome (IRDS), pneumonia, meconium aspiration.

Whether a pneumothorax occurred in the first four weeks of life was also noted together with the timing, the side of the air leak, and the number of drains required for adequate treatment.

Jaundice was noted by recording the maximum serum bilirubin levels during the first three weeks after birth, and the duration of phototherapy.

Transfusions were recorded, the volumes of both blood and plasma and when they were given. In addition the haemoglobin was noted whenever a sample was taken.

Convulsions were recorded whenever they occurred, using clinical criteria. The presence of a persistent ductus arteriosus which required treatment was noted, as well as the type of treatment (fluid restriction, indomethacin or frusemide, or surgical ligation) and the age when treatment was started.

Biochemical data relating to plasma levels of sodium, potassium, urea, creatinine and calcium were noted. Hypoglycaemia (BMstix < 1.1 mmol) was also recorded, as was information relating to feeding and drugs.

Statistical   Analyses

The data were coded (appendix 4) and analysed initially using the statistical package SPSS. Only data for the first 3 weeks of life were used because after this time many infants were discharged from hospital and because this was the time at which the first ophthalmological examination took place. The association between 33 paediatric variables (Table 28) and both the incidence and worst stage of ROP was initially analysed using univariate tests (Kruskal-Wallis analysis of variance, the Mann-Whitney test or X^2 test as appropriate).

Variables thus found to be significant at the 1% level (reduced from conventional 5% level because of multiple tests) were then entered into an appropriate multivariate model: dichotomous logistic regression, using the statistical package GLIM, for incidence of ROP; and ordinal logistic regression with the proportional odds model (McCullagh, 1980), using the statistical package PLUM, for stage of ROP. A stepwise procedure was employed whereby at each stage a variable was added to the model if it was significant at the 5% level, or deleted if it was not.

Similar analyses were perfomed for a further 2 variables (abnormal cranial ultrasound and number of blood gases) on the reduced numbers (n=288 and n=257 respectively) for whom these data were available.

Classification of ROP

Acute ROP (Committee for the classification of retinopathy of prematurity, 1984)

stage1	demarcation line lying within the plane of the retina at the junction of the vascularised and avascular retina
stage 2	ridge; the demarcation line extends out of the plane of the retina
stage 3	ridge with extraretinal fibrovascular proliferation
stage 4	retinal detachment

Cicatricial ROP (Reese et al, 1953)

stage 1	small mass of opaque tissue in the periphery of the fundus without visible retinal detachment
stage 2	larger mass of opaque tissue in the periphery of the fundus with localised retinal detachment; some retinal traction may be present
stage 3	large mass incorporating a traction retinal fold to the optic disc
stage 4	retrolental tissue covering part of the pupillary area
stage 5	retrolental tissue covering the entire pupillary area

Grading of Cranial Ultrasound Findings

Periventricular leucomalacia (PVL) (Trounce et al, 1986)

grade 0   no visible changes

grade 1   persistent "flare"; an echodensity in the periventricular area
           persisting for more than 2 weeks

grade 2   precystic PVL; a triangular echodense area with its apex lying at
           the lateral border of the lateral ventricle

grade 3   cystic PVL; resolution of the echodensity in grade 2 to form
           discrete echofree cavities, representing cyst formation

Haemorrhage (Levene et al, 1985)

grade o   no haemorrhage

grade 1   germinal layer haemorrhage; echoes in and around the region of
           the germinal matrix

grade 2   intraventricular haemorrhage; echoes within the lateral
           ventricles with distension or formation of an intraventricular clot

grade 3   parenchymal haemorrhage; an echodense area involving the
           ventricle and the surrounding parenchyma. There is complete
           loss of the outline of the ventricular structures.

Ventricular dilatation (Levene, 1981)

grade 0   no dilatation

grade 1   transient dilatation

grade 2   persistent but non-progressive dilatation; ventricular index
           increasing above the 97th centile but then arresting and
           following a normal rate of growth

grade 3   progressive dilatation requiring treatment; ventricular index
           rapidly increasing and crossing the 97th centile, such that
           treatment was given

grade 4   persistent asymmetrical dilatation

CHAPTER 3 - RESULTS OF EPIDEMIOLOGICAL STUDY

505 infants satisfied the entry criteria and were studied. The median gestational age was 31 weeks (interquartile range 29-33 weeks; figure 1) and the median birthweight 1410 gm (interquartile range 1140-1560 gm; figure 2).

Over the study period 3492 examinations were carried out, 2451 (70.2%) during the first 12 weeks of life. Of the latter, a speculum and scleral indentation were used in 2419 (98.7%). 476 babies (94.3%) were seen two or more times and 279 (55.2%) were examined five or more times in that initial 12 week period (figure 3).

Acute ROP developed in 248 (49.1%) of the 505 infants. The maximum stages reached (table 1) were: stage 1 in 150 infants (29.7%), stage 2 in 77 (15.2%), stage 3 in 19 (3.8%), and stage 4 in 2 (0.4%). The distributions of the maximum stages of acute disease according to gestational age and birthweight are shown in figures 1 and 2. Greater severity of acute ROP is significantly associated with a low gestational age or birthweight. Resolution of acute ROP was complete in all 277 infants with stage 1 or 2 disease.

Ideally, cicatricial ROP is determined at 4-6 months corrected age, but this was not always possible in this study; 81 infants were lost to follow-up before 4.5 months corrected age, including 20 who died. Cicatricial disease had already developed in 1 infant who died at 3 months corrected age; he is included in the cicatricial group. The risk of cicatricial changes developing for the remaining 60 infants was assessed as follows. For 14, outcome was uncertain owing to an insufficient number of examinations. 37 were known to be normal and not at risk - either acute ROP had undergone complete resolution, or the retina had become fully vascularised without retinopathy developing.

A further 9 were presumed normal since mild ROP (stages 1 or 2) was resolving at the time of the last examination. Thus adequate information was available on 471 of the original 505 infants.

Although resolution occurred in 16 of the 21 infants with acute stage 3 or 4 ROP, cicatricial ROP developed in 5 (1.1%) infants (nine eyes) in this group (table 2); 1 infant had cicatricial disease in only one eye. Cicatricial changes were seen in 2.0% of those with acute changes, and 23.8% of infants with stage 3 or 4 disease. One eye of 1 infant was treated by retinal cryotherapy; this eye subsequently progressed to stage 3 cicatricial disease. No infant is blind because of ROP.

Review of birth notification data from Leicestershire, Nottingham, and Southern Derbyshire Health Authorities revealed a total of 42 infants of birthweight 1700 gm or less, who had not been examined but met the maternal residence criteria for this study. None of these infants had been admitted to the neonatal units in the study area; they either had not been admitted to hospital or, being resident near a county border, had been cared for in a unit outside the study area. There was 1 infant of birthweight 751-1000 gm, 18 of 1001-1500 gm, and 23 of 1501-1700 gm. The birthweight-specific incidences of ROP found in the examined babies were applied to these 42 infants. From these calculations an estimate was made of the incidence and severity of ROP for the total population of 547 infants of birthweight 1700 gm or less in this geographically defined area. With the corrected estimate for the 547 infants, the estimated incidence of acute ROP in this area was 48.4% (264.8 infants), reaching a maximum of stage 1 in 162.3 (29.7%), stage 2 in 80.8 (14.8%), and stage 3 or 4 in 21.7 (4.0%) infants. The incidence of cicatricial ROP was 1.0%.

There was no significant difference in acute ROP data between boys and girls (table 3).

Data were also analysed according to ethnic origin. Of the cohort of 505, 402 (79.6%) were caucasian (both parents), 64 (12.4%) were Asian (both parents) or Asian-caucasian mixed (n=4), and in 24 (4.8%) at least one parent was black. The remaining 15 infants (3.0%) were oriental or other race not mentioned above, or this information was either missing or unknown. Arbitarily, mixed matings were grouped as Asian or black on the basis of one parent. Prematurity distributions for caucasians and Asians did not differ significantly. For a fixed gestation Asians were not smaller than their caucasian counterparts. Median gestational ages for caucasian, Asian and black groups were 31.0. weeks, 31.0 weeks and 29.5 weeks, and median birthweights 1420 gm, 1410 gm and 1400 gm respectively. Acute ROP developed in 50.2% of caucasian infants, 48.4% of Asian infants and 37.5% of black infants (table 3). There was a disproportionate tendency for stage 3 or 4 disease to develop in Asian infants (14.1% vs 2.7% in caucasians). Of the 4 infants with mixed caucasian-Asian parentage, the mother was caucasian in 2; stage 3/4 disease developed in 1 infant of each combination. Although prematurity distributions for caucasians and Asians did not differ significantly, any slight difference must be controlled for. A table of frequencies for the 490 infants (excluding the 15 from small ethnic groups), subdivided by stage of worst ROP, gestational age group, and ethnic origin, was produced and various log-linear models were fitted. When all other significant associations in the table were taken into account, the stage of ROP was significantly related to the race of the infant ($X^2 = 15.56$, 6df).

To determine the survival rate for caucasians and Asians, the data relating to the number of infants within our birthweight category who died before the 3

weeks of age and therefore did not enter the study were analysed. 466 Asian and caucasian infants survived 3 weeks and 118 did not (10 Asian), giving crude estimates of 3 week survival in the two groups of 78.8% and 86.5% respectively. Again controlling for any differences in prematurity (birthweight and gestational age), survival to 3 weeks was significantly associated with the race of the infant (logistic regression Asian infants survive better p = 0.04). From the model an estimate of the relative risk of Asian to caucasian 3 week survival was obtained, which was 2.5 with a 95% confidence interval of 1.05 - 5.92. Thus, for the same degree of prematurity Asian infants are on average 2.5 times more likely than caucasian infants to survive this period.

Figure 1 - Presence and stage of ROP according to gestational age group
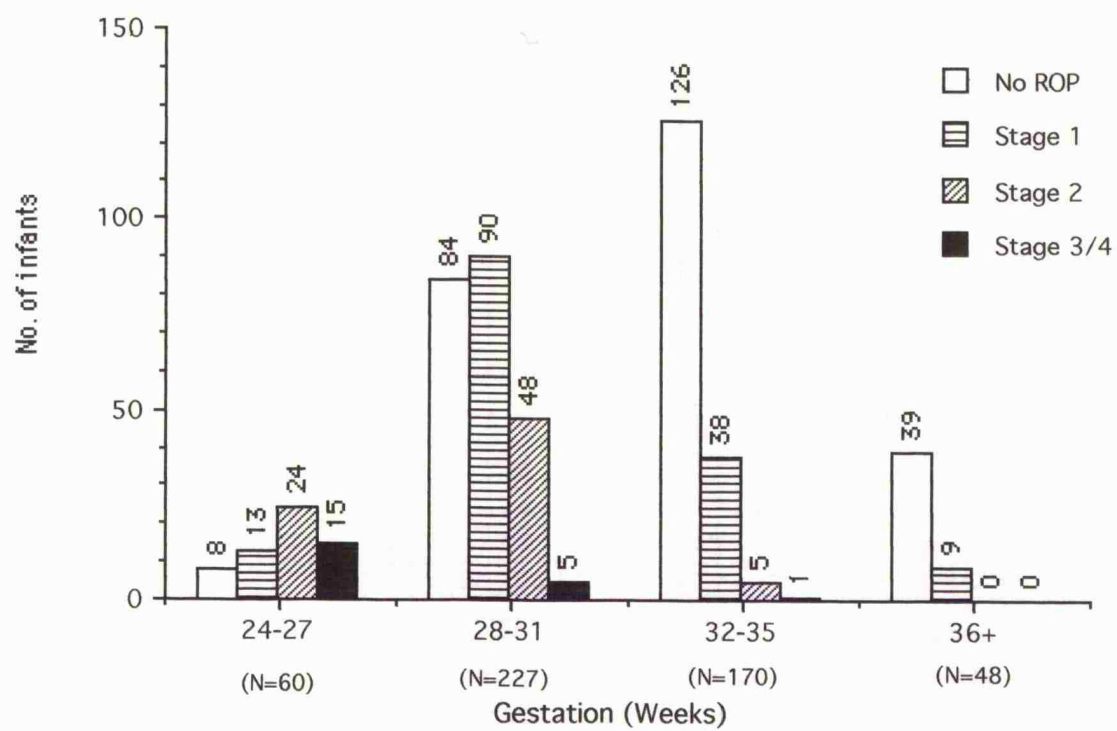
Figure 2 - Presence and stage of ROP according to birthweight group
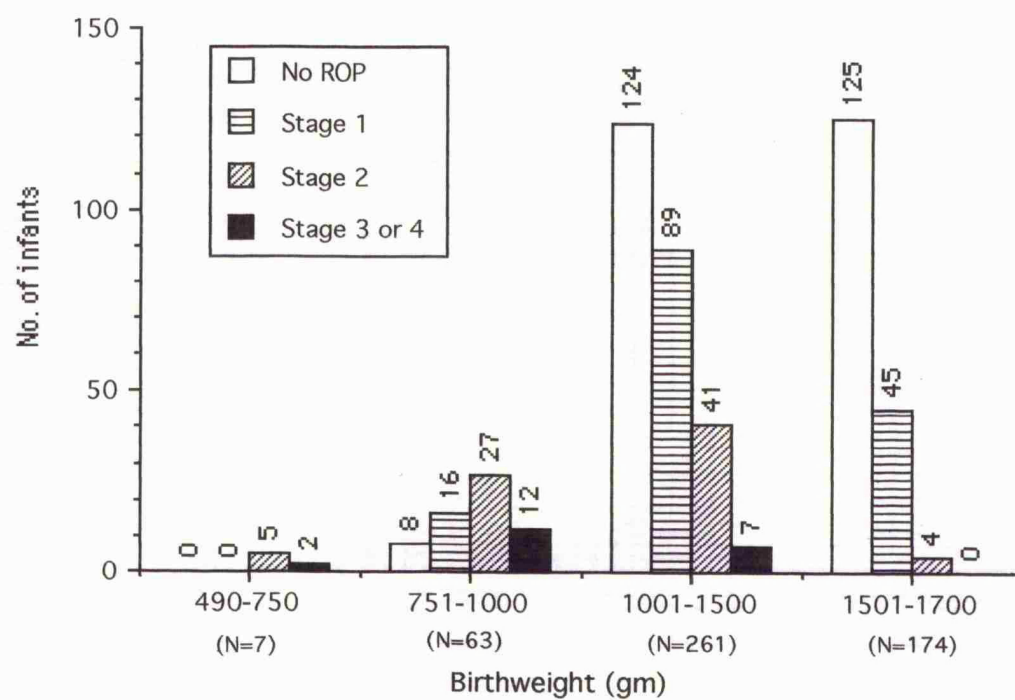
Figure 3 - Number of eye examinations in first 12 weeks of life
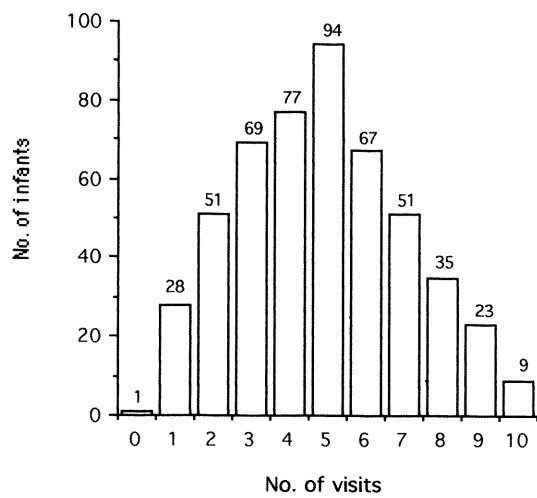
Table 1 - Maximum stage of acute ROP reached in 248 infants (n=505)

Acute ROP	No of infants (%)
1	150 (29.7%)
2	77 (15.2%)
3	19 (3.8%)
4	2 (0.4%)

Table 2 - Grade of cicatricial ROP in 5 affected infants

Infant	Birthweight (gm)	Gestational age (weeks)	Grade cicatricial ROP Right	Left
1	910	26	2	3
2	1300	27	3*	0
3	880	25	3	1
4	1180	28	3	1
5^	990	27	3	2

* Cryotherapy carried out. ^ Died aged 3 months corrected age.

Table 3 - Acute ROP according to sex and ethnic origin

	Number (%) with acute ROP of stage			
Sex	0	1	2	3/4
Male	133 (48.2%)	85 (30.8%)	45 (16.3%)	13 (4.7%)
Female	124 (54.1%)	65 (28.4%)	31 (14.0%)	8 (3.5%)
Ethnic origin				
Caucasian	200 (49.8%)	129 (32.1%)	62 (15.4%)	11 (2.7%)
Asian	33 (51.6%)	11 (17.2%)	11 (17.2%)	9 (14.1%)
Black	15 (62,5%)	6 (25.0%)	2 (8.3%)	1 (4.2%)
Total*	257 (50.9%)	150 (29.7%)	77 (15.2%)	21 (4.2%)

* Includes 15 infants from small ethnic groups or whose origin was unknown.

CHAPTER 4 - DISCUSSION OF RESULTS OF EPIDEMIOLOGY STUDY

The results of this study, the first prospective epidemiological study of ROP in the UK for over 35 years, show that acute ROP is common, affecting almost half of the study infants, with a significant association between severity and shorter gestation. Fortunately, most acute ROP underwent complete resolution and cicatricial ROP developed in only 2.0% of those with acute retinopathy.

There is almost no information available on the epidemiology of ROP (Alberman, 1985). In the UK the most recent survey prior to this one was undertaken in 1953 before the modern era of neonatal intensive care (Medical Research Council, 1955). Its results cannot be directly compared with recent findings, since examination techniques, ROP classification, and the nature of the preterm population have all changed substantially. Two retrospective community-based studies of low birthweight survivors have been carried out in Canada (Saigal et al, 1982 and 1984). Ophthalmology was only one aspect of these studies and the acute findings cannot be directly compared with ours because they used a different classification system. The first study (Saigal et al, 1982) of infants with birthweights of 1500 gm. or less born between 1973 and 1978, found an incidence of blindness of 3.7%. In the second study (Saigal et al, 1984) infants of birthweight 1000 gm and less born between 1977 and 1980 were studied and an incidence of 7% was reported. The only prospective population-based study to date was done in New Zealand (Darlow et al, 1988) in which the incidence of ROP was assessed for all very low birthweight (below 1500 gm) infants born in that country over a year. Of the 337 survivors with birthweights below 1500 gm, 313 (93%) were examined. The frequency of examination was low, and only 88 (28%) had more than two examinations, compared with 94.1% in our study. The incidence of acute ROP was low at 19.9% for infants of birthweight below 1500 gm and 49.0% for those with

birthweight below 1000 gm. Although details of less severe cicatricial disease in the New Zealand study are still being collated, Darlow reported total blindness in 6 infants (2.0%), whereas in our study no infant was blinded by ROP.

We have also compared our results with those for similar birthweight groups in four hospital-based studies (Keith et al, 1984, Reisner et al, 1985, Flynn et al, 1987, Schaffer et al, 1985; see table 4). The incidence of acute disease is consistently higher in our study. Since all these studies used the current international classification of acute ROP, diagnostic criteria are unlikely to be an important cause of these differences. Differences in the timing and frequency of examinations, and the duration of follow-up in early postnatal life are likely to be more important. Follow-up in large tertiary referral units is inevitably incomplete, an aspect not relevant to our study since all our babies were cared for within the study area. The examination protocol for our study was the most rigorous we have encountered and almost certainly accounts for the high incidence of the minor, transient acute changes which might not have been identified if examinations had been less frequent, or if an eyelid speculum and scleral indentation had not been used. In 1981 Palmer considered the optimum time for a single screening examination for acute ROP to be at 7-9 weeks. Had we adopted the strategy of a single (Palmer, 1981) or an initial examination (Darlow, 1988) at 6-9 weeks, we would have missed many cases of acute ROP. Thus for a single examination at 6, 7, 8 or 9 weeks 52%, 43%, 39%, and 40% of acute ROP would have been missed in our babies of birthweight below 1500 gm. It could be argued that we have quoted Palmer out of context, since he advised this time for a single examination for the purpose of service screening for substantial ROP, whereas our aim was to determine the incidence of all stages of acute ROP. Nevertheless, the point remains; to

determine accurately the incidence of acute ROP, frequent examination is necessary.

In contrast to our high incidence of acute retinopathy, the incidence of cicatricial ROP in this study is low compared with other studies and substantially below the estimate of Phelps (Phelps, 1981). It is more difficult to examine an older infant than a newborn, and it is not appropriate to use an eyelid speculum, so minor degrees (stage 1) of cicatricial changes may be missed. However, this factor is common also to other studies. The reasons for our low incidence of cicatricial ROP are not known but possibilities include: differences in the survival rate for the most immature newborn infants, variations of neonatal management, and environmental and ethnic influences. In this respect, comparison of hospital-based and community population-based studies is inappropriate.

These results show that there are ethnic differences in acute ROP. In our cohort, although prematurity distributions for caucasians and Asians did not differ significantly and for a fixed gestation Asians were not smaller than their caucasian counterparts, the following significant associations were noted. Black infants had shorter gestations, but any stage of ROP was less likely to develop. Stage 3 disease was more likely to develop in Asian infants. One possible explanation for this finding is that Asians, for a fixed level of prematurity/sickness, survive better, although Clarke and colleagues' study in Leicestershire (Clarke et al, 1988) suggested the opposite. We found that for the same degree of prematurity Asian infants are on average 2.5 times more likely than caucasian infants to survive the neonatal period. The only comment we have been able to trace on racial differences in ROP is a study which reported a higher incidence of stage 1 but not of stages 2 and 3 acute ROP in Bedouin than Jewish infants (Monos et al, 1987).

Most studies have used birthweight as the indicator of prematurity. Birthweight is positively correlated with gestational age and in many instances it would be reasonable to use birthweight in this way. An infant is always measured at birth and it is an objective value, provided that the scales are accurate and that the measurement is carried out in a standard way. However difficulties arise when an infant is small or large for gestational age. It could be argued that gestational age would be a more relevant measure to obtain in studies of ROP since the condition appears to be a disease of the immature retina.

There are a number of ways in which gestational age can be measured. Firstly, an estimate can be obtained from the mother's "dates" i.e. the date of the last menstrual period and knowledge of her menstrual cycle. Secondly, the result of an ultrasound scan early in the pregnancy may be helpful (Robinson, 1973), especially when there is agreement with the "dates". This method was of course not available generally until the later 1970s. Thirdly, the gestational age can be assessed by clinical examination of the newborn infant. A number of methods have been published, the one most often used being that described by Dubowitz et al (Dubowitz et al, 1970) by which the gestational age to within 2 weeks is obtained by scoring of a number of external and neurological characteristics. However there were no infants below 28 weeks' gestation in the series studied by Dubowitz which makes it unhelpful for the extremely low birthweight infants admitted to neonatal units nowadays. Whatever methods are used to assess prematurity, whether gestational age or birthweight, it is clear that there is a close relationship between incidence and severity of ROP and preterm birth.

It is recognised that even with meticulous neonatal care advanced stages of ROP still occur. From the low incidence of cicatricial disease found in this study, it could be construed that ROP is no longer a substantial clinical problem. Unfortunately, as many studies have shown, this conclusion would be incorrect. Visual impairment caused by ROP still occurs; this is particularly important since the survival of the infant most at risk is on the increase (Valentine, 1989).

Table 4 - Comparison of incidence of acute and cicatricial ROP in four hospital-based studies and this study

Country	Birthweight (gm)	n	ROP incidence (%) Acute	ROP incidence (%) Cicatricial	This study n	This study ROP incidence (%) Acute	This study ROP incidence (%) Cicatricial
Australia[1]	<1000	108	53.0	19.0	70	88.5	4.3
USA[2]	≤1300	214	55.6	4.2	205	75.4	2.4
USA[3]	≤1500	328	48.1	7.0	331	60.1	1.5
Israel[4]	≤1500	464	34.9	9.0	331	60.1	1.5
NZ[5]	≤1500	313	19.9				
NZ[5]	<1000		49.0				

[1] Keith et al, 1984, [2] Flynn et al, 1987, [3] Schaffer et al, 1985, [4] Reisner et al, 1985, [5] Darlow et al, 1988

CHAPTER 5 - RESULTS OF PAEDIATRIC FACTORS STUDY

419 infants satisfied the entry criteria and also had paediatric data collected. The worst stage of ROP seen in those infants is shown in table 5.

Cranial ultrasound data

321 infants (77%) had cranial ultrasound examinations. The ultrasound findings and the worst stage of ROP seen are shown in tables 6 to 8.

1) Intracerebral haemorrhage

197 (61.6%) of the infants scanned showed no signs of intracerebral haemorrhage on ultrasound scanning; 101 of them (51.3%) had ROP. 72 infants had germinal layer haemorrhages only (22.5% of the total scanned) and 42 of them (58.3%) developed ROP. Of the 47 infants who had an intraventricular haemorrhage (IVH) on scan (14.7% of all those scanned), 37 developed ROP (78.7%). In four infants (1.2%) parenchymal haemorrhage was seen on ultrasound scan and they all had ROP, two with stage 3/4.

The occurrence of any haemorrhage is significantly associated with the development of ROP ($X^2 = 28.7$, 6df, $p < 0.0001$). If those infants who only germinal layer haemorrhage are included with those who had no bleeding, the occurrence of more severe bleeding (IVH or parenchymal haemorrhage) remains significantly associated with stage of acute ROP ($X^2 = 26.4$, 3df, $p < 0.001$).

2) Ventricular dilatation

36 infants (11.2%) showed signs of ventricular dilatation on ultrasound scanning. In 22 of these the increase in ventricular size was transient and in this group 14 infants developed ROP. Of the remaining 14 infants whose ventricles were dilated on scan, two had persistent non-progressive dilatation

and both babies had stage 2 ROP, 11 had progressive dilatation which required treatment of whom 7 developed ROP, and 1 infant had persistent asymmetrical dilatation and developed stage 1 ROP.

3) Periventricular leucomalacia (PVL)

Ultrasound evidence of periventricular leucomalacia was seen in 52 infants (16.3%). Of these infants 39 (75%) also developed ROP. The scans of 17 infants showed cystic PVL and 14 of these children had ROP, five developed stage 1, five stage 2 and four had stage 3/4. In 35 infants the ultrasound scans showed persistent echodensity in the periventricular area, persisting for more than 2 weeks (the so-called persistent "flare") and 25 of these infants developed ROP. There is a significant association between the occurrence of PVL and the stage of acute ROP ($X^2 = 13.8$, 3df, p = 0.003).

Table 9 shows the results of summarising the data into two groups; the "normal scan findings" group which comprised the infants with an intracerebral haemorrhage grade 0 or 1, ventricular dilatation score of 0 or 1, PVL score of 0, and the "abnormal scan findings group" which included those with intracerebral haemorrhage grade 2 or 3, ventricular dilatation score of 2, 3 or 4, PVL score of 1, 2 or 3. By this definition, 236 infants had normal ultrasound scan appearances, 122 of whom (51.7%) developed ROP. 85 infants had abnormal ultrasound findings and 62 (73%) developed ROP. There was a significant association between cranial ultrasound appearances and stage of ROP ($X^2 = 23.92$, 3 df, p < 0.001).

Cicatricial ROP and cranial ultrasound findings

Six infants in this cohort developed cicatricial ROP. Five had cranial ultrasound examinations and the findings are summarised in table 10. The numbers are very small and cannot be tested statistically. However it is

interesting to note that haemorrhage was seen in four of these infants and three of these had the more severe grades of bleeding. In addition, two infants showed signs of PVL; one also had ventricular dilatation and the other infant showed persistent "flare".

Seizures/Convulsions

Information on this variable was recorded for 418 infants. 15 (3.6%) had at least one convulsion, seven did not develop ROP and eight had some degree of retinopathy, four had stage 1,three stage 2 and one stage 3/4. Since the numbers were small, an association between overall incidence of ROP and presence or absence of convulsions was tested for and none was found ($\chi^2 = 0.00$, 1 df, p = 1.0).

Persistent ductus arteriosus (PDA)

81 of the 419 infants (19.3%) had a PDA which required treatment either with fluid restriction, indomethacin and/or surgical ligation. Of these infants, 62 also had ROP, 21 had stage 1, 27 stage 2 and 14 stage 3/4 (table 11). There was a significant association between the finding of a PDA requiring treatment and stage of ROP ($\chi^2 = 59.48$, 3 df, p < 0.001). 10 of the 62 infants with a significant PDA and ROP had asymmetric eye signs in the acute stages (table 12).

Cicatricial ROP and PDA

Five infants with paediatric data developed cicatricial ROP (table 13). Three of these infants showed cicatricial changes in both eyes, one infant in the right eye and the fifth child in the left eye. Only two infants had a PDA requiring treatment, one with cicatricial ROP in both eyes and the one with changes in the left. These numbers are too small to analyse for any association between cicatricial disease and PDA.

Duration of assisted ventilation

This variable was expressed as the duration in days of intermittent positive

pressure ventilation (IPPV) and/or intermittent mandatory ventilation (IMV)

and only information for the first three weeks of life was used (Table 14).

There is a statistically significant association between the number of days of

assisted ventilation and the occurrence and stage of ROP.

Duration in oxygen

The details are shown in table 15. The number of days that extra oxygen was

given in the first three weeks was significantly associated with ROP.

Number of intubations

The total number of intubations carried out in the first three weeks was

analysed in relation to ROP. The results are shown in table 16. There is

evidence of a statistically significant association.

Bradycardias requiring stimulation

Table 17 shows the occurrence of ROP in infants who had or did not have

bradycardias requiring stimulation in the first three weeks. There is a

significant univariate association.

Bradycardias requiring oxygen

Table 18 shows that there is a significant association between the occurrence

of bradycardias requiring oxygen and the development of ROP.

Apnoeas requiring stimulation or oxygen

There was a significant association between apnoeas requiring stimulation or

oxygen and ROP (table 19 and 20).

Cyanotic spells requiring oxygen

Table 21 shows the number of infants who had these episodes and who developed ROP. There is a significant univariate association between the stage of ROP and these episodes.

Monitoring of oxygen

Umbilical arterial lines (UAC)

414 infants had information recorded on whether an umbilical arterial catheter had been inserted to monitor blood gases. 153 infants (37%) had an UAC placed and 109 of these infants developed ROP (table 22). A large majority (20/24) of the infants who developed stage 3 or 4 ROP had had an UAC placed. There was a significant univariate association between the placing of an UAC and the stage of ROP (X^2 = 60.1, 3 df, p < 0.001). The length of time the UAC was in place was longer for those who developed stage 3 or 4 ROP than for those who had no ROP or had less severe disease (table 23).

Peripheral arterial lines

51 infants in the study had a peripheral arterial line placed in the first week and 36 developed ROP (table 24).

Blood transfusions

Having one or more transfusions in the first three weeks was significantly associated with ROP (table 25). The volume of blood transfused, expressed as volume per kg birthweight, was also found to have a significant association with ROP (table 26).

Pneumothorax

29 of the 419 infants suffered at least one pneumothorax and 23 of them developed ROP (table 27). The occurrence of pneumothorax was significantly associated with ROP.

Multivariate analysis

Prior to performing multivariate analysis, univariate analysis was carried out with 35 variables (table 28) for both incidence and severity of acute ROP.

Incidence of ROP

On univariate analysis, 22 variables were found to be significantly associated with the incidence of ROP at the 1% level (Table 29). When these variables were analysed using dichotomous logistic regression gestational age, birthweight and duration of ventilation were found to be the only significant and independent variables (Table 30).

Severity of acute ROP

A similar univariate analysis performed to consider the variables associated with the stage of acute ROP, i.e. the severity of the disease, resulted in 20 variables being significant at the 1% level (Table 31). Multivariate analysis of these variables was carried out using ordinal logistic regression with the proportional odds model. Again gestational age, birthweight and duration of ventilation were the only significant variables (Table 32).

Abnormal cranial ultrasound and the number of blood gases were found to be univariately associated with both the incidence and stage of ROP. However, multivariate analyses of these data did not show that these variables were significantly associated with either incidence or stage of ROP.

Table 5   Worst stage of ROP in 419 infants with paediatric data

Worst stage of acute ROP	Number of infants
0	203
1	129
2	63
3/4	24

Table 6   Intracerebral haemorrhage and acute ROP

		ROP stage				
		0	1	2	3/4	Total
	0	96	66	28	7	197
Intracerebral	1	30	23	14	5	72
haemorrhage	2	10	14	15	8	47
grade	3	0	1	1	2	4
	Total	136	104	58	22	320

Table 7   Ventricular dilatation and acute ROP

		ROP	stage			
		0	1	2	3/4	Total
	0	125	96	47	17	285
Ventricular	1	8	4	6	4	22
dilatation	2	0	0	2	0	2
score	3	4	3	3	1	11
	4	0	1	0	0	1
	Total	137	104	58	22	321

f

Table 8   Periventricular leucomalacia   (PVL) and acute ROP

		ROP	stage			
		0	1	2	3/4	Total
	0	124	86	44	14	268
PVL	1	10	12	9	4	35
score	2	0	0	0	0	0
	3	3	5	5	4	17
	Total	137	103	58	22	320

Table 9   Cranial ultrasound appearances and worst stage of ROP

	ROP stage				
	0	1	2	3/4	Total
Normal scan	114	78	35	9	236
Abnormal scan	23	26	23	13	85
Total	137	104	58	22	321

$X^2 = 23.92$, 3 df, p < 0.001

Table 10   Cicatricial ROP and cranial ultrasound findings

Infant number	Haemorrhage grade	Dilatation grade	PVL grade	Cicatricial ROP
127	3	0	1	both eyes
239	2	3	3	right eye
293	2	0	0	both eyes
389	0	0	0	left eye
461	1	0	0	both eyes

Table 11   Persistent Ductus Arteriosus (PDA) and Stage of ROP

		ROP stage 0	1	2	3/4	Total
PDA	No	184	108	36	10	338
	Yes	19	21	27	14	81
Total		203	129	63	24	419

$X^2 = 59.48$, 3 df, p < 0.001

Table 12   Symmetry of ROP appearance in those infants with persistent ductus arteriosus

		ROP stage (left eye) 0	1	2	3/4	Total
ROP	0	19	1	0	0	20
stage	1	1	19	2	0	22
(right	2	0	2	23	2	27
eye)	3/4	0	0	2	10	12
	Total	20	22	27	12	81

Table 13   Persistent Ductus Arteriosus (PDA) and cicatricial ROP

Study number	Eye with cicatricial ROP	PDA?
127	Both	No
239	Right	No
293	Both	Yes
389	Left	Yes
461	Both	No

Table 14   Duration of assisted ventilation (duration of IPPV/IMV in days) by stage of ROP

ROP stage	n	Median	Min	Max
0	203	0	0	21
1	129	1	0	21
2	63	8	0	21
3/4	24	17	0	21

Kruskal-Wallis ANOVA, p < 0.001

Table 15   Duration in oxygen (days) by stage of ROP

ROP stage	n	Median	Min	Max
0	203	1	0	21
1	129	3	0	21
2	63	15	0	21
3/4	24	19.5	0	21

Kruskal-Wallis ANOVA, p < 0.001

Table 16   Intubations (total number in first three weeks) by stage of ROP

ROP stage	n	Median	Min	Max
0	203	0	0	10
1	129	0	0	12
2	63	1	0	11
3/4	24	3	0	8

Kruskal-Wallis ANOVA, p < 0.001

Table 17   Bradycardias requiring stimulation by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	129	43	15	3	190
Yes	74	86	48	21	229
Total	203	129	63	24	419

$\chi^2 = 56.9$, 3df, $p < 0.001$

Table 18   Bradycardias requiring oxygen by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	185	92	32	10	319
Yes	18	37	31	14	100
Total	203	100	63	24	419

$\chi^2 = 64.7$, 3df, $p < 0.001$

Table 19   Apnoeas requiring stimulation by stage of ROP

ROP stage

	0	1	2	3/4	Total
No	158	84	39	16	297
Yes	45	45	24	8	122
Total	203	129	63	24	419

$X^2 = 9.5$, 3df, p < 0.023

Table 20   Apnoeas requiring oxygen by stage of ROP

ROP stage

	0	1	2	3/4	Total
No	187	100	47	19	353
Yes	16	29	16	5	66
Total	203	129	63	24	419

$X^2 = 18.8$, 3df, p < 0.001

Table 21   Cyanotic episodes requiring oxygen by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	175	103	44	12	334
Yes	28	26	19	12	85
Total	203	129	63	24	419

$\chi^2 = 22.2$, 3df, p < 0.001

Table 22   Presence of umbilical arterial line by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	155	79	23	4	261
Yes	44	49	40	20	153
Total	199	128	63	24	414

$\chi^2 = 60.1, 3df, p < 0.001$

Table 23   Duration of umbilical arterial catheter by stage of ROP

ROP stage	n	Median	Min	Max
0	44	5	1	19
1	47	6	1	18
2	39	7	1	18
3/4	20	9.5	1	17

Kruskal-Wallis ANOVA, p = 0.006

Table 24   Presence of peripheral arterial line in first week by
            stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	184	110	49	20	363
Yes	15	18	14	4	51
Total	199	128	63	24	414

$X^2 = 10.7$, 3df, p = 0.016

Table 25   Blood transfusions by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	170	87	23	2	282
Yes	33	42	14	22	137
Total	203	129	63	24	419

$X^2 = 90.0, 3df, p < 0.001$

Table 26   Volume of blood transfusions per kg birthweight by stage of ROP

ROP stage	n	Median	Min	Max
0	182	0	0	44.3
1	125	0	0	45.3
2	63	0	0	50.5
3/4	23	14.4	0	36.8

Kruskal-Wallis ANOVA, p < 0.001

Table 27   Occurrence of pneumothorax by stage of ROP

	ROP stage				
	0	1	2	3/4	Total
No	197	119	51	23	390
Yes	6	10	12	1	29
Total	203	129	63	24	419

$p < 0.001$

Table 28   List of paediatric variables considered in univariate
            analysis (both incidence and stage of ROP)

Continuous variables:

Gestation

Birthweight

Apgar score at one minute

IPPV/IMV duration in days

Number of intubations

Duration in oxygen in days

Number of different drugs administered

Number of pH, PaO_2 or PCO_2 blood gas readings (reduced model only, n=257)

Categorical variables (mostly yes/no):

Illness during pregnancy

Pregnancy-induced hypertension

Place of birth

Multiple birth

Sex

Resuscitation required

Peripheral arterial line

Small for gestational age

Exchange transfusion

APH

Fetal distress

Fits

Positive CSF

Respiratory disease

UAC

PDA requiring treatment

Positive blood cultures

Chest infection

Surgery

Chronic respiratory disease

Pneumothorax

Bradycardias requiring stimulation or oxygen

Apnoeas requiring stimulation or oxygen

PPF/FFP or blood transfused

Cyanotic spells requiring oxygen

Table 28 (continued)

Abnormal bilirubin
Abnormal cranial ultrasound (reduced model only, n=288)

Table 29   Incidence of ROP: variables found significant at 1%
            level using univariate analysis

<u>Continuous variables:</u>

Gestation

Birthweight

Apgar score at one minute

IPPV/IMV duration in days

Number of intubations

Duration in oxygen in days

Number of different drugs administered

Number of pH, PaO_2 or PCO_2 blood gas readings (reduced model only, n=257)

<u>Categorical variables (mostly yes/no):</u>

Peripheral arterial line

Small for gestational age

Respiratory disease

UAC

PDA requiring treatment

Positive blood cultures

Chest infection

Surgery

Chronic respiratory disease

Pneumothorax

Bradycardias requiring stimulation or oxygen

Apnoeas requiring stimulation or oxygen

PPF/FFP or blood transfused

Cyanotic spells requiring oxygen

Abnormal bilirubin

Abnormal cranial ultrasound (reduced model only, n=288)

Table 30   Incidence of ROP: variables found significant at 5%
level using dichotomous logistic regression

Variable	Estimate	(SE)	OR	(95% CI)	P
Gestation (wks)	-0.15	(0.053)	0.86	(0.78, 0.95) per week	0.004
Birthweight (g)	-0.0019	(0.00056)	0.83	(0.74, 0.92) per 100g	0.001
Ventilation (days)	0.091	(0.027)	1.89	(1.44, 2.73) per week	<0.001

SE = standard error, OR = odds ratio

Table 31   Stage of ROP: variables found significant at 1% level
using univariate analysis

Continuous variables:

Gestation

Birthweight

Apgar score at one minute

IPPV/IMV duration in days

Number of intubations

Duration in oxygen in days

Number of different drugs administered

Number of pH, PaO_2 or PCO_2 blood gas readings (reduced model only, n=257)

Categorical variables (yes/no):

Respiratory disease

UAC

PDA requiring treatment

Positive blood cultures

Chest infection

Surgery

Chronic respiratory disease

Pneumothorax

Bradycardias requiring stimulation or oxygen

Apnoeas requiring stimulation or oxygen

PPF/FFP or blood transfused

Cyanotic spells requiring oxygen

Abnormal bilirubin

Abnormal cranial ultrasound (reduced model only, n=288)

Table 32   Stage of ROP: variables found significant at 5% level
using ordinal logistic regression with the proportional
odds model

Variable	Estimate	(SE)	OR	(95% CI)	P
Gestation (wks)	-0.17	(0.049)	0.85	(0.77, 0.93) per week	<0.001
Birthweight (g)	-0.0023	(0.00050)	0.79	(0.72, 0.87) per 100g	<0.001
Ventilation (days)	0.094	(0.018)	1.93	(1.50, 2.47) per week	<0.001

SE = standard error, OR = odds ratio

CHAPTER 6 - DISCUSSION OF RESULTS OF PAEDIATRIC FACTORS STUDY

Of the infants studied in this survey of paediatric factors and ROP, there were 203 (48.4%) who did not show any signs of the disease and 216 (51.6%) who developed it. Since this sample was derived from the same population as the infants studied for the epidemiology survey it is not surprising that the proportion which developed ROP should be similar in both surveys.

Cranial ultrasound findings

Fewer infants in this study showed evidence of intracerebral haemorrhage, ventricular dilatation and periventricular leucomalacia (PVL) compared with the findings of Trounce and colleagues (Trounce et al, 1986). It is unlikely that the difference in findings between the two studies can be explained by different definitions of haemorrhage and PVL since the definitions of the ultrasound appearances were identical in this and in Trounce's study. There is however a small difference in the definitions used for ventricular dilatation. Using the definition of Trounce et al, the findings of this study are similar to theirs. The two studies differed in their entry criteria; Trounce selected those infants weighing 1500 gm or less at birth whereas we selected by birthweight of 1700 gm or less. In addition our study infants had to survive three weeks before they could be entered into the study. This latter entry criterion would tend to reduce the number of abnormal ultrasound findings since the infants with the worst scans would have been more likely to perish in those first three weeks. My findings of abnormal cranial ultrasound scans are lower in all subgroups of haemorrhage, ventricular dilatation and PVL when compared with those of Trounce et al except in the percentage of those infants who showed germinal layer bleeds (grade 1 haemorrhage as described by Levene et al, 1985). 72 of 320 infants (22.5%) had a grade 1 haemorrhage in my study. In Trounce's study 18.5% showed evidence of this grade of haemorrhage. Since

Trounce scanned the infants in his study more frequently than I did, it is possible that some transient features would have been missed in my observations. However it might be expected that persistently abnormal appearances would still be seen even with less frequent scans.

The study by Sinha and coworkers (Sinha et al, 1985) showed a lower incidence (12.8%) of subependymal haemorrhage (synonymous with germinal layer haemorrhage), but as high a percentage with intraventricular bleeding as Trounce. The percentage with PVL reported by Sinha was however lower than that reported by Trounce and more similar to my findings, although Sinha does not specifically describe "persistent flare" as one of the subgroups of PVL.

Since the development of the brain and the eye are embryologically closely related, and the cerebral and retinal circulations have a common origin, it might be expected that there could be an association between ROP, a vascular condition, and haemorrhagic and ischaemic events in the brain of preterm infants. The findings in this present study show that there is such an association, using univariate analysis, between ROP and these events as demonstrated by cranial ultrasound.

Other authors have reported a significant association, when using univariate analysis, between ROP and IVH as shown by CT or ultrasound appearances (Procianoy et al, 1981, Flynn, 1983, Biglan et al, 1984, Purohit et al, 1985, Amato et al, 1986, Hammer et al, 1986, Hungerford et al, 1986, Brown et al, 1987, Prendiville et al, 1988, Brown et al, 1990, Darlow et al, 1992).

Ventricular dilatation has not been found to have a significant association with ROP (Prendiville et al, 1988). Similarly, the findings of this present study,

although the numbers are small, do not show any trend towards ventricular dilatation being more common in infants with ROP.

This present study is the first one to be reported which has studied ROP and PVL and the results would suggest that there is a relationship between the two. It is considered that PVL is ischaemic in origin since it occurs in the watershed areas within the periventricular white matter least well-supplied by the developing arterial circulation (Banker et al, 1962, Volpe, 1979, Rushton et al, 1985). Since ROP has been proposed to have an ischaemic basis too (see chapter 1), it might be expected that there could be an association between this condition and PVL. Hungerford and coworkers (Hungerford et al, 1986) mentioned evidence of hypoxic-ischaemic brain injury on CT or ultrasound scans and a statistically significant association between this and ROP. However, they did not elaborate on what they meant by hypoxic-ischaemic brain injury. Other workers (Lucey et al, 1984) have described two infants who had circulatory collapse and severe blinding ROP. Our group have previously described infants who had both severe ROP and marked changes on cranial ultrasound scanning compatible with severe ischaemic infarction (Ng et al, 1989). In that report we suggested that in some infants cerebral hypoperfusion contributing to PVL might also be a factor in contributing to the severity of ROP.

Our study has shown that ROP and PVL are associated on univariate analysis. However, multivariate analyses using our data have shown that cranial ultrasound findings of IVH and/or PVL were not significant independent variables in the occurrence or severity of ROP. One possible explanation for this is that ROP and IVH/PVL are related by being consequences of a pathway initiated by ischaemia, and therefore are not independent of each other. Factors reported to be associated with PVL include antepartum haemorrhage,

birth asphyxia, recurrent apnoea, septicaemia, persistent ductus arteriosus, pneumothorax, and hypercarbia (Sinha et al, 1985, Trounce et al, 1988). These factors are recognised causes of systemic hypotension and alterations in cerebral blood flow (Ogata et al, 1976, Lou et al, 1979), and several of them have also been noted in relation to ROP, as shown by our results and by other authors (see chapter 1).

Some authors using multivariate analyses have used occurrence of ROP as the outcome variable, while others have studied severity of the condition, and yet others have considered both. We did the latter and it was interesting that both models gave very similar results, with low birthweight, young gestational age and long duration of ventilation being associated with both the incidence and stage of ROP. These similarities perhaps reflect the fact that most infants in the study had mild ROP. These results are comparable to those found by others, irrespective of whether incidence or stage of ROP was the outcome variable.

As in our study, in most models either low birthweight or low gestational age or both have been found to be the most significant independent factors. Since ROP is a condition which affects only those infants who are born prematurely and therefore have immature retinal vasculature, it is not surprising to find such a strong statistical association with birthweight and gestational age. It could of course be argued that since one of the main criteria for entry into most of the studies was low birthweight and/or short gestational age, these variables would have a powerful effect on the models used in the analysis. Nevertheless, even in the one study which did not have strict birthweight or gestational age inclusion criteria (Hammer et al, 1986), birthweight was one of the independent variables found to be associated with acute ROP.

Reviewing the published work on other variables which are independently associated with the occurrence of ROP, duration of ventilation is frequently found to be one of these (Flynn, 1983, Hammer et al, 1986, Brown et al, 1990). Our study shows a similar result. The length of time which an infant is ventilated for is affected by several factors such as severity of respiratory distress syndrome, development of bronchopulmonary dysplasia and intercurrent illnesses. Circulatory and oxygenation disturbances with resulting metabolic changes are associated with these neonatal conditions and also with mechanical ventilation itself (Yu et al, 1977, Lou et al, 1979, Perlman et al, 1983, Fenton et al, 1990). The variable of duration of ventilation when it is used in the analysis may therefore be the common factor which summarises these other confounding variables. However it is probably not the duration of ventilation per se which is a contributory cause of ROP, but rather that it is a marker for the underlying pathophysiological mechanisms which have a role in the pathogenesis of this disease.

Apnoeas/bradycardias (Flynn 1983), acidosis (Prendiville et al 1988), number of episodes of $PaO_2 > 12$ kPa (Prendiville et al 1988), treatment with xanthine (Hammer et al 1986) and treatment with indomethacin (Darlow et al 1992) are some of the variables that have also been reported to be significantly associated with the occurrence of ROP. Some of these events are known to be correlated with illnesses such as infections, intracranial conditions for example intraventricular haemorrhage, or events resulting in hypoxaemia so these variables could be considered to be indicators of neonatal illness. Such illnesses are known to be associated with disturbances in circulation and oxygenation. Hence their independent contribution to the occurrence of ROP in these models could be explained possibly by this relationship with neonatal illness. Thus different models have produced different variables in detail but which could all be considered to be indicators of illness and instability.

When the outcome variable has been the severity of ROP, the various different models have, in addition to gestation and birthweight, similarly produced significant variables which indicate illness such as acidosis (Bossi et al, 1984, Koerner et al, 1986, Prendiville et al, 1988), various blood gas measurements (Bossi et al, 1984, Koerner et al, 1986, Prendiville et al, 1988), duration of ventilation (Bossi et al, 1984, Koerner et al, 1986), and pneumothorax (Prendiville et al, 1988).

Our initial hypothesis was that prematurity is the main trigger for the initiation of the disease process, and that the severity of ROP is influenced by the severity of neonatal illness. However, our analyses found that duration of ventilation was the only other variable after gestation and birthweight which had an independent effect on both occurrence and severity of acute ROP. Thus it would appear that the degree of neonatal illness contributes to the trigger for the development of ROP as well as contributing to its progression.

Although I collected blood pressure and oxygenation data in the form of arterial blood gas values in an attempt to assess the relationship with ROP, these data were measured for clinical reasons and were not continuous, that is they were made at single points in time. Unfortunately, we have not been able to use these data in a statistically valid way, since the measurements are biased greatly towards those infants who were ill and who would have had more measurements taken than those who were well, some of whom had no such readings taken at all. In addition the measurements do not show any but the most serious fluctuations so our study cannot inform further the hypothesis that disturbances in blood pressure and/or oxygenation have an effect on the occurrence or severity of ROP. More recent work using continuous monitoring of oxygen levels by transcutaneous methods has shown an

association between fluctuations in arterial oxygen values and more severe ROP (Saito et al, 1993).

Our study has not been able to clarify the role of oxygen in the production of ROP. Using continuous transcutaneous oxygen monitoring, a recent study has shown that there was a significant association between the amount of time spent with arterial oxygen levels of 80 mm Hg or higher and the incidence and severity of ROP (Flynn et al, 1992).

The results of our study and those of other workers who have used multivariate analysis would support the hypothesis that prematurity together with "illness" factors trigger the proliferative process in immature retinal vessels. However, interpretation of such studies is fraught with difficulty since different variables are entered into the models, definitions of similar variables used in the analysis vary between studies, different statistical methods and models are used and the entry criteria into the study are also variable. Whilst such studies are useful in showing significant associations and may indicate that the condition has a multifactorial aetiology, they do not necessarily identify causative factors.

From this study and other similar studies it is not possible to show how these variables may interact. It can only be postulated that the underlying mechanisms might be related to the effects of circulatory fluctuations and thus oxygenation on the retinal vessels and tissues. At present the best that can be recommended is that such immature infants should be maintained in as stable a state as possible, particularly in the first few weeks of life.

CHAPTER 7 - CONCLUSIONS

The first aim of this thesis which was to describe some of the epidemiology of ROP in a geographically-defined population in the UK has been achieved. Acute ROP is common in infants weighing less than 1700 gm at birth, affecting 49.1% of the infants we studied. However more severe acute ROP (stage 3 and 4) is uncommon, being found in 4.2% of the cohort. Progression to cicatricial ROP occurred in 1.1% (5 infants) and no infant was blind because of ROP. Greater severity of acute ROP is significantly associated with a low gestational age or birthweight, and with Asian origin.

The second aim was to describe and investigate some of the paediatric factors, including cranial ultrasound appearances, which may be associated with ROP. Univariate analysis of the paediatric data showed associations between several of them and acute ROP. In particular, cranial ultrasound appearances of haemorrhage and of ischaemic events (periventricular leucomalacia) were significantly associated with occurrence and stage of ROP. Multivariate analysis, however, showed that the cranial ultrasound appearances did not have an independent association with either the incidence or severity of acute ROP, whereas gestational age, birthweight and duration of ventilation were the significant independent variables for both incidence and severity of the disease. Since the duration of ventilation can be considered to be an indicator of the severity of neonatal illness, these results support the hypothesis that prematurity and neonatal illness together contribute to the initiation and progression of acute ROP.

More detailed studies of the contribution of neonatal illness, for example the effect of changes in blood pressure and oxygenation, on the occurrence of ROP will require continuous measurements of these variables. This will depend on

the availability of suitable equipment in sufficient numbers. Since severe ROP (stage 3 and 4) fortunately seems to develop only in a small number of infants, future clinical studies will probably require to be carried out on a multicentre basis. Clinical studies would necessarily be limited by ethical issues so that animal models would need to be used in order to investigate in more detail the hypothesis that ischaemia/hypoxaemia contributes to the occurrence and severity of ROP.

. O. P. E Y E E X A M I N A T I O N F O R M

IAME

IOSPITAL NUMBER

;TUDY NUMBER   [ ][ ][ ][4]

IATE OF BIRTH   (DD/MM/YY)   [ ][ ][ ][ ][ ]

;EX (1 = Male   2 = Female)   [ ]

IATE OF EXAMINATION   (DD/MM/YY)   [ ][ ][ ][ ][ ]

XAMINER (1 = A.R.F.)   [ ]

RIGHT EYE

```
        1 2 3 4 5 6 7 8 9 10 11 12
21 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
22 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
23 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
```

LEFT EYE

```
        1 2 3 4 5 6 7 8 9 10 11 12
21 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
22 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
23 [ ]  [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]
```

ZONE	STAGE AT CLOCK HOURS
= CHANGES PRESENT	BLANK = NORMAL
= NO CHANGES	1 = DEMARCATION LINE
= POOR VIEW	2 = RIDGE
= NO EXAMINATION	3 = 2+ EXTRARETINAL PROLIFERATION
	4 = 3+ RETINAL DETACHMENT

Mark Highest Stage At Every
Clock Hour

                                               R   L

Stage 3: 1 = MILD   2 = MODERATE   [ ] [ ]
          3 = SEVERE 9 = NOT EXAMINED
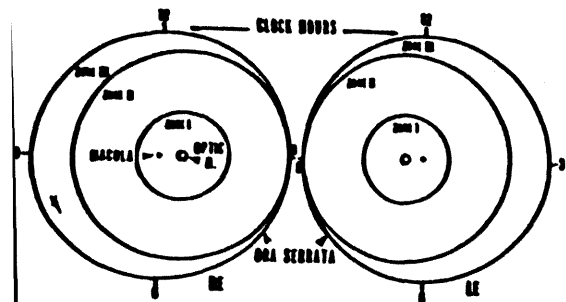
Stage 4: 1 = EXUDATIVE   2 = TRACTIONAL   [ ] [ ]
          3 = COMBINED   9 = NOT EXAMINED

2·

NAME

DATE OF EXAMINATION

OTHER FINDINGS

1 = PRESENT   2 = NOT PRESENT   9 = NOT EXAMINED   R   L

A: DILATION/TORTUOSITY POSTERIOR VESSELS   ☐ ☐

B: IRIS VESSEL DILATION   ☐ ☐

C: PUPIL RIGIDITY   ☐ ☐

D; VITREOUS HAZE   ☐ ☐

E: HAEMORRHAGE   ☐ ☐

0=0   1= +   2=++   3= +++   4= ++++   9= NO EXAMINATION   R   L

F: ARTERIAL TORTUOSITY   ☐ ☐

G: VENOUS CONGESTION   ☐ ☐

H: T.V.L.   ☐ ☐

I: HYALOID (1= +, 2= -, 9= NOT EXAMINED   ☐ ☐

CICATRICIAL RLF (REESE 1953)

= PRESENT, 2= NOT PRESENT, 9= NOT EXAMINED

                                                                R   L

) Small mass opaque tissue in periphery without detachment   ☐ ☐

i) Larger mass opaque tissue in periphery with local detachment ☐ ☐

ii)Larger mass in periphery with traction fold to disc   ☐ ☐

v) Retrolental tissue covering part of pupil   ☐ ☐

) Retrolental tissue covering entire pupillary area   ☐ ☐

                                                               R   L

.C.D.   ☐☐|·|☐☐   ☐☐|·|☐☐

.C.D.   ☐☐|·|☐☐   ☐☐|·|☐☐

                                                         +/-

EFRACTION SPHERE   ☐☐☐|·|☐☐   ☐☐☐|·|☐☐

EFRACTION CYLINDER   ☐☐☐|·|☐☐   ☐☐☐|·|☐☐

EFRACTION AXIS (0 - 360°)   ☐☐☐   ☐☐☐

RETINOPATHY OF PREMATURITY STUDY

NAME:

HOSPITAL NO.:   STUDY NO.   ☐☐☐ | I |

ADDRESS: Sex M = 1, F = 2   ☐

Tel. no.:   County: L=1, N=2   ☐
                                                         D=3, other=4
G.P.:

DATE OF BIRTH ☐☐☐☐☐☐   Time ☐☐☐☐ hours

Place of birth: LRI/LGH = 1
                 NCH/NUH = 2
                 Derby   = 3   ☐
                 Other   = 4

GESTATION: ☐☐ weeks

Singleton = 1 Multiple = 2 if twin   ☐   Position ☐
               = 3 if triplet etc.

MOTHER

Name   Hospital no.   Age ☐☐ years

Ethnic group   ☐   Occupation:

Father's ethnic group   Occupation:

Marital state
Blood group
SMOKING: No = 1, Yes = 2, Unknown = 9
        No. cigs/ day Leave blank if non-smoker   ☐   ☐☐
                       Unknown = 9

PAST MEDICAL HISTORY
List: ☐☐   ☐☐   ☐☐

Family history: None=0, Yes=1, Unknown=9

                                              ☐   ☐

                                              Eye   Other

Obstetric history:

                                    ☐☐   ☐

                                    LB + SB Abortions

RETINOPATHY OF PREMATURITY STUDY   page 2

PREGNANCY

LMP: EDD:

Illness during pregnancy:

[|] [|] [|]

Hypertension   No=1, Yes=2   Proteinuria   No=1, Yes=2   [ ] [ ]

Details and treatment:

APH   No=1, Yes=2   [ ]

    Details:

IUGR   No=1, Yes=2   [ ]

    Details:

DRUGS DURING PREGNANCY: None=0, Unknown=9

[ ] [ ] [ ] [ ] [ ]

Ruptured membranes   Duration   < 24 hrs.= 1
                                      > 24 hrs.= 2   [ ]
                                      unknown= 9

             if > 24 hrs., RMDI in days   [| |]

             HVS result if known

LABOUR

Onset   Spontaneous=1 Induced=2 No labour=3   [ ]

Fetal distress   Present=1 absent=2 unknown=9   [ ]

Drugs: None=0, Unknown=9, Epidural=1, Entonox=2
       Pethidine=3, GA=4, Other=5   [ ] [ ] [ ]

RETINOPATHY OF PREMATURITY STUDY   page 3

<u>DELIVERY</u>

Vaginal = 1, LSCS = 2

Cephalic=1, Forceps=2, Rotational forceps=3, Breech=4, Vacuum extraction=5
Other=6

<u>BABY</u>

BIRTH WEIGHT   grams

Length   cm.

Head circumference   cms.

Small for gestational age No=1, Yes=2

Condition at birth

APGAR   @ 1 min.   @ 5 min.

Resuscitation required
None=1, Facial O_2 = 2, Bag and mask=3, ETT=4

Comments

Drugs: No=1, Yes=2

Temperature on admission ^{o} C

Blood group

<u>SUMMARY OF DIAGNOSES</u>

NAME & NO.		ROP STUDY		DATA FLOW SHEET A								
	DATE											
VENTILATION IPPV etc.												
Max. recorded pressures												
Max. rate												
OXYGEN Max. given												
O_2 monitoring Searle $TcPO_2$												
PNEUMOTHORAX Side & no. of drains												
Type of RESPIRATORY DIS.												
Bradycardias $<$80/min. No. requiring stim. No. requiring O_2 (include bagging)												
Apnoeas $>$15 secs. No. requiring stim. No. requiring O_2 (include bagging)												
Cyanotic spells req. O_2 (i.e. those not assoc. c apnoea or brady)												
FITS Type												
No.												
Jaundice Max. bilirubin												
Phototherapy												
Vol. exchange transfusion												
PDA req. treatment												

Appendix 2

ROP STUDY   DATA FLOW SHEET B

NAME & NO.	DATE										
Weight, in grams											
TPN Milk, type											
Vol. of fluid/kg/day											
Haemoglobin											
Transfusion, mls.											
PPF/FFP given, mls.											
Hypoglycaemia <1.1											
Hyperglycaemia >6.0											
Na											
K											
Urea											
Creat.											
Calcium											
Alk. phos.											
DRUGS											
Infection Type											
microbiol.											
NEC											
Vit. E levels, mg/L											
Other events											

R.O.P. STUDY MATERNAL QUESTIONNAIRE

Baby's name:

1) Did mother suffer any illness during the pregnancy e.g. 'flu, gastroenteritis. If yes, please specify and indicate timing of illness and treatment if any:

Did mother suffer from asthma or hayfever during the pregnancy?

2) What drugs/medicines/tablets/tonics did mother take during the pregnancy? List, and indicate frequency of taking, and stage of pregnancy in which it was taken:

3) What did mother take for headache, backache, heartburn, any other aches and pains, and for other minor ailments? List, if not included in answers to question 2).

4) Did mother have cravings for particular foods during the pregnancy? If so, what?

5) Smoking: Did mother smoke during pregnancy? If yes, how many a day?
   Alcohol during pregnancy? If yes, how much?

6) Are there any relevant past medical or family history?

   a) Eye problems?

   b) Any other?

Name of questioner:

THANK YOU FOR YOUR ASSISTANCE

RETINOPATHY OF PREMATURITY DATA CODING

FIXED DATA (demographic data, ante- and perinatal data)

1st line

1- 4   Study no.: _ _ _ 1

5   Sex: M=1, F=2

6   Address: LHA=1, NHA=2, SDHA=3, Other=4

7-12   Date of birth

13-16   Time of birth (24 hour clock)

17   Place of birth: LRI=1, LGH=2, NCH=3, NUH=4, Derby=5, Other=6

18-19   Gestation in completed weeks

20   Singleton=1, Twin=2, Triplet=3, Quadruplet=4

21   Position if multiple birth

22-23   Maternal age

24   Maternal ethnic group: Caucasian=1, Asian=2, Negro=3, Chinese=4, Mixed=5, Other=6

25   Paternal ethnic group: Caucasian=1, Asian=2, Negro=3, Chinese=4, Mixed=5, Other=6

26   Alcohol in pregnancy: none=0, occasional (1-2 drinks/week)=1, moderate/social (1/day)=2, a lot (>1/day)=3, unknown=9

27   Smoking in pregnancy: none=1, yes=2, unknown=9

28-29   No. of cigarettes/day: non-smoker=blank, unknown=9

30-35   Past medical history: none=00 in first two squares, diabetes=01, epilepsy=02, asthma/hayfever=03, renal problems=04, cardiac=05, DVT/pulm. embolus=06, deafness=07, depression=08, anaemia=09, chromosome problem=10, gastro. problem=11, surgery=12, skin problem=13, arthritis=14, hormone problem(thyroid)=15, hypertension=16, vit. E deficiency=17, migraine=18, sickle-cell trait=19

36-37   Family history: none=0, yes=1

        36 = eye problems, include short sight, long sight, squint

        37 = other, in more than one person in the family

38-39   Parity: Live births plus stillbirths, including this child

40   Abortions: number

41-46   Illness during pregnancy (non-obstetric):
        none=00 in first two squares, unknown=99 in first two squares
        'flu-like=01, URTI=02, UTI=03, asthma/hayfever=04, abdo. pain=05,
        headaches=06, anaemia=07, D&V=08, renal=09, surgery (including
        amnio.)=10, neuro. (including non-eclamptic fits)=11,
        depression=12, herpes=13, TB=14, haematological=15, STD=16,
        dental=17, cardiac=18, hypoglycaemia=19, liver problem (incl.
        hepatitis)=20

47-48   Hypertension in pregnancy: no=1, yes=2, unknown=9
        Proteinuria in pregnancy: no=1, yes=2
        If eclampsia, score 3 in each box

49   APH: none=1, yes=2   include early bleeds

50   Antenatal evidence of IUGR: no=1, yes=2

51-60   Drugs in pregnancy:
        none=00 in first two squares, unknown=99 in first two squares
        Iron=01, vit. D/calcium=02, antibiotics=03, paracetamol=04,
        aspirin=05, decongestants (not antihistamines)=06, antihistamines=07,
        antihypertensives=08, insulin=10, anticonvulsants=11, ritodrine or
        similar = 14, theophylline=15, antacids=16, asthma inhalers=17,
        hormone replacement=18, other=90

61   Ruptured membranes: Duration <24 hours =1, >24 hours =2, unknown=9

62-64   If ROM >24 hours, ROM-to-delivery interval in days

65   Labour onset: spontaneous=1, induced=2, no labour=3

66   Fetal distress (include dips in fetal heart rate, meconium-stained
        liquor): present=1, absent=2, unknown=9

67-69   Drugs in labour: none=0, unknown=9, epidural=1, Entonox=2,
        pethidine (or other opiate)=3, GA=4, other (incl. syntocinon)=5

70   Vaginal delivery=1, LSCS=2

71   Cephalic=1, forceps=2, rotational forceps=3, breech=4, vacuum
        extraction=5, other=6, unknown=9

72-75   Birthweight in grams

76-78   OFC in cm. Leave blank if not recorded

79   Small for gestational age (Usher and McLean 1969): no=1, yes=2

2nd line

1- 2   Apgar at 1 minute: unknown =99

3- 4   Apgar at 5 minutes: unknown =99

5   Resuscitation required: none=1, facial O_2=2, bag and mask=3, ETT=4

6   Drugs given in resuscitation: no=1, yes=2

7- 9   Temperature on admission to NNU

10   Outcome: discharged=1, died=2, transferred=3

11-16 Date of discharge/death/transfer

17-20 Cranial ultrasound data

21   Care place in first week: same as birthplace=blank, transferred to
       LRI=1, LGH=2, NCH=3, NUH=4, DCH=5, other=6

NEONATAL EVENTS DATA (variables 6 and 7, the latter is more detailed)

Variable 6:   1st line

1- 4   Study number: _ _ _ 6

5- 7   IPPV/IMV duration in days   None=000
8- 9   CPAP duration in days
10-11   No. of intubations, not including resusc. at birth
12-13   Max. insp. press.
14-15   Max. exp. press.
16-18   Max. rate

19-20   Duration in days in FiO2   0.22-0.30
21-22   0.31-0.50
23-24   0.51-0.70
25-26   0.71-0.90
27-28   0.91-1.00

29   UAC: no=0, yes=1
30-31   Duration of UAC in days
32   Age first inserted

33   Peripheral arterial line: no=0, yes=1
34-35   Duration in days, total
36-37   Age first inserted

38   TcPO2 used: no=0, yes=1, Derby=3

39   Pneumothorax: no=0, right=1, left=2, bilateral=3
40-41   No. of drains, total

42   Initial respiratory disease: none=0, IRDS/HMD=1, meconium
        aspiration=2, pneumonia=3, congenital abnorm.=4, other=5

43-45   Bradycardias,   total no. (< 80/min.) requiring action   none=000
46-48   total no. requiring oxygen
49-50   Age first noted in days
51-52   Age when max. no. noted

53-55   Apnoeas,   total no. (> 15 secs.) requiring action   none=000
56-58   total no.requiring oxygen
59-60   Age first noted
61-62   Age at max. no.

63-64   Cyanotic spells requiring oxygen, total no.   none=00
65-66   Age first noted

67   Seizures/fits: none=0, yes=1
68-69   Age first noted

70-72   Max. serum bilirubin
73-74   Age at max. serum bilirubin
75-76   Phototherapy, duration in days   none=00

77-79   Exchange transfusion, volume in ml.   none=000
80   Age at first exchange, in days

Variable 6:   2nd line

1   PDA requiring treatment: no=0, yes=1
2- 3   Age when treatment started

4- 7   Min. weight in grams
8- 9   Age at min. weight
10-11 Age when birthweight regained

12-14 TPN duration   none=000
15-16 Age first started
17-18 Age lipid started

19-20 Milk feeds: age first started
21-22 Type: breast/EBM=01, bank EBM=02, Nenatal=03, Prematalac=04,
       LBW SMA=05, SMA=06, C&G Premium=07, Osterfeed=08,
       Pregestimil=09, unknown=99

23-25 Fluids: Min. volume. ml/kg/day
26-27 Age at min. volume
28-31 Max. volume. ml/kg/day (before breast feeds started)
31-33 Age at max.

34-36 Blood transfusion: Total volume in ml.   none=000
37-38 Age at first transfusion

39-41 PPF/FFP: Total volume in ml.   none=000
42-43 Age at first transfusion

44   BMstix < 1.1: no=0, yes=1
45   Confirmed with lab. no=0, yes=1

46-49 Hb max.: _ _ . _ gm/L
50-51 Age at max. Hb

52-55 Hb min.: _ _ . _ gm/L
56-57 Age at min. Hb

58   Sodium < 125   no=0, yes=1, not done=9
59   Sodium > 145   no=0, yes=1, not done=9
60   Calcium < 1.5   no=0, yes=1, not done=9
61   Urea > 10   no=0, yes=1, not done=9
62   Alk. phos. > 700   no=0, yes=1, not done=9

63   Positive blood cultures: no=0, yes=1
64   Positive CSF: no=0, yes=1

65   Chest infection (CXR + clinical, +/- positive secretions): no=0, yes=1
66   NEC (radiological + clinical): no=0, yes=1, probable=2

67   Surgery: no=0, yes=1

68   Chronic respiratory disease: no=0, yes=1

69   Congenital abnormalities: no=0, yes=1

70   Potassium > 8.0   no=0, yes=1, not done=9

Variable 6:   3rd line

1- 2   Vitamins, age started
3- 4   Iron, age started
5- 6   Vit. D, age started
7   Vit. K, age started

8   Antibiotics: no=0, yes=1
9-10   Age started, in days
11-12   No. of courses

13   Bicarb./THAM given: no=0, yes=1
14-15   Mmol. given, total nearest whole mmol.
16-17   Age first started
18   No. of doses
19-20   Age at last dose

21   Frusemide: no=0, yes=1
22-24   No. of doses

25   Aminophylline: no=0, yes=1
26-27   Age started
28-29   Duration of treatment, including time on theophylline

30   Caffeine: no=0, yes=1
31-32   Age started
33-34   Duration in days

35   Doxapram: no=0, yes=1
36-37   Age started
38-39   Duration in days

40   Indomethacin: no=0, yes=1
41   No. of doses
42-43   Age first started

44   Anticonvulsants: no=0, yes=1
45-46   Age first started

47   Pancuronium: no=0, yes=1

48   Other drugs, includes GA, dexamethasone: no=0, yes=1

49   Tolazoline: no=0, yes=1
50   Dopamine: no=0, yes=1

Variable 7:   1st line

1- 4   Study no.: _ _ _ 7

5-16   No. of days ventilated in each of first 12 weeks,   none=0
17-28   No. of intubations in each of first 12 weeks,   none=0
29-40   No. of days in oxygen in each of first 12 weeks,   none=0

41-44   No. of pneumothoraces in each of first 4 weeks,   none=0
45-48   Side of pneumothorax in each of first 4 weeks,   none=0, right=1,
         left=2, bilateral=3

49-72   No. of bradycardias requiring stimulation in each of first 12 weeks,
        none=0, leave blank if discharged before 12 weeks
73-80   No. of bradycardias requiring oxygen in each of first 4 weeks,
        none=0, leave blank if discharged before 12 weeks

Variable 7:   2nd line

1-16   No. of bradycardias requiring stimulation in each of 5th to 12th   weeks,
        none=0, leave blank if discharged before 12 weeks

17-40   No. of apnoeas requiring stimulation in each of first 12 weeks,
        none=0, leave blank if discharged before 12 weeks
41-64   No. of apnoeas requiring oxygen in each of first 12 weeks,
        none=0, leave blank if discharged before 12 weeks

65-76   No. of cyanotic episodes requiring oxygen in each of first 12 weeks,
        none=0, leave blank if discharged before 12 weeks

Variable 7:   3rd line

1- 9   Max. bilirubin recorded in each of first 3 weeks

10-15   Max. sodium recorded in each of first 2 weeks
16-21   Min. sodium recorded in each of first 2 weeks

22-25   Max. potassium recorded in each of first 2 weeks
26-29   Min. potassium recorded in each of first 2 weeks

30-35   Max. urea recorded in each of first 2 weeks
36-39   Max. creatinine recorded in each of first 2 weeks

40-43   Max. calcium recorded in each of first 2 weeks
44-47   Min. calcium recorded in each of first 2 weeks

For all the above biochemical values, if only one level recorded for that week,
code this in both max. and min. boxes.

48-80   Volume of blood transfusions, in ml., in each of first 11 weeks,
        none=000

Variable 7:   4th line

1- 3   Volume of blood transfusions, in ml., in 12th week,   none=000

4-39   Volume of PPF/FFP in ml., in each of first 12 weeks,   none=000

40-75   Max. Hb recorded in each of first 12 weeks, none recorded=000
        If only one level recorded for that week, code this in both max. and
        min. boxes.

Variable 7:   5th line

1-36   Min. Hb recorded in each of first 12 weeks, none recorded=000
        If only one level recorded for that week, code this in both max. and
        min. boxes.

BIBLIOGRAPHY

Adamkin DH, Shott RJ, Cook LN, Andrews BF. "Nonhyperoxic retrolental fibroplasia" Pediatrics 1977: **60:** 828-830

Addison DJ, Font RL, Manschot WA. "Proliferative retinopathy in anencephalic babies" Am J Ophthalmol 1972; **74:** 967-976

Alberman ED. "Epidemiology of retinopathy of prematurity" In: Silverman WA, Flynn JT. eds. Contemporary Issues in Fetal and Neonatal Medicine, 2, Retinopathy of Prematurity. Blackwell Scientific Publications 1985, 249-266

Amato M, Pasquier S, von Murait G. "Incidence of retinopathy of prematurity in low birth weight infants with peri-ventricular haemorrhage" Neuropediatrics 1986; **17:** 191-192

Aranda JV, Saheb N, Stern L, Avery ME. "Arterial oxygen tension and retinal vasoconstriction in newborn infants" Am J Dis Child 1971; **122:** 189-194

Aranda JV, Sweet AY. "Sustained hyperoxemia without cicatricial retrolental fibroplasia" Pediatrics 1974; **54:** 434-437

Ashton N, Ward B, Serpell G. "Role of oxygen in the genesis of retrolental fibroplasia: a preliminary report" Br J Ophthalmol 1953; **37:** 513-520

Ashton N, Cook C. "Direct observation of the effect of oxygen on developing vessels: preliminary report" Br J Ophthalmol 1954; **38:** 433-440

Ashton N. In personal communication cited by Tizard JPM. "Indications for oxygen therapy in the newborn" Pediatrics 1964; **34:** 771-786

Ashton N, Henkind P. "Experimental occlusion of retinal arterioles: Using graded glass ballotini" Br J Ophthalmol 1965; **49:** 225-234

Ashton N. "Oxygen and the growth and development of retinal vessels: In vivo and in vitro studies" Am J Ophthalmol 1966; **62:** 412-435

Ashton N. Retrolental fibroplasia now retinopathy of prematurity"
Br J Ophthalmol 1984; **68:** 689

Avery ME, Oppenheimer EH. "Recent increase in mortality from hyaline membrane disease" J Pediatr 1960; **57:** 553-559

Balentine JD. "Pathology of oxygen toxicity" Academic Press, London, 1982

Bancalari E, Flynn J, Goldberg RN, Bawol R, Cassady J, Schiffman J, Fewer W, Roberts J, Gillings D, Sim E. "Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity" Pediatrics 1987; **79:** 663-669

Banker BQ, Larroche J-C, "Periventricular leukomalacia of infancy: A form of neonatal anoxic encephalopathy" Arch Neurol 1962; **7:** 386-410

Bauer CR. "The occurrence of retrolental fibroplasia in infants of birthweight 1000 grams and less" Clin Res 1978; **26:** 824A

Baum JD, Tizard JPM. "Retrolental fibroplasia: management of oxygen therapy" Br med Bull 1970; **26:** 171-174

Biglan AW, Brown DR, Reynolds JD, Milley JR. "Risk factors associated with retrolental fibroplasia" Ophthalmology 1984; **91**: 1504-1511

Boyd JT, Hirst KM. "Incidence of retrolental fibroplasia in England and Wales in 1951" Br Med J 1955; **ii**: 83-85

Bossi E, Koerner F, Flury B, Zulauf M. "Retinopathy of prematurity: a risk factor analysis with univariate and multivariate statistics" Helv paediat Acta 1984; **39**: 307-317

Brown DR, Milley JR, Ripepi UJ, Biglan AW. "Retinopathy of prematurity: risk factors in a five-year cohort of critically ill premature neonates" Am J Dis Child 1987; **141**: 154-160

Brown DR, Biglan AW, Stretavsky MMA. "Retinopathy of prematurity: the relationship with intraventricular haemorrhage and bronchopulmonary dysplasia" J Pediatr Ophthalmol Strabismus 1990; **27**: 268-271

Bruckner HL. "Retrolental fibroplasia - associated with intrauterine anoxia?" Arch Ophthalmol 1968; **80**: 504-505

Campbell FW. "The influence of a low atmospheric pressure on the development of the retinal vessels in the rat" Tr ophth Soc UK 1951; **71**: 287-300

Campbell K. "Intensive oxygen therapy as a possible cause of retrolental fibroplasia: A clinical approach" Med J Australia 1951; **2**: 48-50

Campbell PB, Bull MJ, Ellis FD, Bryson CQ, Lemons JA, Schreiner RL. "Incidence of retinopathy of prematurity in a tertiary newborn intensive care unit" Arch Ophthalmol 1983; 101: 1686-1688

Cantolino SJ, O'Grady EE, Herrera JA, Israel C, Justice J, Flynn JT. "Opthalmoscopic monitoring of oxygen therapy in premature infants: Fluorescein angiography in acute retrolental fibroplasia" Am J Ophthalmol 1971; 72: 322-331

Clarke M, Clayton DG, Mason ES, MacVicar J. "Asian mothers' risk factors for perinatal death - the same or different? A 10 year review of Leicestershire perinatal deaths" Br Med J 1988; 297: 384-387

Committee for the classification of retinopathy of prematurity. "The international classification of retinopathy of prematurity " Br J Ophthalmol 1984; 68: 690-697

Cross KW. "Cost of preventing retrolental fibroplasia?" Lancet 1973; ii: 954-956

Crosse VM. "The problem of retrolental fibroplasia in the city of Birmingham" Tr ophth Soc UK 1951; 71: 609-612

Crowe J, Rea PA, Rolfe P. "Retinopathy of prematurity, intraventricular haemorrhage and oxidative damage" Pediatrics 1986; 77: 129-130

Darlow BA. "Incidence of retinopathy of prematurity in New Zealand" Arch Dis Child 1988; 63: 1083-1086

Darlow BA, Horwood LJ, Clemett RS. "Retinopathy of prematurity: risk factors in a prospective population-based study" Paediatr Perinat Epidemiol 1992; 6: 62-80

Davey Smith G, Phillips AN. "Confounding in epidemiological studiBanker et al, 1962, y not be all they seem" Br Med J 1992; 305: 757-759

Dollery CT, Hill DW, Mailer CM, Ramalho PS. "High oxygen pressure and the retinal blood vessels" Lancet 1964; ii: 291-292

Dormandy TL. "Free-radical oxidation and antioxidants" Lancet 1978; i: 647-650

Dubowitz LMS, Dubowitz V. "Clinical assessment of gestational age in the newborn infant" J Pediatr 1970; 77: 1-10

Editorial. "Oxygen restriction and retinopathy of prematurity" Lancet 1992; 339: 961-963

Evans PJ. "Retrolental fibroplasia" Tr ophth Soc UK 1951; 71: 613-616

Exline Jr. AL, Harrington MR. "Retrolental fibroplasia: clinical statistics from the premature center of Charity Hospital of Louisiana at New Orleans" J Pediatr 1951; 38: 1-7

Feman SS, Podgorski SF, Cotton R. "Changing patterns in retinopathy of prematurity" Ann Ophthalmol 1984: 16: 1056-1058

Fenton AC, Field DJ, Woods KL, Evans DH, Levene MI. "Circulatory effects of fast ventilator rates in preterm infants" Arch Dis Child 1990; **65:** 662-666

Fielder AR, Ng YK, Levene MI. "Retinopathy of prematurity: age at onset" Arch Dis Child 1986; **61:** 774-778

Flower RW. "Perinatal retinal vascular physiology" In: Silverman WA, Flynn JT. eds. Contemporary Issues in Fetal and Neonatal Medicine, 2, Retinopathy of Prematurity. Blackwell Scientific Publications 1985, 97-120

Flynn JT. "Acute proliferative retrolental fibroplasia: multivariate risk analysis" Tr Am Ophthal Soc 1983; **31:** 549-591

Flynn JT, Bancalari E, Bachynski BN. "Retinopathy of prematurity: Diagnosis, severity and natural history" Ophthalmology 1987; **94:** 620-629

Flynn JT, Bancalari E, Snyder ES, Goldberg RN, Feuer W, Cassady J, Schiffman J, Feldman HI, Bachynski BN, Buckley E. et al "A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity" New Engl J Med 1992; **326:** 1050-1054

Forrester RM, Jefferson E, Naunton WJ. "Oxygen and retrolental fibroplasia: A seven-year survey" Lancet 1954; **ii:** 258-260

Garner A. "The pathology of retinopathy of prematurity" In: Silverman WA, Flynn JT. eds. Contemporary Issues in Fetal and Neonatal Medicine, 2, Retinopathy of Prematurity. Blackwell Scientific Publications 1985, 19-52

Garner A, Kissun R. "The role of ischaemia in the pathogenesis of retinal neovascularisation" In: Ben Ezra D, Ryan SJ, Glaser BM, Murphy RP. eds. Ocular circulation and neovascularisation. Dordrecht; Martinus Nijhoff/Dr W Junk Publishers 1987, 131-134

Gole GA. "Animal models of retinopathy of prematurity" In: Silverman WA, Flynn JT. eds. Contemporary Issues in Fetal and Neonatal Medicine, 2, Retinopathy of Prematurity. Blackwell Scientific Publications 1985, 53-95

Gordon HH. "Oxygen therapy and survival rate in prematures" (letter) Pediatrics 1957; 19: 967

Gunn TR, Aranda JV, Little J. "Incidence of retrolental fibroplasia" Lancet 1978; i: 216

Gunn TR, Easdown J, Outerbridge EW, Aranda JV. "Risk factors in retrolental fibroplasia" Pediatrics 1980; 65: 1096-1100

Guy LP, Lanman JT, Dancis J. "The possibility of total elimination of retrolental fibroplasia by oxygen restriction" Pediatrics 1956; 17: 247-249

Hack M, Fanaroff AA, Merkatz IR. "The low birthweight infant - Evolution of a changing outlook" New Engl J Med 1979; 301: 1162-1165

Hammer ME, Mullen PW, Ferguson JG, Pai S, Cosby C, Jackson KL. "Logistic analysis of risk factors in acute retinopathy of prematurity" Am J Ophthalmol 1986; 102: 1-6

Hey E. "Retrolental fibroplasia as one index of perinatally acquired handicap"
In: Chalmers I, McIlwaine G. eds. Perinatal Audit and Surveillance.
Proceedings of the Eighth study group of the Royal College of Obstetricians and
Gynaecologists, 1980

Houlton ACL. "A study of cases of retrolental fibroplasia seen in Oxford"
Tr ophth Soc UK 1951; **73:** 583-590

Hungerford J, Stewart A, Hope P. "Ocular sequelae of preterm birth and their
relationship to ultrasound evidence of cerebral damage" Br J Ophthalmol 1986;
70: 463-468

James LS, Lanman JT. eds. "History of oxygen therapy and retrolental
fibroplasia" Pediatrics 1976; **57 (supp):** 591-642

Kalina RE, Karr DJ. "Retrolental fibroplasia: Experience over two decades in
one institution" Ophthalmology 1982; **89:** 91-95

Katzman G, Satish M, Krishnan V, Marcus D, Bovino J. "Comparative analysis of
lower and higher stage retrolental fibroplasia (RLF)" Pediatr Res 1982; **16:**
294A

Keith CG. "Retrolental fibroplasia, a classification of the developing and
cicatricial changes" Aust J Ophthalmol 1979; **7:** 189-194

Keith CG, Kitchen WH. "Retinopathy of prematurity in extremely low
birthweight infants" Med J Aust 1984; **141:** 225-227

King MJ. "Retrolental fibroplasia: A study of two hundred and thirty-eight cases" Arch Ophthalmol 1950; **43:** 694-709

Kingham JD. "Acute retrolental fibroplasia" Arch Ophthalmol 1977; **95:** 39-47

Kinsey VE. "Retrolental fibroplasia: Cooperative study of retrolental fibroplasia and the use of oxygen" Arch Ophthalmol 1956; **56:** 481-529

Kinsey VE, Arnold HJ, Kalina RE, Stern L, Stahlman M, Odell G, Driscoll Jr. JM, Elliott JH, Payne J, Patz A. "PaO$_2$ levels and retrolental fibroplasia: A report of the cooperative study" Pediatrics 1977; **60:** 655-668

Koerner F, Bossi E, Wetzel C, Flury B. "Retinopathy of prematurity: the influence of gestational age and retinal maturity on the statistical behaviour of risk factors" Graefe's Arch Clin Exp Ophthalmol 1986; **224:** 40-45

Kushner BJ, Gloeckner E. "Retrolental fibroplasia in full term infants without exposure to supplemental oxygen" Am J Ophthalmol 1984; **97:** 148-153

Levene MI. "Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound" Arch Dis Child 1981; **56:** 900-904

Levene MI, Williams JL, Fawer C-L. "Ultrasound of the infant brain" Oxford Blackwell Scientific Publications (Spastics International Medical Publications) 1985

Long JG, Philip AGS, Lucey JF. "Excessive handling as a cause of hypoxemia" Pediatrics 1980; **65:** 203-207

Long JG, Lucey JF, Philip AGS. "Noise and hypoxemia in the intensive care nursery" Pediatrics 1980; 65: 143-145

Lou HC, Lassen NA, Friis-Hansen B. "Impaired autoregulation of cerebral blood flow in the distressed newborn infant" J Pediatr 1979; 94: 118-121

Lucey JF, Dangman B. "A reexamination of the role of oxygen in retrolental fibroplasia" Pediatrics 1984; 73: 82-96

MacMahon P, Fleming PJ, Speidel BD, Dunn PM. "Low inspired oxygen concentrations in very low-birthweight infants needing ventilatory support: an approach to the prevention of retrolental fibroplasia" Br J Obst Gynae 1986; 93: 361-363

McCord JM. "Oxygen-derived free radicals in postischaemic tissue injury" New Engl J Med 1985; 312: 159-163

McCormick AQ, "Retinopathy of prematurity" Curr Probl Pediatr 1977; 7: 3-28

McCullagh P. "Regression models for ordinal data" J Royal Statistical Soc 1980; Series B: 42(2), 109-142

McDonald AD. "Neurological and ophthalmic disorders in children of very low birthweight" Br Med J 1962; i: 895-900

Medical Research Council "A report to the Medical Research Council by their council on retrolental fibroplasia in the United Kingdom" Br Med J 1955; ii: 78-82

Monos T, Yassur Y, Lifchitz T, Shani L, Zmora E, Karplus M. "ROP in Soroka medical center neonatal ICU" In: Ben Ezra D, Ryan SJ, Glaser BM, Murphy RP. eds. Ocular circulation and neovascularisation. Dordrecht; Martinus Nijhoff/Dr W Junk Publishers 1987, 193-196

Mushin AS. "Retinopathy of prematurity - A disease of increasing incidence?" Tr ophth Soc UK 1974; 94: 251-257

Naiman J, Green R, Patz A. "Retrolental fibroplasia in hypoxic newborn" Am J Ophthalmol 1979; 88: 55-58

Ng YK, Fielder AR, Shaw DE, Levene MI. "Epidemiology of retinopathy of prematurity" Lancet 1988; ii: 1235-1238

Ng YK, Fielder AR, Shaw DE, Levene MI. "Retinopathy of prematurity: risk factors" Proceedings of 60th annual meeting, British Paediatric Association 1988; page 30

Ng YK, Fielder AR, Levene MI, Trounce JQ, McLellan N. "Are severe acute retinopathy of prematurity and severe periventricular leucomalacia both ischaemic insults?" Br J Ophthalmol 1989; 73: 111-114

Ogata ES, Gregory GA, Kitterman JA, Phibbs RH, Tooley WH. "Pneumothorax in the respiratory distress syndrome: incidence and effect on vital signs, blood gases, and pH" Pediatrics 1976; 58: 177-183

Owens WC, Owens EU. "Retrolental fibroplasia in premature infants: II. Studies on the prophylaxis of the disease; The use of alpha tocopheryl acetate" Am J Ophthalmol 1949; 32: 1631-1637

Palmer EA. "Optimal timing of examination for acute retrolental fibroplasia" Ophthalmology 1981; **88:** 662-668

Patz A. "The role of oxygen in retrolental fibroplasia" Pediatrics 1957; **19:** 504-524

Patz A. "Retrolental fibroplasia" Surv Ophthalmol 1969; **14:** 1-29

Pharoah POD, Alberman ED. "Mortality of low birthweight infants in England and Wales 1953 to 1979" Arch Dis Child 1981; **56:** 86-89

Perlman JM, McMenamin JB, Volpe JJ. "Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage" New Engl J Med 1983; **309:** 204-209

Phelps DL. "Retinopathy of prematurity: An estimate of vision loss in the United States 1979" Pediatrics 1981; **67:** 924-926

Phelps DL, Rosenbaum AL. "Effects of marginal hypoxemia on recovery from oxygen-induced retinopathy in the kitten model" Pediatrics 1984; **73:** 1-6

Prendiville A, Schulenberg WE. "Clinical factors associated with retinopathy of prematurity" Arch Dis Child 1988; **63:** 522-527

Procianoy RS, Garcia-Prats JA, Hittner HM, Adams JM, Rudolph AJ. "An association between retinopathy of prematurity and intraventricular haemorrhage in very low birth weight infants" Acta Paediatr Scand 1981; **70:** 473-477

Purohit DM, Ellison RC, Zierler S, Miettinen OS, Nadas AS. "Risk factors for retrolental fibroplasia: experience with 3025 premature infants" Pediatrics 1985; **76:** 339-344

Reese AB, King MJ, Owens WC. "A classification of retrolental fibroplasia" Am J Ophthalmol 1953; **36:**1333-1335

Reisner SH, Amir J, Shohat M, Krikler R, Nissenkorn I, Ben-Sira I. "Retinopathy of prematurity: incidence and treatment" Arch Dis Child 1985; **60:** 698-701

Robinson HP. "Sonar measurement of fetal crown-rump length as means of assessing maturity in first trimester of pregnancy" Br Med J 1973; **iv:** 28-31

Rubinstein K. "Mechanism of retrolental fibroplasia" Br J Ophthalmol 1952; **36:** 303-312

Rushton DI, Preston PR, Durbin GM. "Structure and evolution of echo dense lesions in the neonatal brain" Arch Dis Child 1985; **60:** 798-808

Sacks LM, Schaffer DB, Anday EK, Peckham GJ, Delivoria-Papadopoulos M. "Retrolental fibroplasia and blood transfusion in very low-birth-weight infants" Pediatrics 1981; **68:** 770-774

Saigal S, Rosenbaum P, Stoskopf B, Milner R. "Follow-up of infants 501 to 1500 gm birth weight delivered to residents of a geographically defined region with perinatal intensive care facilities" J Pediatr 1982; **100:** 606-613

Saigal S, Rosenbaum P, Stoskopf B, Sinclair JC. :Outcome of infants 501 to 1500 gm birth weight delivered to residents of the McMaster Health Region" J Pediatr 1984; **105:** 969-976

Saito Y, Omoto T, Cho Y, Hatsukawa Y, Fujimura M, Takeuchi T. "The progression of retinopathy of prematurity and fluctuation in blood gas tension" Graefe's Arch Clin Exp Ophthalmol 1993; **231:** 151-156

Schaffer DB, Johnson L, Quinn GE, Boggs TR. "A classification of retrolental fibroplasia to evaluate vitamin E therapy" Ophthalmology 1979; **86:** 1749-1760

Schaffer DB, Johnson L, Quinn GE, Weston M, Bowen FW. "Vitamin E and retinopathy of prematurity" Ophthalmology 1985; **92:** 1005-1011

Shahinian L, Malachowski N. "Retrolental fibroplasia: A new analysis of risk factors based on recent cases" Arch Ophthalmol 1978; **96:** 70-74

Shohat M, Reisner SH, Krikler R, Nissenkorn I, Yassur Y, Ben-Sira I. "Retinopathy of prematurity: Incidence and risk factors" Pediatrics 1983; **72:** 159-163

Silverman WA, Blodi FC, Locke JC, Day RL, Reese AB. "Incidence of retrolental fibroplasia in a New York nursery" Arch Ophthalmol 1952; **48:** 698-711

Silverman WA. "Retrolental fibroplasia - A modern day parable" Oliver TK. series ed. Monographs in Neonatology. New York, Grune and Stratton 1980

Sinha SK, Davies JM, Sims DG, Chiswick ML. "Relation between periventricular haemorrhage and ischaemic brain lesions diagnosed by ultrasound in very pre-term infants" Lancet 1985; ii: 1154-1156

Slater TF, Riley PA. "Free-radical damage in retrolental fibroplasia"
Lancet 1970; ii: 467

Sorsby A. "The incidence and causes of blindness in England and Wales 1948-1962" Reports in Public Health and Medical Subjects no. 114, HMSO 1966

Szewczyk TS. "Retrolental fibroplasia: Etiology and prophylaxis"
Am J Ophthalmol 1952; 35: 301-311

Tarkkanen A, Mustonen R. "Retrolental fibroplasia: Cases seen at the Helsinki University Hospital 1956-1974" Acta Ophthalmol 1978; 56: 169-178

Terry TL. "Extreme prematurity and fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report"
Am J Ophthalmol 1942; 25: 203-204

Terry TL. "Fibroplastic overgrowth of persistent tunica vasculosa lentis in premature infants. II. Report of cases - clinical aspects" Arch Ophthalmol 1943; 29: 36-53

Terry TL. "Fibroplastic overgrowth of persistent tunica vasculosa lentis in premature infants. IV. Etiologic factors" Arch Ophthalmol 1943; 29: 54-68

Tizard JPM. "Indications for oxygen therapy in the newborn" Pediatrics 1964; 34: 771-786

Tizard JPM. "Modern management of oxygen therapy in the newborn"
Proc roy Soc Med 1971; **64:** 771-773

Tripathi B, Ashton N. Knight G. "Effect of oxygen on the developing retinal
vessels in tissue culture. IV. Effect of hyperoxia on rabbit retinal vessels in
tissue culture" Exp Eye Res 1974; **19:** 449-475

Trounce JQ, Rutter N, Levene MI. "Periventricular leucomalacia and
intraventricular haemorrhage in the preterm neonate" Arch Dis Child 1986;
61: 1196-1202

Trounce JQ, Shaw DE, Levene MI, Rutter N. "Clinical risk factors and
periventricular leucomalacia" Arch Dis Child 1988; **63:** 17-22

Usher R, McLean F. "Intrauterine growth of live-born Caucasian infants at sea
level: Standards obtained from measurements in 7 dimensions of infants born
between 25 and 44 weeks gestation" J Pediatr 1969; **74:** 901-910

Valentine PH, Jackson JC, Kalina RE, Woodrum DE. "Increased survival of low
birth weight infants: impact on the incidence of retinopathy of prematurity"
Pediatrics 1989; **84:** 442-445

Volpe JJ. "Cerebral blood flow in the newborn infant: relation to hypoxic-
ischemic brain injury and periventricular haemorrhage" J Pediatr 1979; **94:**
170-173

Yu VYH, Rolfe P. "Effect of continuous positive airway pressure breathing on cardiorespiratory function in infants with respiratory distress syndrome" Acta Paed Scand 1977; **66:** 59-64

Yu VYH, Hookham DM, Nave JRM. "Retrolental fibroplasia - controlled study of 4 years' experience in a neonatal intensive care unit" Arch Dis Child 1982; **57:** 247-252

Zacharias L. "Retrolental fibroplasia: A survey" Am J Ophthalmol 1952; **35:** 1426-1454