RETINOPATHY OF PREMATURITY IN BRITISH COLUMBIA: 1952-1983

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ABSTRACT

In recent years, concern about a new epidemic of retinopathy of prematurity (ROP) has focused attention on the increasing incidence of the disease and the factors responsible for its most severe consequences. Two studies designed to address these issues were done using data from three sources: the B.C. Health Surveillance Registry (Registry), Physicians's Notices of Livebirth (PNOB), and the Vancouver General Hospital (VGH).

In the first study, Registry and PNOB records were used to determine crude annual birth weight-specific incidence rates for ROP in infants liveborn in the Province of British Columbia (B.C.) in the period 1952-1983. These rates showed that, in B.C., the original epidemic of the disease ended in 1954. Linear regression lines fitted for each of four birth weight categories showed that, in the 29 year period after 1954, there was a significant increase in the incidence of ROP-induced blindness in infants weighing less than 1000 grams at birth. To refine this observation, the data were sub-divided: the 29 year period, to two smaller periods, 1955-1964 and 1965-1983; the less than 1000 gram birth weight category to two sub-categories, 500-749 and 750-999 grams. Since the inter-period incidence should have been similar if the birth weight-specific incidence had not changed since the end of the original epidemic, the crude weight-specific rates for ROP-induced blindness in the early period were used to calculate the expected number of cases in the later period. When weight-standardized incidence ratios (SIR's) and 95% confidence limits were calculated, the results showed that, in the 750-999 gram sub-category, the SIR was significantly increased. Infants born in the period 1965-1983 were 3.07 times more likely to be ROP: blind than their equal weight counterparts in the

earlier period. In infants weighing 500-749 and 1000 grams or more, there was no evidence to suggest an increase in incidence after 1954.

The second study was done to determine the cofactors that differentiate infants who are blinded by ROP from those who are not. Infants were included if (i) they were born in B.C. between 1955 and 1983, (ii) they were known to the Registry as being ROP: blind (cases) or not blind (controls), and (iii) they were born in or admitted to the VGH within 28 days of birth. When the data from all three data sources were dichotomized and analyzed using univariate techniques, two variables, respiratory distress syndrome (RDS) and neonatal weight loss, showed a significantly protective effect. The effect of RDS disappeared when the data were stratified by birth interval indicating that the observed association was confounded by time. When the variables were reanalyzed in continuous form, none were significantly associated with visual outcome. However, since the power of the cofactor study was extremely low, none of the variables that were included can be eliminated as potential cofactors for the induction of blindness in infants with ROP.

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INTRODUCTION

In recent years, concern about increases in the incidence of retinopathy of prematurity (ROP) has focused attention on a disease once thought to be well understood. Much of this attention has focused on attempts to substantiate an alleged new epidemic. However, with the re-emergence of interest in this supposedly iatrogenic disease, the data implicating supplemental oxygen, the factor once described as the 'sole and sufficient cause for ROP', have been re-examined. The perceived new epidemic, and the discovery of cases not exposed to oxygen or exposed but closely monitored has undermined the sanctity of the 'oxygen as cause' theory. Many now see oxygen as an important by no means the only cause for ROP.

The renewed interest in ROP, and the re-examination of the data previously collected has undermined yet another idea once considered sacrosanct: that exposure to supplemental oxygen in the early neonatal period caused not only the onset of the disease but for the blinding that occasionally results from it. Although there are no grounds to substantiate this idea, there are no alternative theories that suffice to explain why some infants with ROP progress to the stage of blindness while others do not.

The recent studies done to establish the existence of the new epidemic or to determine the factors etiologically related to the disease have been hampered by the fact that they were hospital-based, hence difficult to extrapolate and potentially biased. A preliminary study done in the Province of British Columbia (B.C.) suggested that, because it has a long-standing disease registry, B.C. might be a unique jurisdiction in which to study changes

in the incidence of ROP. To exploit this unique position, a follow-up to the preliminary study was designed to:

i. determine if an increase in the incidence of ROP observed in the preliminary study was 'real' and if so, to identify the infants at increased risk, and

ii. identify the factors or co-factors that lead to the induction of blindness in infants who have ROP.

This thesis, which describes the follow-up study and details the history of ROP, is organized as follows:

Chapter I: details the emergence of ROP as a problematic disease entity, discusses the early perceptions of the clinical and pathological signs, and examines the evidence pointing to the first epidemic of the disease,

Chapter II: briefly reviews the factors originally suggested as possible etiologic, examines the evidence that ultimately implicated the use of supplemental oxygen as a cause, and describes the policy responses that brought the original epidemic to an end,

Chapter III: describes the history of the disease, and the policies and technological advances relating to it, since the end of the original epidemic,

Chapter IV: describes the rationale and methods used for the follow-up studies,

Chapter V: outlines the results of those studies, and

Chapter VI: discusses the results, the policy implications and the studies that need to be done to clarify the issues raised.

CHAPTER I
RETINOPATHY OF PREMATURITY: EMERGENCE OF THE DISEASE

I.1 BOSTON 1941-1942

In 1941, a Boston ophthalmologist, Dr. Stewart Clifford, noted opacities in the eyes of two unrelated infants. The infants, both blind, were subsequently referred, the first, to Dr. Paul Chandler, the second, to Dr. Theodore Terry. Chandler and Terry were quick to realize that they were confronted with not one but two children afflicted with a condition neither had seen previously[1]. A year later, Terry published the first in a series of reports that described what he originally thought was a previously unknown disorder[2]. This series[3-8] served to define a problem that would attract international attention. Before the etiological factors could be identified and steps taken to minimize the risk, an estimated 10,000 children would be blinded and modern medical care itself would be implicated, not for curing the disease but rather, for causing it.

I.2 NAMING THE DISEASE

Although he first called the new disease 'persistence of the tunica vasculosa lentis'[2], Terry was soon referring to it as 'retrolental fibroplasia'[3]. This term would eventually become entrenched in the literature but before it did, a number of alternate names proposed[9,10]. In fact, the penchant for coining new names became so prevalent that, by the end of the 1940's, there were at least 19 different names describing what appears to have been, the same clinical entity[11].

By 1949, 'retrolental fibroplasia' was being referred to as descriptively deceptive label because it described only the most severe manifestations of the disease[12]. Two years later, a more appropriate term[14], 'retinopathy of

prematurity', was introduced[13]. Unfortunately, for the next three decades, the two terms were used interchangably. In 1984, an expert international committee recommended that earlier term, 'retrolental fibroplasia', should be abandoned in favor of the more accurate 'retinopathy of prematurity' or ROP[15].

I.3 EARLY CLINICAL DESCRIPTIONS

In his original report, Terry noted that the original cases were premature and both bilateral, greyish-white membranes behind their crystalline lenses. Since no exact counterpart for these membranes was known to occur prenatally, he concluded that the membrane represented a new disease that occurred postnatally. Originally, he thought the membrane resulted from a persistence of the entire vascular structure of the primary vitreous[2] or from a fibroplastic overgrowth of a persistent tunica vasculosa lentis[2-4,7,8]. While accepted by some[9], this view was rejected by others who argued that the disease was congenital[9,10] or that it was part of a syndrome involving cerebral and retinal neuro-ectoderm[10].

Resolution of these early conflicts started in 1948 when Owens and Owens[16] described the onset and progression of ROP in 9 infants, all premature and all normal at birth. In these infants, the first detectable anomaly* was a slight dilation of the retinal arteries and veins. As the disease progressed, the dilation increased and the vessels became tortuous. Shortly thereafter, grayish elevations began to appear on the surface of the retina and eventually, the anterior portion of the swollen retina, covered with newly formed blood vessels, billowed forward in folds forming the

---

* in their original study[16], these anomalies occurred as early as 80 days; in a later study, as early as 3 to 5 weeks after birth[17]

retrolental membrane described by Terry. In the infants most severely affected, the membrane was complete; in others, it was incomplete[16].

The early clinical studies[16,17] showed that ROP was not congenital and not related to a persistence of the primary vitreous. Furthermore, they showed that, although many infants were born with remnants of the tunica vasculosa lentis in place[16,18-20], these remnants disappeared so that, prior to onset, the eyes of affected infants were completely normal. Unfortunately, when they first appeared, the observations made by Owens and Owens were only minimally useful in clarifying the clinical picture. Some authors persisted in the belief that the disease originated in the vitreous[12,18,21]. Others refused to accept the idea that it was not related to a persistence of the hyaloid artery or another fetal structure, the pupillary membrane[24].

In time, it was found that, although pupillary membranes and remnants of the hyaloid artery could be present, they were too rare to be implicated as factors in the development of ROP[22-25]. This better understanding of the normal picture in the eyes of premature infants helped but failed to eliminate all of the early clinical confusion. There was yet another factor, pertaining to what appeared to be the confusing array of signs that were associated with the disease, that had to be resolved. In some reports, hemorrhaging was linked to the onset of symptoms[18,25-27]; in others, hemorrhages were thought to be unrelated to onset but necessary precursors for the progression of the disease beyond dilation and tortuosity[27]. In some affected infants, there were a myriad of symptoms including posterior synechias, corneal opacities, cataracts, secondary glaucoma, microphthalmia, endophthalmia, nystagmus, strabismus, photophobia and myopia[4,7,10,21,28-36]. In other infants, the disease developed and progressed in the absence of some or all of these anomalies. Some cases with ROP presented with retinas

that were totally detached, some showed no detachment and some, only partial detachments in localized areas[22].

For a time, the diversity of clinical signs fueled speculation as to the origin and meaning of retinal detachment. Owens[37] and others[18,21,23,31] argued that detachments were the result of the earlier manifestations of the disease. Others argued that delayed retinal coaptation, itself a form of retinal detachment, was a predisposing factor[38]. Few disagreed with the idea that the formation of a complete membrane behind the crystalline lens was one of the characteristic changes that took place as the disease progressed. However, reports of infants with severe ROP but not the membrane[26], and disagreements as to the nature of the membrane, further complicated the attempts to define the clinical picture. Most physicians who saw cases with a retrolental membrane supported the view that it was formed by the fusion of a swollen and, in some cases, detached retina. However, even this was not universally accepted as there were those who argued that the membrane originated not with the retina but rather, with the ciliary body[38,39].

Not all of the clinical confusion related to the more advanced stages of the disease. Although dilation and tortuosity of the retinal vessels were usually described as the first observable signs of onset[18-20,25,26,40], there were disagreements. For example, some authors argued that clouding of the vitreous[41,42] or peripheral retinal detachments[38] were diagnostic for the onset of the disease. Again, delineation of the normal picture eventually minimized many of these disagreements. Numerous authors reported that, although an early sign, vitreal clouding was not necessarily the first sign[36,38,43] and at least one author[44] noted that clouding was, in fact, a normal occurrence in an immature eye. Mann[45] reported that early retinal

detachments were also common in premature infants and others noted that, because infant lenses are doubly refractile, retinas could appear detached when in fact, they were not[46].

Another group of investigators argued that dilation and tortuosity were preceded by a short period of vascular constriction[36,47,48]. Initially, this idea appeared to be contradicted by the fact that, in the published case reports, vasoconstriction was seldom mentioned. However, this was far from conclusive evidence since the eyes of affected infants often went from being completely normal to obviously abnormal in very short periods of time[40]. Furthermore, the changes characterizing the early stages were often difficult to see unless the examinations were done with the pupils fully dilated. Thus, unless mydriatics were used routinely and unless examinations were done early and often, a vasoconstrictive phase preceding dilation and tortuosity could have easily been overlooked.

The lack of agreement with respect to the signs associated with both the early and the later stages led some authors to conclude that several similar but unrelated diseases were being described[12,21,25,39]. Others argued that there were two forms of the same disease, one affecting the anterior portion of the eye, the other, the posterior[118,49]. In 1952, it was suggested that "... the disease itself (was) changing in character, for the description by Terry differs widely from more recent ones"[46]. Eventually these speculations were stilled, primarily as a result of the introduction of hospital policies calling for weekly ophthalmologic examinations of premature infants. As the disease was seen to develop and progress in an ever increasing number of infants, it became obvious that, although the clinical manifestations were variable, ROP represented a single and an easily identifiable disease entity.

I.4 CONSENSUS VIEW OF THE CLINICAL PICTURE

By the early 1950's, most authors had acceded to the idea that ROP was a progressive disease with two distinct clinical phases: an active phase (aROP) followed by an inactive or cicatricial phase (cROP)[25]. Classification systems designed to categorize these phases[51-53] eventually helped to bring about a consensus view of the clinical picture. In the most widely used of these systems[14], the active form of the disease was described as follows:

STAGE 1: VASCULAR STAGE
-marked by tortuosity and dilation of the retinal vessels, areas of retinal neovascularization, and transient periods of vasoconstriction prior to dilation

STAGE 2: RETINAL STAGE
-marked by vitreal haze, more pronounced neovascularization, elevated patches on the retina, and retinal hemorrhaging

STAGE 3: STAGE OF EARLY PROLIFERATION
-occurs with the extension of the retinal vessels into the vitreous and localized retinal detachments

STAGE 4: STAGE OF MODERATE PROLIFERATION
-reached when half the retina is elevated and there are total or partial detachments

STAGE 5: STAGE OF ADVANCED PROLIFERATION
-marked by total detachment of the retina and massive intraocular hemorrhages in the vitreous.

In the early years, the failure to diagnose infants with other than the most severe forms of the disease created the impression that, once symptoms became manifest, ROP was irreversible. By the early 1950's, it was known that this was not the case. The disease process could arrest or spontaneously regress from any of the stages defined for aROP. In fact, spontaneous regressions were so frequent that many considered them to be a characteristic feature of the disease[13,14,25,26,31,42,54-56]. What wasn't as well known were the precise frequencies with which these regressions occurred. Zacharias[36] cited

data suggesting that 60% of cases underwent spontaneous regression. Patz[48] and Bousquet and Laupus[26] suggested that rates were 73% and 39% respectively. These discrepancies were of some importance because, along with the severity of the clinical signs in the active phase, regression was a major factor determining the extent of the damage entrenched in the cicatricial phase. The consensus view of the clinical picture of this phase, again described in the context of the most widely used classification system, is as follows[14]:

GRADE I: MINOR CHANGES
-marked by a decrease in vessel diameter, areas of irregular retinal pigmentation, small masses of opaque tissue in periphery of fundus, and myopia

GRADE II: DISC DISTORTION
-occurs when the vessels pull to one side, pigment appears around the disc, and there are small masses of opaque tissue in the periphery of the fundus

GRADE III: RETINAL FOLD
-characterized by retinal folds that incorporate the retinal vessels and extend to a peripheral mass of opaque tissue

GRADE IV: INCOMPLETE RETROLENTAL MASS
-marked by the presence of a retrolental mass

GRADE V: COMPLETE RETROLENTAL MASS
-occurs when the mass of fibrous tissue fills the entire retrolental space, there are elongated ciliary or dentate processes[57], shallow anterior chambers, anterior or posterior synechias, and microphthalmia

As numerous authors were quick to point out, the disease defied strict classification. The stages of the active phase and the grades of the cicatricial phase often blended into each other. Moreover, changes secondary to the primary retinal lesions were not uncommon. To quantify these changes, Reese and Stepanik[57] examined 672 cases with late active or early cROP. Since cases with the most severe forms of damage were more likely to be included

in their study, their results (Table I.1) did not reflect the frequency with which the various grades of cROP occured. However, they did show the distribution of secondary changes across grades and the extent of the overlapping that occurs when residual damage is graded. The data also lent credence to what was, at the time, the widespread belief that, although there were often differences in the degree of involvement between the two eyes[21,22], the disease was, for the most part, bilateral[21,22,25,35-37].

I.5 EARLY PATHOLOGICAL DESCRIPTIONS

The pathological changes associated with ROP were even more difficult to define. Many of the problems stemmed from the clinical confusion itself, others from the fact that, in the early years, there was only a limited understanding of the normal pattern of growth and differentiation in the developing eye. A third factor pertained to the problem of obtaining appropriate specimens. In the 1940's, eyes examined pathologically were removed from affected infants because of suspected retino-blastoma. Since these infants were in the most advanced stages of ROP, their eyes produced almost no information relating to the primary lesions[10,12,39, 58].

When clinical attention shifted to early aROP, interest in the pathological changes followed suit. However, the shift in emphasis did little to alleviate the problems. By the time the first clinical signs appeared, infants were usually past the immediate postnatal period and hence, had a good chance for survival[59]. In addition, ROP-affected eyes, particularly those in the early stages, usually didn't require enucleation[36]. Therefore, as the clinical picture unfolded and physicians became more adept at differentiating ROP from other conditions, affected eyes became progressively more difficult to obtain.

TABLE I.1

FREQUENCY OF SECONDARY CHANGES ASSOCIATED WITH CICATRICIAL ROP

CLINICAL SIGNS	GRADES OF CICATRICIAL ROP - NUMBER AND PERCENTAGE OF EYES AFFECTED										
	NORMAL	I	I-II	II	II-III	III	III-IV	IV	IV-V	V	TOTAL
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
No. eyes affected	32	63	12	45	21	160	39	82	60	795	1309
microphthalmos					(3.7)	6 (2.6)	1 (6.1)	5 (18.3)	11 (13.5)	107 (10.2)	130
corneal opacities					(0.6)	1 (2.6)	1 (2.4)	2	(11.9)	95 (7.8)	99
changes of anterior chamber:											
i. deep									(1.1)	9 (0.7)	9
ii. shallow		2 (3.2)		1 (2.2)		8 (5.0)	9 (23.1)	19 (23.2)	25 (41.7)	311 (39.1)	375 (29.4)
iii. very shallow						2 (1.2)	2 (5.1)	2 (2.4)	2 (3.3)	204 (25.7)	212 (16.6)
synechias:											
i. anterior						(2.6)	1	(5.0)	3 (12.3)	98 (8.0)	102
ii. posterior	(1.6)	1	(4.4)	2 (9.5)	2 (2.5)	4 (12.8)	5 (11.0)	9 (31.7)	19 (46.0)	366 (31.9)	408
glaucoma				(4.8)	1 (1.9)	3 (7.7)	3 (8.5)	7 (15.0)	9 (16.0)	127 (11.7)	150

TABLE I.1 [CONTINUED]

CLINICAL SIGNS	NORMAL No. (%)	I No. (%)	I-II No. (%)	II No. (%)	II-III No. (%)	III No. (%)	III-IV No. (%)	IV No. (%)	IV-V No. (%)	V No. (%)	TOTAL No. (%)
buphthalmos				(4.8)	1		(1.2)	1	(4.6)	37 (3.0)	39
ciliary processes						4 (2.5)	2 (5.1)	5 (6.1)	2 (3.3)	147 (18.5)	160 (12.5)
dentate processes				1 (2.2)		3 (1.9)	3 (7.7)	5 (6.1)	9 (15.0)	85 (10.7)	106 (8.3)
cataract					(2.5)	4	(1.2)	1 (5.0)	3 (3.8)	30 (3.0)	38
enophthalmos				(4.8)	1 (6.2)	10 (7.7)	3 (4.9)	4 (18.3)	11 (13.0)	103 (10.3)	132
pale fundus (21.9)	7 (15.9)	10 (16.7)	2 (4.4)	2	(1.2)	2 (2.6)	1 (2.4)	2		(1.5)	26
fundus details indistinct	5 (15.6)	9 (14.3)	2 (16.7)	1 (2.2)							17 (0.9)
attenuated retinal vessels	3 (9.4)	7 (11.1)	1 (8.3)	6 (13.3)	1 (4.8)		14 (35.9)	10 (12.2)	3 (5.0)		45 (3.3)
localized retinal detachment and fold; pigment conus		10 (15.9)	1 (8.3)	10 (22.2)	3 (14.3)	47 (29.4)					71 (5.6)

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* modified from Reese and Stepanik[57]

In spite of the problems, by the mid 1950's, there were numerous pathological reports, some contradictory and some limited to observations made in a single eye[13,31,38,39,59-62]. In 1951, Friedenwald, Owens and Owens[59] reported that the earliest detectable changes occurred in the nerve fiber layer of the retina. At onset, this layer thickened and showed localized areas with marked proliferation of the capillary endothelium[14]. As the disease advanced, the nerve fiber layer thickened to many times its normal size and newly formed capillary strands extended through the internal limiting membrane, coursed along the surface of the retina and branched into the vitreous. With still more advanced lesions, areas of retinal detachment occurred and small folds, bridged by newly formed vessels, formed in the areas of the retina that were no longer attached. With the most severe clinical manifestations of aROP, the entire retina was detached. In infants with cROP, the disorganization was such that it was difficult to differentiate ROP from other diseases that result in retinal detachment[14].

The idea that ROP was initially confined to the nerve fiber layer of the retina was supported by a number of authors[36,63]. Still others supported the contention that, in the later stages of cROP, the pathological changes were not ROP-specific[13]. However, again there were disagreements[14,54,62,64,65] and again, these disagreements were resolved as normal development in the eye became better understood. For years, it had been known that vascularization of the retina is one of the last developmental processes to occur[45]. Prior to the sixth to seventh month of gestation, the retina is nourished by the neighboring choroid and the hyaloid vascular system of the vitreous. At approximately the 100 mm. stage of fetogenesis, capillary buds, sprouting from the trunks of the hyaloid vessels, begin to invade the retina and spread

outward toward the periphery. Initially, this proliferation is limited to the nerve fiber layer, later it penetrates to the deeper layers of the retina[45].

Friedenwald[66] was the first to emphasize that the incidence of ROP was highest in infants with incompletely differentiated retinas. Once this was recognized, it became clear that much of the early pathologic confusion was a function of the fact that the eyes examined were premature, hence, incompletely differentiated. However, Friedenwald did find that ROP-affected eyes differed from those that were undergoing normal vascularization. In the latter, the sprouting capillaries proliferated in an orderly pattern throughout the nerve fiber layer; in the former, there were regions of avascularity associated with regions of overgrowth of the capillary endothelium.

I.6 INCIDENCE: DEFINITION OF THE EPIDEMIC

Terry's idea that ROP was an unknown disease associated with prematurity[2], was soon called into question. Case descriptions, if not of ROP then of diseases similar to ROP, were uncovered in literature prior to the 1940's[18,21,24]. Furthermore, most of these descriptions related to the occurrence of the disease in infants at or close to term at the time of birth. Within a few years, it was widely held that what Terry had called attention to was the increased incidence of a rare but previously known disease. The validity of this assumption will never be known. If the cases reported prior to the 1940's were affected, they undoubtably had severe cROP. However, as mentioned, if it has developed unobserved, this phase of the disease is difficult to differentiate from other diseases that present with similar patterns of destruction[13,36,59].

In his 1942 report, Terry made reference not only to his original case, and the case seen by Dr. Chandler, but to three other cases subsequently seen at the Massachusetts Eye and Ear Infirmary[2]. The following year, he reported that he had personally seen seven affected infants and claimed knowledge of 13 others[4]. By 1944, he had data on 105 cases[6] and by 1945, he knew of 162 cases in such diverse locations as Boston, Chicago and Hartford, Connecticut[7]. His rapidly expanding database and an unpublished study by Dr. Clifford[8] led Terry to predict that "(o)ver ten percent of the infants born very prematurely ... can be expected to be blind from retrolental fibroplasia."[7]

The first prospective study done using substantial numbers of infants to define the incidence of ROP was described in 1948[16]. This study included 111 premature infants who were born in, or admitted to, the premature nursery of the Johns Hopkins Hospital between July 1945 and June 1947. Thirty three, 4 of whom subsequently developed ROP (12.1%), were born weighing less that 1360 grams. In the remaining infants, all weighing 1360 to 2000 grams, the incidence was only 1.3%. A year later, Owens and Owens[17] reported the incidence in 63 premature infants who were born weighing 1360 grams or less and were admitted to Johns Hopkins prior to June 1948. Although they do not say so, it is likely that this latter group included the 33 comparable weight infants from in the earlier study. This being the case, what is remarkable in the second study is the apparent increase in incidence - from 12.1% in the period July 1945 - June 1947 to 26.7% (8 of 30) in the period July 1947 - May 1948.

The idea that there really was an increase in incidence at the Johns Hopkins Hospital gained credence from the results of two subsequent studies. In the first, Owens and Owens recalled and examined 120 premature infants who were born in, or were admitted to, the hospital in the period 1935-1944.

None of the 23 children weighing less that 1360 grams at birth or the 97 weighing 1360-2000 grams were found to have the sequela associated with ROP[16]. In the second study, which was prospective, 5 of 15 or 33% of the infants who were born in the period June 1948-March 1949 and who weighed < 1360 grams, were affected[17]. None of these observations were conclusive. Only a limited number of the infants weighing <1360 grams survived the early neonatal period. Those who did were likely to have been subjected to different diagnostic criteria in the various studies. Lastly, it is quite possible, particularly in the retrospective study, that some children had ROP that had regressed such that it was difficult to diagnose. Nevertheless, the results did suggest that, in the hospital, the incidence was low in the period 1935-1944 and increased progressively thereafter.

The early incidence studies, coupled with those done to define the clinical picture, were instrumental in bringing about the widespread introduction of policies calling for weekly ophthalmologic examinations of premature infants. These policies, and a concomitant increase in concern about ROP, led to a dramatic increase in the volume of literature defining the incidence of the disease. Most of the literature tended to substantiate the concerns first voiced by Terry[7]. This, and the fact that prior to 1942 ROP was not considered to be a problem in any hospital, quickly led to there being general agreement for the idea that the incidence was not only increasing but increasing rapidly[11,21,24,26,27,34,36,38,50,67,81].

I.7 GEOGRAPHICAL VARIATIONS IN INCIDENCE

As the volume of data increased, it became apparent that the disease was occurring more frequently in some places than in others[7]. A synopsis of

the incidence data published in the 1940's (Table I.2) shows that, initially, cases were limited to large metropolitan areas in the eastern United States. Furthermore, the data, most of which were collected when only the most severely affected cases were being diagnosed, shows there was substantial inter-area variation between those areas where the disease was known.

With the delineation of the early changes associated with aROP, comparing incidence data from various locations became more difficult. Reported rates often differed in terms of the number of cases studied, the number of births surveyed, the birth weight groups and/or the ascertainment periods taken into consideration. In addition, the inclusion criteria used in the various studies often varied such that some related only to cases with severe cicatricial damage while others included cases with early aROP. In addition, comparisons were often confounded by the fact that, in areas where ROP was either rare or previously unknown, physicians often lacked the expertise to accurately diagnose the disease[36].

Although these problems raised the specter of misdiagnosis and hence, under- or over-ascertainment, evidence suggesting that the disease was spreading accumulated. Numerous reports claimed ROP had suddenly appeared and incidence had subsequently increased in areas where previously, no cases had been diagnosed. In 1950, Mallek and Spohn[11] reported that, in Vancouver, B.C., ROP was not known in infants born prior to 1948. The following year, Turnbull[82] reported that cases in Montreal thus eliminating the possibility that, within Canada, the emergence of the disease was localized to a particular geographic region.

In 1951, Crosse reported that in Birmingham, England, ROP did not occur prior to 1946. However, following the birth of the first case in 1946 and a second case two years later, the number of cases rose rapidly[69,83]. A similar

TABLE I.2
GEOGRAPHICAL VARIATION IN INCIDENCE PRIOR TO 1950

		BIRTH WEIGHT					
		LESS THAN 3 POUNDS (< 1361 GMS)			3 - 4 POUNDS (1361 - 1814 GMS)		
CITY	PERIOD	#ROP	#BIRTHS	%	#ROP	#BIRTHS	%
Boston	1938-1942	9	44	20.5	1	106	0.95
	1943-1947	10	38	26.3	33	162	20.2
Providence, R.I.	1941-1947	7	30	23.3	9	195	4.6
Baltimore	1935-1944	0	23	-	0	63	-
	1945-1947	4	33	12.1	1	39	2.5
Hartford, Conn.	1948	4	7	57.0	4	28	14.3
New York	1939-1946	5	65	7.7	1	142	0.7
Cincinnati	1943-1947	2	22	9.1	5	74	6.8
Birmingham, England	1945	0	21	-	0	83	-
		LESS THAN 1361 GRAMS			1361-1500 GRAMS		
Denver	1948	2	10	20.0	0	4	-
		LESS THAN 1260 GRAMS					
Chicago	1922-1947	5	216	2.3			

Modified from: Kinsey and Zacharias[71]

pattern of emergence and subsequently increasing incidence was also noted in Oxford[84] and in three other English cities identified only as X, Y and Z[83]. These observations led Coxon[68] and others[46] to conclude that while the disease did not appear until later and the incidence was lower, the English experience was mimicking that of the American.

Numerous other reports published at the same time indicated that ROP, although rare, was becoming known in continental Europe. In 1951, LeLong et. al.[85] reported that, in Paris, the incidence in premature infants had risen to 7-8%. In the same year, Hedlund-Kristiansen[86] described the first case diagnosed in Sweden. Subsequent reports[87,88] showed that 0.9% of premature infants weighing less than 2000 grams at the Samariten Hospital in Stockholm were affected. Additional cases were also reported in children born in other parts of Sweden in the period 1945-1950[87]. Sporadic cases were reported in other European countries: one in Holland in 1950[89], another in 1951[90]; one in Spain in 1950[91], two in 1951[92]; two in Switzerland in 1949[93]; two in Italy in 1950[94]. Given the available data, it is impossible to tell whether some or all of these sporatic cases reflected an increasing awareness of the clinical manifestations of ROP or whether they reflected the increasing incidence reported in the USA and elsewhere.

Cases that may have reflected previously undefined but normal baseline rates were also reported in countries such as Israel[95], Cuba[96], and South Africa[97]. However, not all cases observed in countries outside of Europe and/or North America could be or were attributed simply to an increasing awareness of the disease. In one of the first accounts from Australia, Ryan noted that no cases were born in Melbourne prior to 1948. However, in the three year period 1948-1950, the disease had not only appeared but the incidence rates amongst infants born weighing less than

1600 grams at the Women's Hospital had risen to 17%, 19% and 14% respectively. In other parts of Australia, the disease was either unknown or much less frequent[38].

I.8 LOCAL AND TEMPORAL VARIATIONS IN INCIDENCE

While other countries were observing the delayed but nevertheless increasing incidence of ROP, American observers were noting local and temporal variations in incidence. In hospitals where the disease had been known for some time, the periods of increasing incidence were often followed by periods of decreasing or fluctuating rates. For example, in two institutions in the City of New York, incidence showed a pattern of steady increase in the period 1943-1947 followed by a period when the rates fluctuated[76]. Similar observations were reported from the Bellevue Hospital in New York[74], the University of Chicago Hospital[36,70], the Hartford Hospital in Connecticut[36], and the Boston Lying-In Hospital[98]. Only a few of these observations were tested for statistical significance. Given the small numbers of cases, it is unlikely that many of them would have been significant had they been so tested. Furthermore, there were undoubtably ascertainment factors - changes in the diagnostic criteria, in the ages at which infants were surveyed and diagnosed, etc. - that were implicated in the observed instability in the rates. Nevertheless, the observations were taken seriously and although they confused the picture with respect to the incidence of the disease, they later served as valuable clues in the search for the etiological factors that were contributing to what was, by this time, a clearly recognized epidemic.

Variations in incidence were not always limited to those observed at the intra- or international level or to those observed from one year to the

next within the same institution. Throughout the period when the epidemic was being defined, evidence accumulated that suggested that the increased incidence was linked to specific hospitals rather than to particular cities or regions. In Chicago, at a time when almost 40% of the premature infants born in or admitted to the University of Chicago Hospital were developing ROP, the incidence in the Cook County Hospital, one of the largest hospitals in the USA, was negligible[99]. A similar observation was made in Iowa City: in the Eye Clinic, incidence ranged from 25% to 40%; at the University Hospital, there were no cases[99]. In New Orleans, 3000 infants were examined at the Charity Hospital without a single case being diagnosed while in other city hospitals, the number of cases was accumulating[100,101]. In the period 1948-1950, 21 of the 23 cases diagnosed in Melbourne, Australia were born in one of two large maternity hospitals servicing the city[38]. In Vancouver, B.C., 13 of 15 cases came from one large hospital while the remaining two came from two different hospitals[11].

Attempts to define the emerging epidemic in terms of the characteristics of the hospitals where the disease was occurring were hampered by the fact that, in many of the reports, the particulars of the hospitals were either excluded or only minimally included. Although they did not identify the hospital, Mallek and Spohn[11] did note that, in Vancouver, the majority of cases came from a hospital that had ideal conditions for the care of premature infants. After reviewing the literature, Crosse and Evans[83] also noted an association between incidence and similar types of institutions. Support for these essentially unsubstantiated observations came in the form of an epidemiological survey of the premature infants who were born and subsequently developed ROP in the State of Maryland[81]. All of the hospitals providing facilities for the care of newborns

were ranked according to their ability to conform with recognized standards of care for premature infants. When the incidence of ROP was correlated with these hospitals, it was found that the frequency in the 5 highest ranking hospitals was two to three times higher than the frequency in hospitals ranked lower.

I.9 INCIDENCE IN RELATION TO BLINDNESS

By the early 1950's, numerous authors were referring to ROP as the major cause of blindness in children[36,46,102,103] and at least one was arguing that, aside from death, it had become the foremost problem in the care of premature infants[102]. In all probability, these generalizations could have been questioned at the national level in countries such as the USA, Canada, and England. However, there was evidence that suggested that, at the regional, city, or hospital level, these generalizations held as truisms, at least with respect to ROP as the major contributor to blindness.

In an incidence survey in blind preschoolers, Reese[21] reported that, in April 1947, 42% of the preschoolers in Illinois with a confirmed cause for their blindness were blind because of ROP. Comparable or quasi-comparable data from New Jersey, New York, Wisconsin and Massachusetts revealed that, in those states, the same was true for 29%, 22%, 14% and 55% of blind preschoolers respectively[21]. In the years after 1947, the incidence of ROP in relation to blindness increased even more dramatically. In 1953, Foote[104] noted that severe cROP accounted for 49% of blindness in children who were less than seven years of age. Indeed, in some localities, the number of children blinded increased so dramatically that the diagnosed cases far exceeded the total number of blind children in the years prior to 1942[71]. This latter observation suggests that, not only had ROP become a major

contributor childhood blindness but also, that the apparent increase in incidence could not be explained by cases misdiagnosed in the 1930's and early 1940's.

CHAPTER II
THE EPIDEMIC YEARS: SEARCH FOR A CAUSE

II.1 The First Decade: 1942-1952

Shortly after seeing his first case, Terry suggested "... perhaps this complication should be expected in a certain percentage of premature infants. If so, some new factor has arisen in extreme prematurity to produce such a condition."[2] This statement triggered what would be a long and frustrating search for the factors causing the disease. The discovery that ROP was known prior to 1942 served only to redefine the problem as being the increasing incidence of a previously rare disorder rather than the emergence of a previously non-existent disease. Since the former requires no less of an explanation than the latter, the shift in focus did little to minimize the scope of the search that followed.

By 1943, Terry had compiled an extensive list of potential etiological factors[5]. Over the next 10 years, a bewildering array of additional factors, some exogenous, others endogenous, some prenatal, others postnatal, were suggested. A few were thought to be causes and simultaneously, cures. Some were suggested on the basis of empirical evidence, others on theoretical considerations alone. A large number, perhaps as many as half, were never discredited either formally, by experimentally derived evidence, or informally, by retrospective or prospective clinical observations.

An extensive, but perhaps not all inclusive list of the factors considered in the period 1942-1952 is included in Appendix I. Initially, the theory that ROP resulted from a persistence of fetal structures or from changes occurring in utero[2,9,10] resulted in attention being focused on prenatal or parental factors. However, with the early work of Owens and Owens[16], there was a perceptible shift in emphasis. Although the question of whether ROP

originated prenatally or postnatally was not resolved[36], investigators began to focus on factors that would impact postnatally. The list of potential etiologic factors was further reduced by the appearance of the disease in places where previously it had not been seen and by the sudden changes that were observed in the incidence in areas where it was well known. As the more obvious explanations were eliminated and as evidence linking ROP to particular hospitals accumulated, people began to reason that the causative agent might be found amongst the medical or therapeutic practices that had been introduced or changed in particular places at particular times.

II.2 OXYGEN: CAUSE OR CURE

Terry[5] was the first to suggest that ROP might be linked to an increase or decrease in the oxygen levels in the blood of premature infants. A few years later, Owens and Owens[17] used, as one of their rationales for administering vitamin E prophylactically, the fact that the vitamin is involved in the control of tissue oxidation. In the same year (1949), Kinsey and Zacharias[71] noted that "... infants in whom retrolental fibroplasia subsequently developed remained in the nursery, (in) water jacket incubator(s) and in oxygen for longer periods than the infants in whom retrolental fibroplasia did not develop." Unfortunately, this observation, and one suggesting that the incidence of ROP increased as the amount of supplemental oxygen increased, was interpreted as a reflection of the poor general health of infants who developed the disease. The fortuitous observation that there was an even stronger association between ROP and water-miscible vitamins and iron[71], and a report by Unsworth[115] stating that oxygen was not implicated, served to temporarily divert attention from the role of oxygen as an etiological factor.

In the early 1950's, three theories resurrected the idea of oxygen as a possible cause. Although the studies on which they were based were flawed and hence not conclusive, all three theories were taken seriously. Until the ROP problem was considered solved, these theories dominated the literature and together, effectively put to rest the search for other factors that might have been implicated in the epidemic.

II.2.1 HYPOXIA AS CAUSE

In 1951[55] and again in 1952[56], Szewczyk suggested that insufficient amounts of oxygen or the too rapid removal of infants from oxygen enriched environments might be factors that precipitate the development of ROP. These ideas were predicated on the following observations:

(i) when the Christian Welfare Hospital in East Saint Louis, Illinois, decreased the length of time that premature infants spent in the enriched environments of oxygen incubators, there was an increase in incidence∞¡,

(ii) cases did not demonstrate the first signs of ROP until after they had been removed from their oxygen enriched incubators[51],

(iii) affected infants were in oxygen an average of 10 days longer than their unaffected counterparts[51], and

(iv) in two sets of twins and one set of triplets, cROP was found in the infants most likely to survive, hence those who received the least amount of supplemental oxygen[56].

Although his studies were not controlled, Szewczyk argued that they supported the idea that ROP could be induced either by absolute* or relative**

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* to wit, the oxygen levels in the tissues are actually deficient

** in the sense that the tissues are suddenly forced to adjust to a lower, although not necessarily abnormally low, level of oxygen

anoxia. As a corollary, he reasoned that, if the disease was 'caused' by a drop in oxygen concentration, it should be 'cured' by a return to its previously high levels. He tested this idea by returning 9 severely affected infants to the high oxygen environments from whence they had come. Within 24 hours, all showed marked improvements in their condition. This led Szewczyk[56] to conclude that the restoration of high oxygen concentrations was an effective treatment for the disease. However, in reaching this conclusion, he overlooked a number of what should have been important observations. Ten infants whose retinal changes were not severe enough to warrant treatment had also improved. In addition, 4 infants not included in his original series failed to respond to treatment[56]. In a later report, Szewczyk conceded that, although his theory predicated that the symptoms in infants who were treated would regress to normal rather than progress to blindness, this was not always the case. When an additional 17 infants were treated, 12 (71%) regressed and five progressed to blindness in one or both eyes[105]. Rather than allow these treatment failures to undermine his theory, Szewczyk sought to explain them in ways that would leave the theory intact. He argued that two of the infants were blinded because his absence from the hospital delayed their return to a high oxygen environment. The blinding of the other infants was attributed to malfunctioning valves which caused the oxygen concentrations in their incubators to drop rapidly[105].

A similar litany of human and mechanical failures was invoked to explain the fact that symptoms could and did develop in infants still being exposed to high oxygen concentrations[26,52,56,106]. Since he straddled the line that separates explanations from excuses, Szewczyk's attempts to keep his theories intact were easy to criticize. However, the theories themselves, formulated and supported by clinical observations rather than by controlled

trials, were vulnerable to more substantive criticisms. In the absence of proper control groups, the possibility that the observations ascribed meaning to many characteristic features of the disease could not be eliminated. By the time the theories were formulated, there was a growing awareness of the fact that there was a high rate of spontaneous regression in infants with aROP. Thus it was possible that, in the treated infants, the symptoms would have regressed in the absence of treatment. In addition, although he noted that the vessels in infants exposed to high concentrations of oxygen constricted while they were being exposed[56,105], Szewczyk's theories made no allowance for the possibility that the symptoms observed after infants were moved from high oxygen environments were secondary to changes that occurred before they were moved.

Had Szewczyk's theories not been supported by others, it is unlikely they would have been given much credence. However, he was not the only one who believed that anoxia was related, either directly or indirectly, with the onset of symptoms[107]. In 1952, Jefferson reported that, in Manchester, England, the incidence of ROP correlated with the methods and policies used in the administration of supplemental oxygen. When little or no oxygen was used, incidence was low. As more infants were exposed to higher concentrations, incidence increased. In fact, with Sorento-type cots, which made the administration of high concentrations of oxygen more efficient, the incidence increased so dramatically that eventually, 75% of infants weighing less than 1814 grams developed signs of aROP. These dramatic increases were followed by equally dramatic decreases when policies calling for the administration of minimal amounts of oxygen and gradual withdrawal to room air were introduced. In Jefferson's view, these observations supported the idea that acclimatizing premature infants to high concentrations of

oxygen and then suddenly transferring them to room air increased the risk for ROP[108].

Others supported Szewczyk's contention that absolute hypoxia rather than hyperoxia was implicated. Evidence for this belief came from two sources, the first, a clinical study that purportedly showed that hyperoxia was not associated with an increase in the incidence of cROP. One group of infants was exposed to restricted levels of oxygen, another to liberal levels averaging concentrations of 60% for a minimum of three weeks. When the groups were compared, the frequency of regression was four times higher in the restricted group while the frequency of cROP was the same in both groups[109]. Although there was neither a random allocation nor a prearranged protocol to assign infants to the two treatment groups, it was assumed that these results showed that an excessively oxygenated environment was not etiologically related to ROP. The idea that hypoxia was implicated came from a second observation, namely that there was a fourfold higher incidence of ROP in infants who were severely hypoxic[109].

The most conclusive support for Szewczyk's theories came from two blinded clinical trials done by Bedrossian et. al.[23,110]. In the first[23], alternate infants who were born weighing <1814 grams were assigned to one of two groups. In both groups, infants <1400 grams were exposed for 17 days; those 1400-1800 grams, 11 days. In the first group, infants received oxygen in concentrations of 50% for 1 to 7 days depending on their birth weight. Thereafter, all were weaned to 40% oxygen for 5 days, 30% for another 5 days and finally, room air. In the second group, infants were transferred directly to room air after being exposed to 60% oxygen for 11-17 days. When the groups were compared, a highly significant difference in incidence was noted. Only 8.3% of infants weaned from 50% oxygen showed signs of the disease

compared to 53.0% of those who were abruptly moved from 60% ($p < 0.001$). In addition, the symptoms in those abruptly moved were more severe than those found in the infants who were weaned[23].

In interpreting the results of this trial, Bedrossian did not allow for the possibility that the difference in incidence between the two groups might have been a function of the differences in the concentrations of oxygen to which the groups were exposed (50% vs 60%). To rectify this, he repeated the trial exposing infants in both the weaned and non-weaned groups to initial oxygen concentrations of 50%[110]. Five of 26 infants (19.2%) weaned according to the regime used in the first trial (50% to 40% to 30% to room air) developed the disease as did 3 of 10 infants weaned in 35% oxygen for 8 days. In contrast, 9 of 16 infants (56.2%) moved abruptly after 7 days, and 6 of 9 (66.7%) moved after 15 days, were affected. Although these differences could also have been a function of exposure, i.e., the fact that infants who were moved abruptly were left in 50% oxygen for longer periods of time, Bedrossian viewed the results as substantiating both his earlier trial and Szewczyk's theory that relative hypoxia was a causal factor.

Bedrossian also followed up on Szewczyk's allegation that ROP did not develop while infants were being exposed to concentrations greater than 21-22% (i.e., room air). In a retrospective review[56], he showed that 68 of 74 cases (91.9%) did not show symptoms prior to removal from their incubators. However, 6 infants developed signs of aROP while still receiving supplemental oxygen. Like Szewczyk before him, Bedrossian attempted to explain these cases within the context of the 'hypoxia as a cause' theory. Rather than attribute their occurrence to human or mechanical error, he hypothesized that these infants had an excess of oxygen in their blood which put them at greater risk for relative hypoxia when there was a reduction in

the oxygen concentration of their air supply[56].

At approximately the same time, others[26,52,106] were also reporting that they had seen the disease develop in infants receiving continuous supplemental oxygen. However, these authors interpreted their observations as evidence against the hypoxia theory. In addition, Patz[52] reported observations that undermined the 'oxygen as a treatment' theory. When two low birth weight infants who developed signs of the disease while in 70% oxygen were suddenly transferred to room air, one showed no change in symptoms for the first 4 days while the other showed a slight but definite worsening. Thereafter, in both infants, the symptoms started to regress spontaneously raising the possibility that a similar phenomenon would have occurred in the cases who purportedly improved when they were reintroduced to high oxygen concentrations[23,55,56,105,110].

The accumulation of evidence contradictory to, or inexplicable within, the hypoxia theory eventually rendered it untenable. In retrospect, had the idea been acted on, the prophylactic use of oxygen to reduce the risk for ROP could have carried with it an increase in risk. However, while it can't be said that it didn't, the fact that oxygen was already freely used in the routine care of premature infants probably precluded the hypoxia theory being used to justify the exposure of large numbers of infants who would not otherwise have been exposed. Ironically, the consequences of the theories were probably more beneficial than harmful. Because he believed that acclimatizing infants to high concentrations of oxygen would sensitize them to decreases in concentration, Szewczyk recommended that exposures for infants born weighing <1814 grams be limited to concentrations of 45% or less[56]. Thus, although he arrived at the right place for the wrong reasons, Szewczyk

ensured that even the supporters of his theories were conscious of the deleterious effects of overusing what would ultimately be accepted as 'the' causative factor.

II.2.2 HYPEROXIA AS CAUSE: CLINICAL OBSERVATIONS

Two years after Kinsey and Zacharias dismissed oxygen as a potential cause[71], an Australian, Kate Campbell, resurrected the idea. Some of her colleagues had been privy to conversations during which the differences in incidence between the United States and England were discussed. One of the observations made during these conversations was that in England, where the disease was relatively rare, oxygen was used sparingly while in the United States, where the incidence was much higher, it was administered more freely. To follow up this observation, Campbell compared the incidence of ROP in 3 groups of premature infants born in Melbourne in the years 1948-1950. Comparisons between the groups indicated that there were substantially more infants with ROP in the group exposed to high levels of supplemental oxygen (18.7%) compared to the group exposed to more moderate levels (6.9%). In addition, in 1950, when efforts were being made to curtail the prophylactic use of oxygen, incidence was dramatically reduced compared to the preceding year (12.7% vs 31.2%)[126].

Campbell's observations were made and reported in a way that precluded anything other than the suggestion that there might be an etiological relationship between oxygen and ROP. Very little useful information relating to oxygen concentration or the duration of exposure was provided. Similarly, her comments pertaining to a decrease in incidence following the curtailment of oxygen hardly sufficed to suggest causality since they were based on a 3 month observation period and could have been due, if

not to ascertainment, then to the temporal variations that were known to occur. In spite of these problems, Campbell's observations attracted widespread international attention. In the 2 to 3 years immediately following the appearance of her report, numerous authors described clinical observations that lent credence to the association. Crosse[69], trying to explain the increase in incidence in Birmingham, England in the period 1945-1950 noted that there was a tendency for supplemental oxygen to be given to more infants, in higher concentrations and for longer periods of time. Similar observations were invoked by Houlton[84] and Ryan[38] to explain increasing incidence in the Oxford District in England and in Melbourne, Australia respectively.

Crosse[83] later reported the results of a retrospective review of incidence in relation to oxygen exposure in the Sorrento Premature Unit in Birmingham. This review, which related to four periods spanning the years 1931-1951, showed that, in the 3 periods when oxygen exposure was minimal (1931-1945, 1946-1948, and July 1950-1951), ROP either wasn't diagnosed (1931-1945 and June 1950-1951) or was but at a low frequency (1946-1948: 3.6%). In the intervening period (1949-June 1950), oxygen was administered liberally and the incidence of ROP increased to 19.2% of infants who survived the early neonatal period. The decrease in incidence following the reduction from liberal to minimal amounts of oxygen (from 19.2% in the period 1949-June 1950 to 0% in the period July 1950-1951) was mimicked in a second premature unit in the city.

The second study done by Crosse[83] corroborated the results of the Campbell study but did so by perpetuating many of its methodological weaknesses. For example, like the Campbell study, the Cross study was not controlled and did not account for factors such as duration of exposure or

concentrations of oxygen received by affected as opposed to unaffected infants. Crosse did attempt to support her results by noting that, in both England and the USA, the appearance of the disease was restricted almost entirely to centres with special premature care units. Although she did not substantiate the allegation, she argued that the occurrence of cases coincided with the increased use of oxygen in units that were already functioning and the establishment of new units equipped with full facilities for oxygen administration.

In 1954, Locke[145] reported the results of a comparison of the incidence of ROP in two time periods at the Royal Victoria Hospital in Montreal. In the first period (February to July 1952), the amount of oxygen delivered was documented but not restricted. Thereafter, oxygen was only administered in the amounts needed to prevent cyanosis. These two exposure periods correlated with a significant difference in incidence in infants weighing <2000 grams at birth. In the early, unrestricted period, 6 of 26 (23.1%) infants developed ROP compared to only 2 of 78 (2.6%) in the later period. Furthermore, in both the infants affected in the restricted period, the symptoms were mild and regressed to normal. Realizing that his observations supported but fell short of providing conclusive evidence for the 'hyperoxia as a cause' theory, Locke concluded[145]:

> In a disease such as retrolental fibroplasia, with a high rate of spontaneous regression, and with an incidence that has been reported to vary with time in the same nursery, one must be cautious in accepting any method purporting to prevent the disease or reduce its severity. In the hyperoxygen theory, however, we have for the first time a theory which finds support from several different observers in different parts of the world.

Two other observations, the first relating to the occurrence of the disease at the Colorado General Hospital, the second, to the incidence in the

State of Maryland, added further support for the hyperoxia theory. In the first study, Gordon, Lubchencko and Hix[146] compared the incidence of ROP in each of four time periods. Throughout the first period (1947 - April, 1950), infants were exposed to 'moderate' levels of oxygen that were episodically reduced.* In the second period (May - Sept. 1950), infants were exposed to continuous oxygen at concentrations that reached 60% or more. October to December 1950 represented a transitional period during which the nursing staff was shown that decreasing the oxygen levels would not lead to an increase in infant mortality. The final period, which was to have been a controlled trial, began on January 1st, 1953. Alternate infants whose conditions did not necessitate longer treatment were exposed to 30-40% oxygen, one group for 1 day, another for 14 days. Since there was no apparent difference in the incidence of ROP between the two groups and since both were exposed to the same reduced levels of oxygen, these two groups were subsequently combined forming a single exposure group. The frequencies of cROP observed in infants weighing <1500 grams in each of the four exposure periods are outlined in Table II.1. As can be seen, incidence appeared to increase when the moderate levels of oxygen administered in the first period were supplanted by the higher levels of the second period. Thereafter, as the levels of oxygen decreased, so too did the frequencies of residual lesions[146].

Less direct but nonetheless useful evidence supporting the hyperoxia theory came from observations made in an epidemiological survey of cases born prematurely in the State of Maryland[81]. Since oxygen data per se was not available, the study was done using 'length of time in an incubator' as an indirect measure of exposure. The results of the survey suggested that there

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* when their incubators lids were opened so staff could minister to their needs

TABLE II.1
INCIDENCE OF RESIDUAL LESIONS IN INFANTS AT THE COLORADO GENERAL HOSPITAL

PERIODS	OXYGEN THERAPY	NO. OF INFANTS	% INFANTS WITH	
			RESIDUAL LESIONS	RETROLENTAL MEMBRANES
I	moderate	80	15	10
II	high	20	45	35
III	transitional	14	29	21
IV	restricted	97	8	2

* Modification of Gordon et. al., 1954 by Committee on Fetus and Newborn of the American Academy of Pediatrics[147]

was indeed, a direct correlation between exposure time and incidence. Since the use of more efficient oxygen incubators had supplanted the use of less efficient tents and masks as the dominate exposure mechanism, the hyperoxia theory predicted that just such a relationship should exist. In contrast, the logical extension of the hypoxia theory, or the idea that infants at increased risk were those who were oxygen-deficient, called for an indirect relationship in the sense that incidence should have decreased as incubator time increased.

II.2.3 OXYGEN: AN UNRELATED ETIOLOGICAL FACTOR

The conflict between the hypoxia and hyperoxia theories, and the widespread belief that supplemental oxygen was efficacious in reducing neonatal mortality, made it difficult for many practitioners to accept the implementation of radical changes in the policies governing exposure. Resolution of this conflict was made even more difficult by the appearance of reports that suggested that oxygen was not a major factor in the etiology of ROP. The first report making such a claim appeared in 1949[115]. Two years later, a retrospective review of infants born in the Charity Hospital of Louisiana and exposed to an average of 50% oxygen for the first four weeks of life failed to identify a single case with ROP[143]. The same year, Silverman et. al.[80] noted:

> A review of the experience shows that the status of the infants who developed the disease was in no recognizable way different from that of their more fortunate crib fellows. ... the amount or duration of oxygen treatment were in no recognizable way related causally to the incidence or severity of the disease.

Others were also skeptical about the suspected association between increased oxygen and increased incidence. Bembridge et. al.[46] reported that

"... (o)ne baby in our series who had received no oxygen developed the disease, and in other centers where oxygen is used freely no cases have occurred." Zacharias et. al.[103] reported that, in the Boston Lying-In Hospital, changes in incidence showed no correlation with oxygen exposure policies. Many of these observations would not stand the test of time. After oxygen was accepted as a cause, plausible arguments were offered to explain the non-occurrence of the disease in infants exposed to high concentrations of oxygen for long periods of time[147]. Unfortunately, these arguments, offered in hindsight, did not change the fact that the non-occurrence of ROP in infants who were exposed, and the documented occurrence of the disease in infants who were not exposed, fueled the reluctance of some to accept the idea of oxygen as a causal factor.

II.2.4 HYPEROXIA AS CAUSE: CONTROLLED CLINICAL TRIALS

II.2.4A FIRST CONTROLLED TRIAL: WASHINGTON, D.C.

The first clinical trial to assess the relationship between oxygen and ROP was done in the Gallinger Municipal Hospital in Washington, D.C.[52]. To minimize differences in susceptibility that could arise from differences in birth weight, the trial was limited to infants weighing <1590 grams at birth. Beginning in January 1951, infants meeting this criterion* were alternately assigned to a high exposure group (Group I) that received 65-70% oxygen for 4-7 weeks or a low exposure group (Group II) where oxygen was limited to less than 40% and exposures were limited to a minimum of 24 hours and a

* infants also had to be born in and transferred to the hospital's premature nursery

maximum of 2 weeks. With the exception of the weaning protocols*, the nursery routines used for infants in both groups were identical.

In 1952, Patz, Hoeck and De La Cruz[52] published the results of the first year of the trial. These results (Table II.2) showed that 17 of 28 (60.7%) infants exposed in Group I and only 6 of 37 (16.2%) in Group II developed the residual signs of cROP. Furthermore, when the data were categorized to reflect severity, it was obvious that the cases with the most severe sequela were clustered in the high exposure group. One point of methodological interest not considered was that 10 of 11 infants excluded from the analyses were assigned to the high exposure group (Group I). Since this unequal distribution of exclusions could have adversely affected the results, a re-examination of the data, making some assumptions and including the exclusions seems in order. If the 10 infants who were excluded from Group I were free of cROP and the one infant excluded from Group II was affected, the relative risk would have been 2.43. Although this is lower than the observed risk of 3.74, it still reflects a substantial increase in risk. Thus, it would appear that the potential exclusion bias in the first year did not unduly undermine the conclusion that was reached, namely that "(t)he data ... suggest strongly that high oxygen administration is a factor in the pathogenesis of retrolental fibroplasia."[52]

In 1954, Patz made passing reference to the results of the second year of the Washington trial[48]. He noted that, in the period January 1951 to May 1953, 12 of 60 infants (20%) weighing <1500 grams in the high exposure group and only 1 of 60 comparable weight infants in the low exposure group

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* gradual weaning over a period of a week for infants in Group I versus weaning in 1-3 days for infants in Group II

TABLE II.2
INCIDENCE OF CICATRICIAL ROP IN INFANTS BORN IN 1951 AND EXPOSED TO HIGH AND LOW LEVELS OF OXYGEN IN THE GALLINGER MUNICIPAL HOSPITAL

EXPOSURE GROUP	TOTAL NO. INFANTS	NO. NOT AFFECTED	ROP GRADE					RELATIVE RISK
			I	II	III	IV	TOTAL	
Group I (high O_2)	28	11	3	7	2	5	17	
								3.74
Group II (low O_2)	37	31	4	2	0	0	6	
Total	65	42	7	9	2	5	23	

* Modified from Patz[52]

developed severe ROP ($x^2 = 1.44$, $p = 0.01$). Since the classification system used and the birth weights of the infants included differed from those used earlier, it is difficult to compare the two sets of data. Nevertheless, the results for the extended period did suggest a substantially increased risk for severe cROP in the high exposure group (R.R. = 11.98).

Patz never did publish a detailed account of the entire trial. In 1957, he admitted that, at least in the early part of the study, concern that restricting oxygen might increase mortality often resulted in the night nurses turning on the oxygen or increasing the flow to infants in the low exposure group[148]. Although it was never said, this discovery may have made those involved in the study somewhat reticent to discuss the results until they were confirmed by others.

II.2.4B SECOND CONTROLLED TRIAL: NEW YORK, N.Y.

In the second trial[102], infants weighing 1000-1850 grams were randomly assigned to a high exposure group that received an average of 69% oxygen or a low exposure group where oxygen was administered only to infants who were cyanotic*. In the high exposure group, oxygen therapy was discontinued abruptly. In the second group, it was discontinued at least once daily and unless there was a recurrence of the cyanosis, was not resumed.

The results of the trial, which ended at a predetermined time, are outlined in Table II.3. As can be seen, infants in the high exposure group were 9 times more likely to develop aROP than their less exposed counterparts. Furthermore, all of the infants who developed severe cROP were in the high exposure group, an observation significant at the 5% level.

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* in the low exposure group, the mean ambient concentration was 38%

TABLE II.3
INCIDENCE OF ACTIVE AND CICATRICIAL ROP
RELATED TO OXYGEN EXPOSURE IN THE BELLEVUE HOSPITAL

EXPOSURE GROUP	TOTAL INFANTS	ACTIVE ROP NUMBER AFFECTED	ACTIVE ROP RELATIVE RISK	CICATRICIAL ROP NUMBER AFFECTED	CICATRICIAL ROP RELATIVE RISK
high O_2	36	22 (61%)	8.61	8 (22%)	-
low O_2	28	2 (7%)		0	
Total	64	24 (37.5%)		8 (12.5%)	
		$x^2 = 17, P < 0.001$		$x^2 = 5.2, P < 0.02$	

* Modified from Lanman et. al.[102]

The data for the second trial, like those of the first[52], were also examined for evidence of a correlation between exposure and neonatal mortality. Although the sample sizes were inadequate, both study teams concluded that restricting oxygen was not contributing to an increased number of neonatal deaths. In the second trial, this led to the conclusion that "... (ROP) is directly related to the excessive administration of oxygen and can be controlled by severely limited oxygen therapy to premature infants."[102]

II.2.4C THIRD CONTROLLED TRIAL: NATIONAL COOPERATIVE STUDY

In designing what would ultimately become the definitive clinical trial, the organizers assumed that the mortality issue was far from resolved. This presented them with a dilemma: substantially reducing the amount of oxygen might significantly increase mortality, exposing large numbers of infants to high concentrations might lead to an unnecessarily high incidence of ROP[149]. To compensate, they predetermined that, to detect a difference between 10% incidence in the high or 'routine' group (oxygen administered in concentrations greater than 50% for a minimum of 28 days) versus 2% in the low exposure or 'curtailed' group (either no oxygen or less than 50% oxygen prescribed on the basis of clinical need), at a confidence level of 0.01, they needed only 50 infants exposed in the routine group. Second, to keep the number of 'routine' exposures to a minimum, they decided to cluster the assignments to this group in the first three months of the trial. This would result in there being sufficient numbers to generate valid estimates of the differences in incidence between the two exposure groups. More importantly, at the end of the 3 month period, the sample sizes would be large enough to assess the relationship between curtailment and mortality.

To facilitate the trial*, investigators from 18 major hospitals in the eastern United States agreed to abide by a uniform protocol in caring for and examining the infants who were enrolled. To be included, infants had to weigh 1500 grams or less at birth, had to have been born in or brought to one of the participating hospitals and had to survive the first 48 hours of life. Until 68 infants** were assigned to the 'routine' exposure group, the study's coordinating centre was notified when infants meeting these criteria were admitted. The centre, rather than the participating hospitals, then made the decisions needed to assign the infants to one of the two exposure groups. The assignments were made in sets of 3 infants within each of the participating hospitals. Within sets, infants were randomly assigned, one to the 'routine' group, two to the 'curtailed' group. Because it was thought that susceptibility might vary inversely with birth weight, the assignments were prognostically stratified so that within each set, the infants were all in one of 3 birth weight categories (1000 grams or less, 1001-1250 grams, 1251-1500 grams). After the 68 infants were assigned to the 'routine' group, the process of random allocation was abandoned and all infants subsequently enrolled were assigned to the 'curtailed' group[150].

A total of 706 infants, including 166 who died before the age of 40 days, were enrolled in the period July 1, 1953 to June 30, 1954. Deaths occurring after 40 days were not considered in the assessment of mortality since it was thought they were unlikely to be related to oxygen exposure. The results of the mortality comparisons between the 'routine' and the 'curtailed' groups are detailed in Table II.4. As can be seen, there were no significant differences

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* which began on July 1, 1953 and continued to June 30, 1954

** an additional 18 infants were added to the 50 needed in the 'routine' exposure group to compensate for the infants who would be lost through death or for other reasons before they could be followed long enough to ensure that a diagnosis was made.

TABLE II.4
MORTALITY IN THE FIRST 40 DAYS OF LIFE IN RELATION TO THE EXPOSURE OF INFANTS ENROLLED IN THE NATIONAL COOPERATIVE TRIAL

EXPOSURE GROUP	TRIMESTER OF STUDY	MORTALITY			RELATIVE RISK
		SINGLE BIRTHS, %	MULTIPLE BIRTHS, %	TOTAL BIRTHS, %	
routine O_2	1	21.7 (13/60)	25.0 (2/8)	22.0 (15/68)	
curtailed O_2	1	25.9 (30/116)	21.4 (6/28)	25.0 (36/144)	0.884
curtailed O_2	2	16.9 (26/154)	3.8 (1/26)	15.0 (27/180)	
	3	20.4 (27/132)	12.8 (5/39)	18.7 (32/171)	
	4	25.4 (46/181)	23.8 (10/42)	25.1 (56/223)	
curtailed O_2	1-4	22.1 (129/583)	16.3 (22/135)	21.0 (151/718)	1.05 *

* routine oxygen: trimester 1 vs curtailed oxygen: trimesters 1-4

** modified from Kinsey[150]

between infants assigned to the routine and the curtailed groups in the first quarter of the trial (22.0% vs 25.0%, R.R. = 0.884) or between infants assigned to the routine group in the first quarter and those assigned to the curtailed group in all quarters (2.0% vs 21.0%, R.R. = 1.05) This led the coordinating committee to conclude that "... reducing the length of stay in oxygen to that deemed necessary to meet (the) acute clinical needs of the infant is without effect on mortality."[150] The calculations done relating the incidence of active and cROP to oxygen exposure excluded the 166 infants who died before the age of 40 days and 34 who could not be followed for a minimum of 2.5 months. This left a final study population of 586: 94.5% of the survivors and 74.5% of the total number of infants enrolled. When the data pertaining to infants who were the product of a single birth were analyzed (Table II.5), those exposed to routine amounts of oxygen were 2.2 times more likely to develop aROP and 3.6 times more likely to be left with some degree of cicatricial residua. Infants of a multiple birth exposed in the 'routine' group (Table II.5) were 2.0 and 4.8 times more likely to develop active and cROP respectively. After eliminating the possibility that the observed differences might be confounded by differences in variables such as birth weight and gestational age, the investigators concluded that there was, in fact, a highly positive association between incidence and exposure..

To determine the relation between the duration of exposure and the incidence of active and cROP, the trial population of infants was subdivided into subsets each containing infants who had been exposed for similar periods of time. The observed relation between duration, multiplicity and the incidence of active and cicatricial disease are shown in Figures II.1 and II.2 respectively. These figures indicate the following:

TABLE II.5
INCIDENCE OF ACTIVE AND CICATRICIAL ROP IN RELATION TO EXPOSURE OF INFANTS ENROLLED IN THE NATIONAL COOPERATIVE TRIAL

EXPOSURE GROUP	INCIDENCE OF ROP								
	SINGLE BIRTHS			MULTIPLE BIRTHS			TOTAL BIRTHS		
	NO. EXPOSED	NO. AFFECTED	R.R.	NO. EXPOSED	NO. AFFECTED	R.R.	NO. EXPOSED	NO. AFFECTED	R.R.
1. ACTIVE ROP									
routine O_2	47	33 (70.2%)	2.2	6	5 (83.3%)	2.0	53	38 (71.7%)	2.1
curtailed O_2	425	133 (31.3%)		108	45 (41.7%)		553	178 (33.4%)	
Total	472	166 (35.2%)		114	50 (43.9%)		586	216 (36.9%)	
2. CICATRICIAL ROP									
routine O_2	47	8 (17.0%)	3.6	6	4 (66.7%)	4.8	53	12 (22.6%)	3.4
curtailed O_2	425	20 (4.7%)		108	15 (13.9%)		533	35 (6.6%)	
Total	472	28 (5.9%)		114	19 (16.7%)		586	47 (8.0%)	

* Modified from Kinsey[150]

FIGURE II.1
ACTIVE ROP: INCIDENCE VS DURATION OF EXPOSURE TO SUPPLEMENTAL OXYGEN

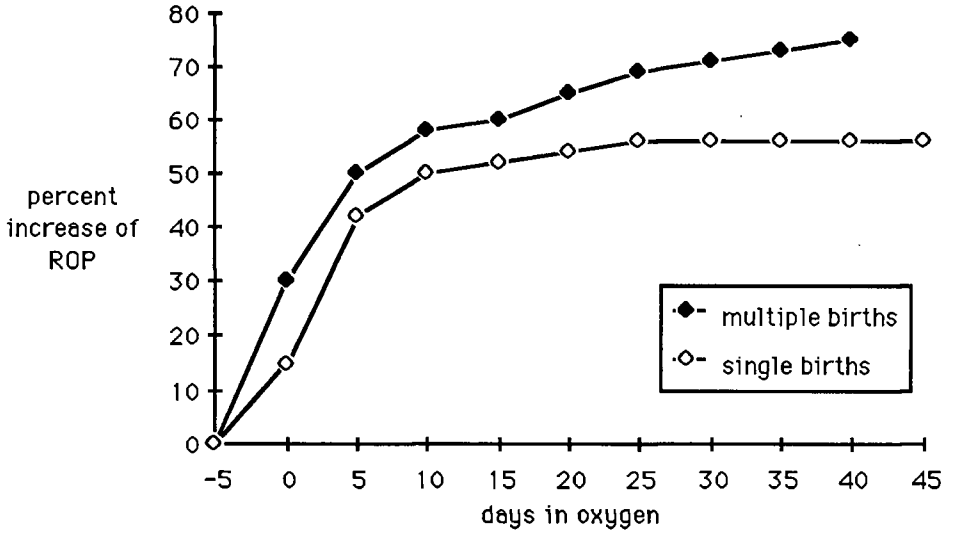
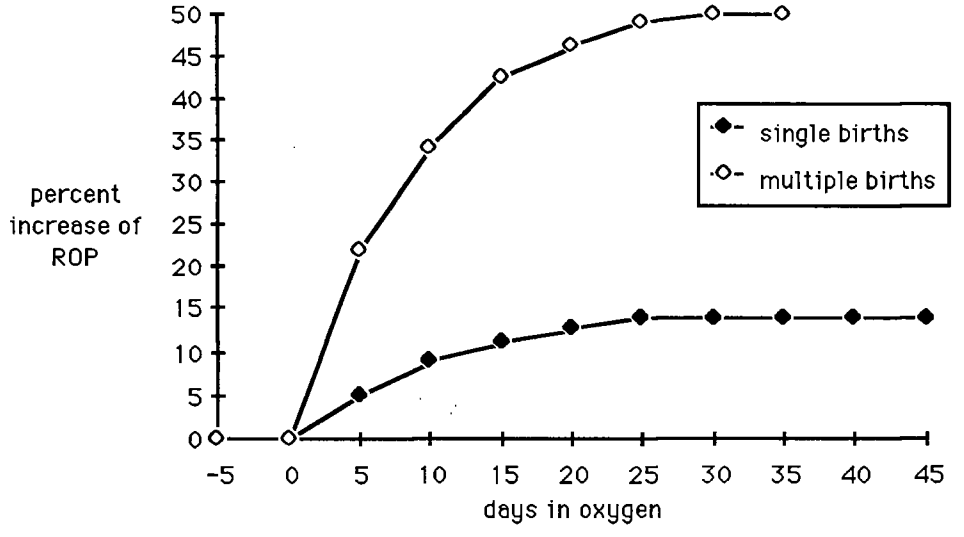


FIGURE II.2
CICATRICIAL ROP: INCIDENCE VS DURATION OF EXPOSURE TO SUPPLEMENTAL OXYGEN



1. there was a direct correlation between exposure length and the incidence of active and cROP,

2. the greatest increase in both active and cROP was associated with exposures for 7 to 10 days,

3. the products of multiple births showed a slightly higher incidence of aROP and a markedly higher incidence of cROP in relation to the length of exposure compared to singletons,

4. exposure for periods of greater than 3 weeks did not appreciably increase the incidence of active or cROP, and

5. cROP was rarely observed in infants who were not exposed to supplemental oxygen*.

A more detailed examination of the data pertaining to cROP (Table II.6) revealed that, with 2 exceptions**, each of the subsets were similar with respect to the average concentration of oxygen and gestational age. Thus, it was concluded that the observed relation between incidence and increased exposure was not due to the effects of these variables. The variation in average birth weight between the groups was, however, problematic since it was commonly believed that incidence and birth weight were inversely related. To clarify this relationship, infants were recategorized according to length of stay in oxygen and birth weight. This re-categorization gave rise to 3 groups comprising the heavier segment of the study population and 3 groups comprising the lighter segment. The results of the analyses done to relate the incidence of cROP and the duration of exposure in infants with similar birth

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* cROP was observed in only 1 of 93 singletons and none of 19 products of a multiple birth who were not exposed to supplemental oxygen

** average concentration in singletons exposed for 21 days or more and average gestational age in multiple births also exposed for 21 days or more

TABLE II.6

INCIDENCE OF CICATRICIAL ROP, AVERAGE CONCENTRATION OF OXYGEN, AVERAGE GESTATIONAL AGE AND AVERAGE BIRTH WEIGHT OF INFANTS GROUPED ACCORDING TO STAY IN OXYGEN

DURATION IN OXYGEN	NO. EXPOSED	NO. ROP	R.R.	AVERAGE CONC. O2 %	NO.	AVERAGE GEST. AGE WK.	NO.	AVERAGE B. WT. GM.	NO.
1. SINGLE BIRTH									
0 days	93	1 (1.1%)	1.0	20	93	32	77	1266	93
1-2	130	7 (5.4%)	4.9	41	119	31	108	1302	130
3-5	86	3 (3.5%)	3.2	44	85	31	66	1272	86
6-10	52	2 (3.8%)	3.5	44	50	31	38	1231	52
11-20	43	6 (14.0%)	12.7	43	43	31	36	1139	43
21+	68	9 (13.2%)	12.0	50	68	31	51	1181	68
average	472	28 (5.9%)		39	458	31	380	1250	472
not known					14		92		
2. MULTIPLE BIRTHS									
0 days	19	0	1.0	20	19	35	15	1325	19
1-2	42	2 (4.8%)		40	36	33	35	1276	42
3-5	25	7 (28.0%)		48	24	33	21	1281	25
6-10	13	3 (23.1%)		46	12	33	10	1354	13
11-20	6	3 (50.0%)		48	6	34	3	1233	6
21+	9	4 (44.4%)		48	9	29	6	1114	9
average	114	19 (16.7%)		40	106	33	90	1280	114
not known							24		

* Modified from Kinsey[150]

weights are shown in Figure II.3. This figure, which differentiates single and multiple births in terms of their heavier and lighter segments, shows that, for singletons, incidence was considerably higher in the lighter compared to the heavier segment of the population. Amongst infants of a multiple birth, differences in birth weight had no appreciable effect on the frequency of cicatricial damage.

The effect of concentration on the incidence of cROP was determined by categorizing the study population according to the average concentration received by each infant for the entire period of that infant's exposure. Eight groups, differing in average concentration by increments of 10%, were created. When these groups were compared, the results (Table II.7) showed that between groups, there were only minimal variations in average birth weight and gestational age. Within groups, both variables were randomly distributed. In contrast, the average duration of exposure differed appreciably between several of the groups.

A similar methodological approach was used to establish a relationship between incidence and concentration that was uninfluenced by variations in the length of exposure. Single and multiple births were subdivided into two groups. In the case of single births, these groups were defined as in oxygen for more or less than 5 days. For multiple births, the groups were differentiated in terms of exposures for more or less than 3 days. Within each of the groups defined to standardize duration, infants were subdivided according to whether they received an average concentration of more or less than 40%. Those not receiving any supplemental oxygen were grouped separately. The incidence for each of the 5 subgroups defined for single and multiple births is shown schematically in Figures II.4 and II.5 respectively. As can be seen, for both single and multiple births, differences in average concentration, ranging

FIGURE II.3 (A)
SINGLE BIRTHS: EFFECT OF BIRTH WEIGHT ON INCIDENCE OF ROP
VS DURATION OF EXPOSURE

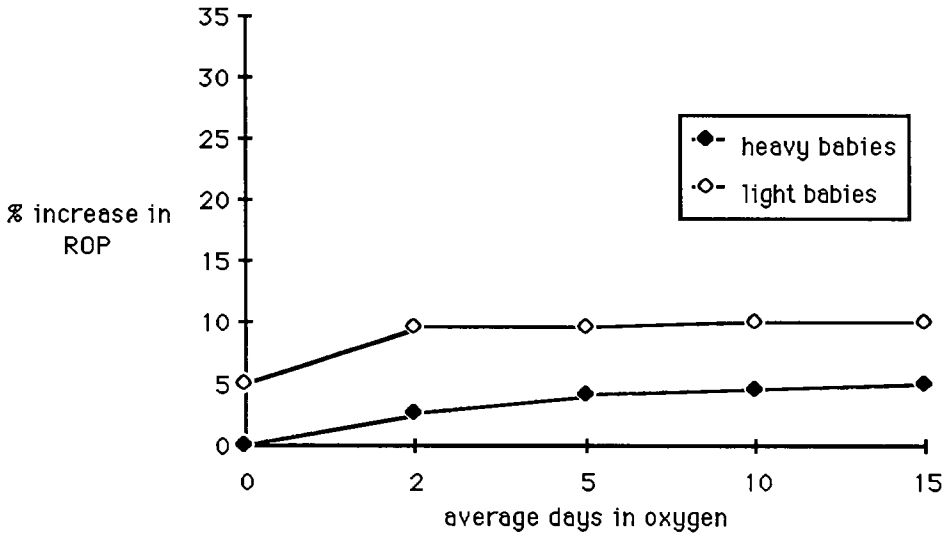


FIGURE II.3 (B)
MULTIPLE BIRTHS: EFFECT OF BIRTH WEIGHT ON INCIDENCE OF ROP
VS DURATION OF EXPOSURE

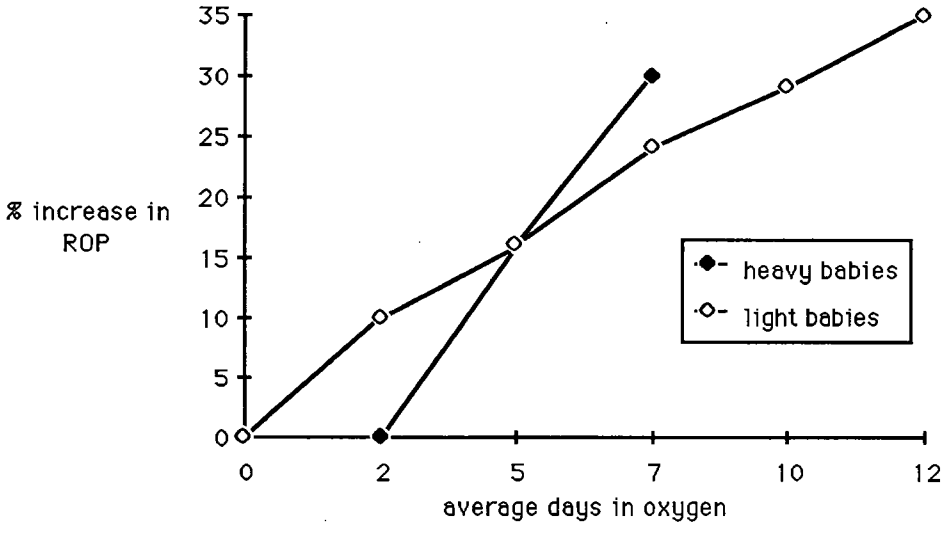


TABLE II.7

INCIDENCE OF CICATRICIAL ROP, AVERAGE DURATION IN OXYGEN, AVERAGE GESTATIONAL AGE AND AVERAGE BIRTH WEIGHT OF INFANTS GROUPED ACCORDING TO CONCENTRATION OF OXYGEN

DURATION IN OXYGEN	NO. EXPOSED	NO. ROP	R.R.	AVERAGE DURATION O2 DAYS	NO.	AVERAGE GEST. AGE WK.	NO.	AVERAGE B. WT. GM.	NO.
1. SINGLE BIRTH									
room air	93	1 (1.1%)	1.0		93	32	77	1266	93
21-29%	14	0		3	14	32	9	1230	14
30-39%	130	8 (6.2%)	5.6	8	130	31	103	1231	130
40-49%	124	7 (5.6%)	5.1	8	124	31	105	1221	124
50-59%	68	7 (10.3%)	9.4	16	68	31	56	1280	68
60-69%	24	2 (8.3%)	7.5	16	24	31	14	1187	24
70-79%	4	0		4	4	31	2	1281	4
80-89%	1	0		1	1		0	1225	1
average	458	25 (5.5%)		8	458	31	366	1240	458
not known	14	3 (21.4%)		2	14	31	14	1315	14
total	472	28 (5.9%)							
2. MULTIPLE BIRTH									
room air	19	0			19	35	15	1325	19
21-29%	9	1 (11.1%)		5	9	33	7	1302	9
30-39%	31	4 (12.9%)		7	31	32	27	1270	31
40-49%	24	7 (29.2%)		4	24	33	21	1307	24
50-59%	13	3 (23.1%)		16	13	31	8	1235	13
60-69%	6	2 (33.3%)		5	6	32	2	1246	6
70-79%	1	1 (100.%)		11	1	33	1	1450	1
80-89%	3	0		3	3	34	3	1125	3
average	106	18 (17.0%)		5.5	106	33	84	1280	106
not known	8	1 (12.5%)		2	8	32	6	1195	8
total	114	19 (16.7%)							

* Modified from Kinsey[150]

FIGURE II.4
SINGLE BIRTHS: RELATION BETWEEN THE INCIDENCE OF cROP AND AVERAGE CONCENTRATION OF OXYGEN FOR INFANTS IN OXYGEN FOR SIMILAR PERIODS OF TIME

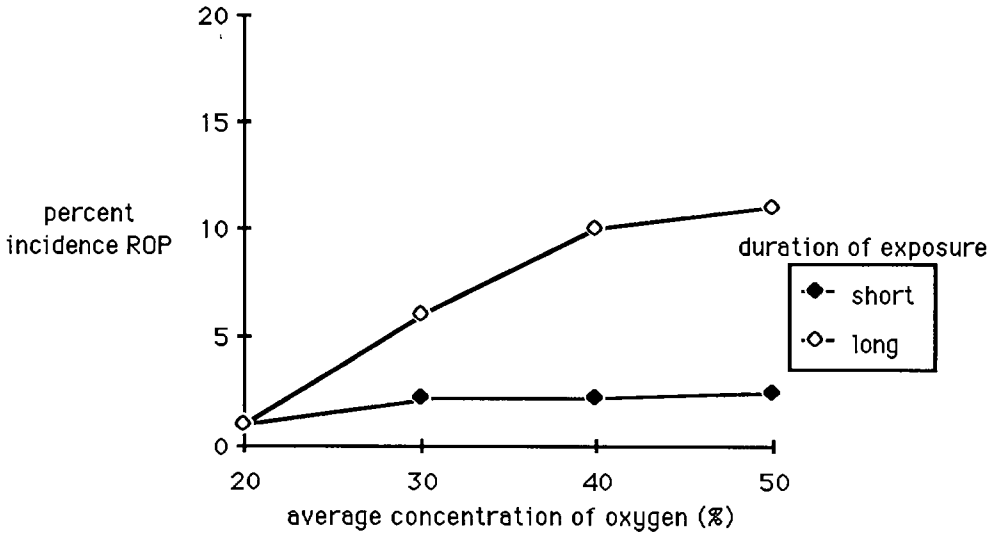
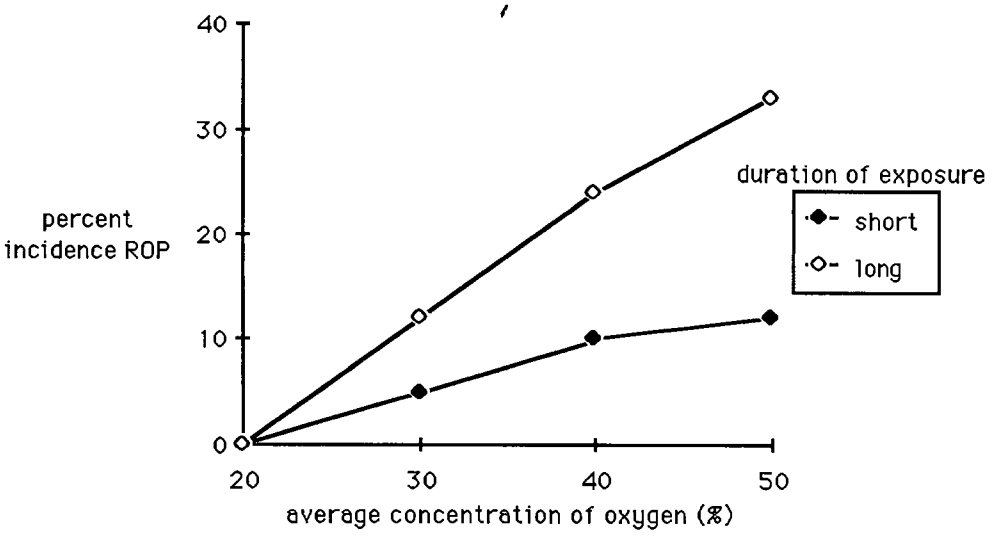


FIGURE II.5
MULTIPLE BIRTHS: RELATION BETWEEN THE INCIDENCE OF cROP AND AVERAGE CONCENTRATION OF OXYGEN FOR INFANTS IN OXYGEN FOR SIMILAR PERIODS OF TIME



from approximately 35% to 50%, had no appreciable effect on the incidence of cROP when infants were exposed for short periods of time (i.e., an average of 2 days). This also held true for single births exposed for longer periods (i.e., an average of 2-3 weeks). For infants of multiple birth, incidence doubled with an increase in concentration from 35% to 50% in infants in oxygen for an average of 12 days.

On the basis of these observations, Kinsey and the other members of the study team concluded:

1. there is no concentration of oxygen above that normally found in room air that is not associated with the risk of developing ROP,

2. for infants of single birth, the incidence of cROP is relatively unaffected by differences in the average concentration of oxygen ranging from 35% to 50%, and

3. for infants of multiple birth, incidence increased with concentration but those increases were appreciable only in infants who were exposed for relatively long periods of time.

Other analyses were done to determine whether or not selected variables were having an effect on either the incidence of the disease, the severity, or the frequency of spontaneous regression. The conclusions drawn from these analyses, which were done using methods similar to those already described, are as follows:

1. the severity of cROP was not dependent on the duration or the average concentration of oxygen,

2. severity was not dependent on factors such as gestational age, birth weight, race, sex, or geographical location,

3. there was no significant difference in the rate of spontaneous regression in the 'routine' compared to the 'curtailed' group,

4. for singletons, the incidence of cROP was not appreciably dependent on gestational age,

5. in both single and multiple births, the incidence of cROP was inversely related to birth weight,

6. age at the onset of ROP was not dependent on birth weight or gestational age but did increase with the length of stay in oxygen particularly for exposures lasting for several weeks, and

7. the incidence of cROP was not influenced by variables such as weight gain, race, sex, type of incubator, number of blood transfusions or infusions, medication or dietary adjuncts, complications of pregnancy, or age of the mother.[150]

II.2.5 HYPO- AND HYPEROXIA AS CAUSE: EXPERIMENTAL STUDIES

In addition to the human evidence, there was non-human, experimental evidence that implicated oxygen as an etiological factor. Michaelson[151], who made no mention of ROP, set the stage for the use of animal models to study the human form of the disease. After examining fetuses from a number of species (including man), he concluded that the capillary system in the retina originates from outgrowths of the retinal veins. When these veins are in close proximity to an artery, the outgrowths extend only a certain distance toward the artery and then stop. This retardation results in the development a well-defined capillary-free zone surrounding the arteries. To explain the zone, Michaelson speculated that some factor emanating from the artery retarded the capillaries growing toward it[151]. In 1951, Campbell[152] described a scenario that suggested that oxygen might be this factor. In normal development, capillaries grow outward from a vein until they encounter an area of the retina where, because of diffusion from a

nearby artery, there is a relatively high oxygen tension. When this area is reached, capillary growth stops creating the vessel-free zone surrounding the artery. When the oxygen tension in the arterial blood stream is reduced, the diameter of the area of high tension is also reduced allowing the capillaries to grow closer to the artery thereby narrowing the diameter of the capillary-free zone.

What Campbell demonstrated was the influence of oxygen on the development of retinal vessels. The first study that purportedly associated the Campbell scenario with ROP[153] appeared to support Szewczyk's theory of 'hypoxia as a cause' [55,56]. However, studies done subsequently[155] eventually discredited this idea. In one of the earliest of these studies, Ashton et. al.[154] exposed newborn kittens to oxygen concentrations ranging from 60-80%. The results of this study were important for two reasons. First, they showed that newborn animals exposed to hyperoxic conditions develop lesions that resemble those seen in infants with aROP. In addition, they suggested that the lesions are secondary to vaso-obliterative changes that result from exposure to high concentrations of oxygen.

Ashton et. al. predicated their study on the belief that kittens born at term were analogous to human infants born prematurely. During gestation, both undergo similar developmental processes in the retina. However, the timing of these processes is different. At term, the infant retina is vascularized to the periphery. In kittens, peripheral vascularization is not complete until 3 weeks of age. Thus develop-mentally, the retinas of kittens at term are roughly equivalent to those of human fetuses at 7 months gestation.

After exposing very young kittens to high concentrations of oxygen (60-80%), Ashton and his colleagues noted the following:

1. during exposure, oxygen preferentially obliterated the ingrowing vessels in the developing retina,

2. after transfer to room air, those vessels remaining patent refilled with blood but, because of the total obliteration of other vessels, the vascular architecture was grossly abnormal,

3. vessel growth recommenced suggesting that the re-established blood supply was inadequate to meet the needs of the retina, and

4. the growth of new vessels into the vitreous was accompanied by retinal detachment.

These observations led Ashton et. al.[154] to conclude that "... obliteration or vasoconstriction of the retinal vessels ... may be the underlying cause of retrolental fibroplasia." Since vaso-constriction, as a prelude to dilation, tortuosity, and neovascularization had been observed in infants with ROP[14,56], this conclusion appeared plausible. Furthermore, it tied together the hyper- and hypoxic theories of causation since it suggested that the damage caused by exposure to supplemental oxygen resulted in a retina that was essentially hypoxic. In a later publication, Ashton was forced to retract his original observation that the growth of new vessels into the vitreous led to retinal detachment. In fact, kitten retinas damaged by oxygen did not detach or otherwise progress to a stage resembling human cROP[156]. This essential difference between human ROP and the disease induced in kittens was also reported by Patz[48]. However, Patz did observe retinal detachment in 2 of 18 puppies treated with similar concentrations of oxygen (60-80%).

The Patz experiments corroborated the Ashton results in other ways.

Mice*, rats*, kittens**, and puppies** all developed ROP-like lesions preceded by a period of vasoconstriction and obliteration when exposed to 60-80% oxygen[48,106]. These observations, coupled with the observation that ROP-like lesions did not occur in animals exposed to low concentrations of oxygen (12-14%) led Patz to the same conclusions reached by Ashton - namely that, in experimental animals, exposure of the immature retina to supplemental oxygen led to the development of vascular changes that were the same as, or at least were similar to, those seen in infants with ROP[48].

Additional evidence supporting the allegation that experimental animals responded to supplemental oxygen in ways that mimicked the human situation came from an observed association between the incidence of ROP-like lesions and the duration of exposure. Ashton[155] first reported, and Patz[157] later confirmed, that with short exposure periods, the vasoconstriction was reversible; when exposures lasted for more than 2 or 3 days, the constriction was irreversible. In a later experiment, Patz produced more evidence directly implicating duration of exposure as the principle factor determining the amount of damage induced. This evidence indicated that oxygen exposure in the range of 35-40% for 10 days produced a significant number of animals who showed signs of hemorrhage and other ocular damage. Given for shorter periods of time, the same concentrations produced no visible retinal lesions[148].

II.3 ACCEPTANCE OF HYPEROXIA AS CAUSE: FROM THEORY TO PRACTICE

By the mid-1950's, the stage was set for the resolution of the ROP

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* at term, the retinal vasculature approximates that of a 4 month human fetus

** equivalent to a 7 month fetus

problem. Because of the clinical observations, the two small clinical trials and the experimental results, the 'hyperoxia as a cause' theory gained ground. However, until the preliminary results of the National Cooperative Study appeared, the medical community as a whole was reluctant to accept the theory. No doubt, some of this reluctance was a function of the fact that past hopes for an early resolution of the epidemic had been based on theories that later proved untenable. Still more of this reluctance can be attributed to the confusion created as proponents of the three oxygen theories produced evidence and arguments to support their own particular viewpoints. Of equal or greater importance was the fact that acceptance of the theory contradicted accepted medical practice and the belief that, in medicine, technological advancements were beneficial rather than harmful.

Prior to 1955, textbooks had routinely encouraged the liberal use of oxygen in the newborn period. For example, the 1953 edition of Pediatrics stated that "... as a rule the oxygen content of the incubator need not exceed 60%, although higher concentrations appear to do no harm and may serve to tide the patient over a spell of anoxia."[158] Similarly, the Textbook of Pediatrics (1954) recommended "(f)or the small premature infant just admitted to the nursery, observation in an atmosphere of 40 to 60% oxygen for a few hours or days ...".[158]

Most hospitals persisted in following these recommendations until the preliminary results of the Cooperative Study put to rest the fear that curtailing oxygen would increase neonatal mortality. However, there was one notable exception. Following the completion of the New York trial[102], the N.Y. City Health Department issued an alert counselling hospitals to curtail the routine use of oxygen[147]. Some months later, the New York State Health Department sent a bulletin to all health officers, chiefs of medical staff

and hospital administrators working outside of New York City that stated "...blindness due to retrolental fibroplasia appears to be entirely preventable ... If oxygen is administered to premature infants, concentrations should be kept below 40%."[159] Similar recommendations soon followed[147,160-162]. For example, in 1955, the Committee on Fetus and Newborn of the American Academy of Pediatrics recommended the following:[147]

1. oxygen should be prescribed only on medical order...*
2. oxygen should not be administered routinely but only upon specific medical indication.
3. concentration(s) should be kept at the lowest possible level that will relieve the symptoms for which it is given, if possible not over 40%.
4. therapy should be discontinued as soon as the indication for it has passed.
5. the indications for supplemental oxygen are general cyanosis (not acrocyanosis) and dyspnea.

Given the results of the National Cooperative Study, the emphasis on limiting oxygen exposures to concentrations not exceeding 40% was surprising. The impetus for the establishment of this level seems to have come from a study done in the Bellevue Hospital in New York[161]. An observed difference in the incidence of cROP between a high exposure group and two lower exposure groups (oxygen = 38% and 30% respectively) led the authors of this study to conclude that ROP "... can be either completely or almost completely eliminated by administering oxygen only at times of clinical need, and then for as brief periods as possible and at concentrations less than 40 per cent."[161] In a letter to the editor of Pediatrics, Kinsey addressed the results of the Bellevue study and the growing tendency to

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* represented a substantial change in practice since, prior to this time, it was not uncommon for the nursing staff to be responsible for oxygen administration.

recommend that exposures not exceed 40% by preannouncing that the results of the Cooperative Study would say that incidence was not affected by concentrations ranging from 33 to 52%[163]. When the final results of the study appeared, he dealt with the issue as follows:[150]

> In view of the evidence from the Cooperative Study that the incidence of (retrolental fibroplasia) is not greatly influenced ... by differences in the average concentration of oxygen in the range of 30% to 50%, and that the disease has been observed to develop in a number of infants ... who received added oxygen but never in concentrations in excess of 40%, the absence of cicatricial (ROP) observed by the Bellevue Hospital investigators may have resulted because the duration of exposure to oxygen was short, rather than because the concentration was kept under 40% ... it is not the present intent to suggest that concentrations of oxygen of 40% or less might not in fact involve less risk of (ROP) ... than concentrations of 50% or less ... but that <u>there seems to be no particular basis for selecting the value of 40%</u>. The results of the Cooperative Study would suggest that <u>the basic policy to be adopted in prescribing oxygen should be to keep the premature infant in oxygen for as short a period of time as possible consistent with the clinical indications of anoxia, regardless of the concentration of oxygen employed</u>.*

With the publication of the final results of the Cooperative Study, an interesting situation arose. It was universally accepted that the study definitively established ROP as an iatrogenic disease caused by oxygen. At the same time, the results - which said that policy should focus on duration rather than concentration - were largely overlooked. Although recognition was given to the importance of minimizing exposure time, the notion that there was a critical concentration of oxygen (40%) continued to dominate the literature. Kinsey had tried to assuage the idea and failed. Armed with the so-called 'definitive' results, he had argued 'you can't get to the 40% policy from here'. The medical community, marching in concert, went anyway.

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* emphasis mine

CHAPTER III
POST EPIDEMIC YEARS

III.1 EPITAPH FOR ROP

In 1954, Patz warned that the evidence implicating oxygen did not rule out the possibility that there were other factors that were causally related[48]. Although occasionally repeated[164], for all practical purposes, this warning was unappreciated for the next quarter of a century. The results of the clinical trials were so enticing that the idea of oxygen as the 'sole and sufficient cause for ROP'[165,166] was quickly entrenched both in practice and in theory.

In a paper entitled 'An Epitaph for Retrolental Fibroplasia', Reese refers to the preliminary report of the Cooperative Study[149] as 'conclusively convicting oxygen' as the causative agent[167]. Although he warned that, even with the judicious use of supplemental oxygen, the occasional case would probably occur, both the title and tone of Reese's paper conveys what became the consensus opinion, namely that:

1. there were no factors other than birth weight and supplemental oxygen exposure etiologically related to ROP,
2. with the judicious use of oxygen, ROP would disappear[161], and
3. those cases that did occur would result from the medical misuse of oxygen in the newborn nursery[168].

III.2 INCIDENCE AFTER OXYGEN RESTRICTION

While there was considerable evidence documenting the occurrence of the epidemic, there was almost none documenting its demise. By the end of the 1950's, only two reports showed dramatic decreases in incidence purportedly related to changes in the exposure policy. In the first, Yankauer et. al.[169] showed that, in New York state, the number of infants blinded by

ROP increased steadily from 1946 to 1953 and thereafter, decreased. In the second report, Lowenfeld[170] reported a similar decrease in blindness due to ROP in preschool-aged children known to the California School for the Blind. The results of both of these studies are shown in Figure III.1. Since incidence rates were not included in either report and since the states differed with respect to the mandatory reporting of blindness*, the data are of little value in determining the incidence of blindness in one state relative to the other. However, they do show that in both states, there was a similar pattern of increasing numbers until 1953 and decreasing numbers thereafter.

In the next substantive reference to a decrease in incidence, which did not appear until 1960, Zacharias[164] noted:

> "With the marked drop of incidence rate of retrolental fibroplasia, interest in this disorder has virtually disappeared. Except for the reports of certain state agencies for the blind, almost no data on incidence of retrolental fibroplasia are being published and probably very few are being collected."

To rectify this situation, Zacharias[164] published the annual incidence rates for infants born in the Boston Lying-In Hospital in the period 1938-1958. These data (Table III.1), which were specific for infants weighing 1814 grams or less, substantiated the decreasing trend in incidence noted earlier. More importantly, they showed a tendency toward decreasing rates in infants with the mild as well as the blinding form of the disease.

Unfortunately, the Zacharias observations were subject to the same limitations as those made by Lowenfeld[170] and Yankauer et. al.[169]. Both of the latter authors had correlated the decrease in the number of infants blinded by ROP to changes in the oxygen exposure policies. However, neither had substantiated the fact that the changes in policy had, in fact, occurred. In

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* in California, reporting blindness was not mandatory; in New York, it was.

FIGURE III.1
NUMBER OF CASES ROP: BLIND IN NEW YORK AND CALIFORNIA BY YEAR OF BIRTH

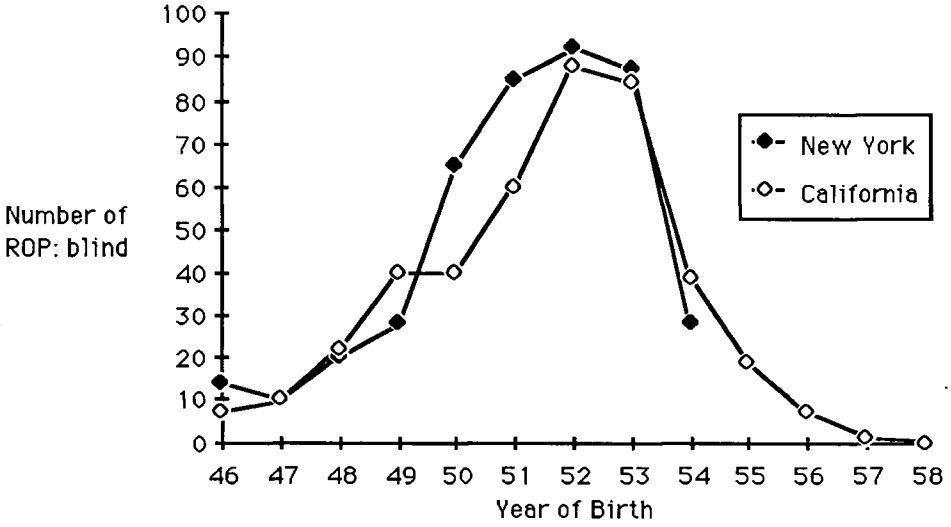


TABLE III.1
INCIDENCE RATES FOR MILD AND SEVERE ROP IN INFANTS* BORN AT THE BOSTON LYING-IN HOSPITAL 1938-1958

YEAR	NUMBER OF INFANTS	INCIDENCE OF MILD ROP	INCIDENCE OF SEVERE ROP
1938	22		18% (4)
1939	25		4% (1)
1940	32		3% (1)
1941	34		0% (0)
1942	37		11% (4)
1943	35		23% (8)
1944	34		26% (9)
1945	37		32% (12)
1946	55		14% (8)
1947	40		15% (6)
1948	42		26% (11)
1949	65	23% (15)	14% (9)
1950	64	39% (25)	8% (5)
1951	66	27% (18)	15% (10)
1952	50	36% (18)	12% (6)
1953	37	38% (14)	3% (1)
1954	50	28% (14)	8% (4)
1955	51	12% (6)	2% (1)
1956	60	12% (7)	7% (4)
1957	46	4% (2)	2% (1)
1958	48	8% (4)	0% (0)
Total	930	(123)	(105)

* weighing 4 pounds or less
** from Zacharias[164]

her study, Zacharias showed that, after 1954, fewer infants had received supplemental oxygen and those who did were exposed to lower concentrations for shorter periods of time. While this suggested that the policies had changed, it was in no way conclusive for the alleged association between policy and incidence.

The early studies were also limited by the small number of observations that were made after the changes in oxygen policy were introduced. This, and the temporal fluctuations in rates observed throughout the epidemic years, raised the possibility that at least some portion of the observed decreases were more a function of the known variations in rates than a reflection of falling rates. Another decade would pass before there was data suggesting a more sustained decrease. These additional data, which appeared in 2 reports[171,172], are shown graphically in Figures III.2 and III.3 respectively. As can be seen, in both data sets, incidence is inferred from tabulations of the number of children affected: in one study, the number affected with ROP severe enough to cause blindness; in the other, the number affected with both active and cROP.

Given the paucity of substantiating evidence, it would not have been unreasonable had the medical community only cautiously accepted the idea that incidence had decreased. In fact, this did not occur. Throughout the 1960's, numerous references alluding to decreases in incidence after the imposition of the 40% policy appeared in the literature. Often, this was done without mention of the limited data that were available. The fact that this practice was not questioned stands as mute testimony to the fact that the decreases themselves were not questioned. In part, this may have happened because those who were in a position to raise questions had no reason to do so. However, the possibility that clinicians were seeing, but not reporting,

FIGURE III.2
NUMBER OF CASES OF ROP LEADING TO BLINDNESS IN ENGLAND AND WALES 1951-1962

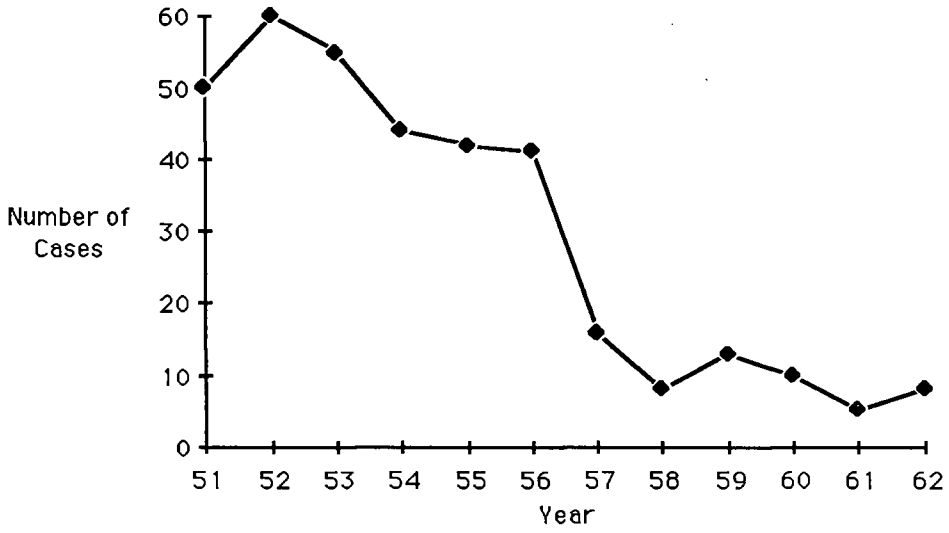
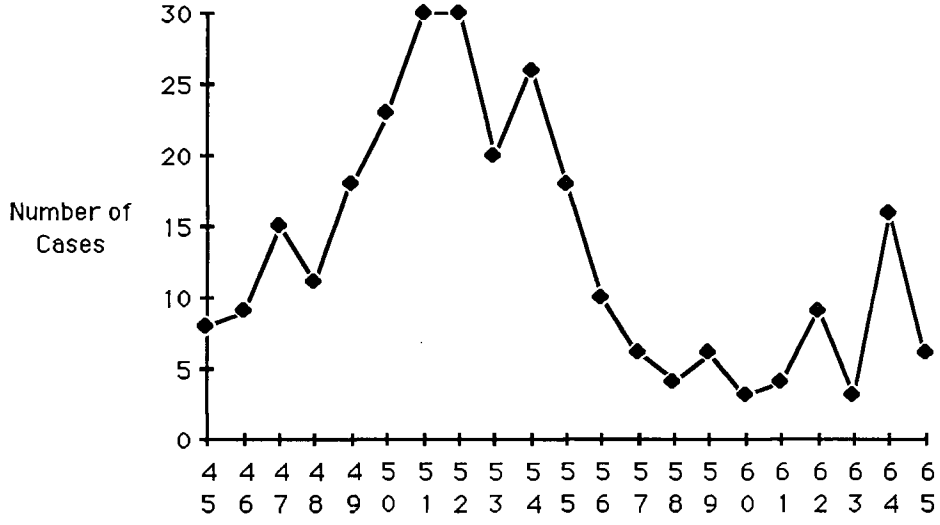


FIGURE III.3
TOTAL NUMBER OF CASES OF ROP BORN IN SWEDEN 1945-1966



fewer cases is unlikely to suffice as a total explanation. There can be little doubt that part of the explanation stems from the fact that the theory of 'oxygen as a cause' had been supplanted by the dogma of 'oxygen as the cause'. Thus, the possibility that the incidence hadn't decreased was simply never entertained.

III.3 THE 40% OXYGEN POLICY: THE NEXT DECADE

This rigidity in the cause and effect viewpoint did more than inure the medical profession to the lack of data underlying the perceived decreases in incidence. It also served to remove ROP from the list of diseases deemed worthy of attention. The little work that was done in the decade following the imposition of the 40% policy focused on the role of weaning in the etiology of ROP, the normal process of vascularization in the eye and the effect of oxygen on that process.

III.3.1 ROLE OF WEANING

As stated earlier, one of the tenets of Szewczyk's hypothesis that hypoxia rather than hyperoxia was causal for ROP held that gradual weaning from high oxygen concentrations would reduce, if not prevent, the toxic effects of the initial exposure[55,56]. Since controlled trials done by Bedrossian[23,110] had supported this allegation, weaning remained an issue even after the hypoxia theory was rejected. Since ethical considerations made repeating the Bedrossian trials impossible, the attempts to clarify the role of weaning had to focus, almost exclusively, on the use of the various animal models that were available. Without exception, the use of these models showed that weaning could not be used to prevent the disease from developing[148,173,174]. In fact, at least one report suggested that weaning

served no function other than to furnish the additional oxygen needed to make an initial nontoxic dose toxic[174]. For many practicing physicians, this was little more than an academic observation. Although they accepted the idea that weaning would increase rather than decrease the risk for ROP, the risk of pulmonary malfunction resulting from a rapid decrease in oxygen concentration often left them with no alternative other than to continue with the use of the technique.

III.3.2 NORMAL VASCULARIZATION AND ROP

With oxygen firmly established as the factor responsible for inducing the abnormal vascular changes seen in infants with ROP, attention turned to the problem of delineating the normal process of vascularization in the retina. This work[175-178] was important for two reasons. First, the difference between the normal developmental pattern and the pattern thought to be synonymous with early aROP was as much dependent on descriptions of the former as the latter. Second, little had been done to refine or expand the picture of normal vascularization since the late 1940's[151].

New observations[175-178], made after the end of the epidemic, reaffirmed the idea that, at term, retinal vessels are far from fully differentiated. In addition, they suggested (i) that the developmental process involves the continual emergence of new vessels and the concomitant obliteration of those that have become redundant[178], and (ii) that the changes seen with the development of ROP are nothing more than exaggerations of the proliferation that occurs normally.

III.3.3 MECHANISM OF OXYGEN ACTION

The new descriptions of normal vascularization fit well with Ashton's

earlier theory that ROP was inextricably linked to normal vascular development. According to this theory, the oxygen-induced obliteration of newly developed capillaries results in a retina that is essentially, hypoxic. Since hypoxia is thought to be the trigger that begins the normal process of vascularization, ROP is simply the eye's attempt to re-introduce a normal process[178]. Although appealing, in the early 1960's, this theory was vulnerable to the fact that there was no evidence substantiating the idea that obliteration causes the vascular changes that subsequently occur. Animal experiments done throughout the 1960's and early 1970's provided this evidence. For example, in 1962, Ashton and Pedlar[179] showed that obliteration is both the primary consequence of prolonged oxygen exposure and the fundamental change that leads to the subsequent chain of events. In 1971, Ashton[180] reported (i) that the transition from functional (i.e., vaso-constrictive) to structural (vaso-obliterative) changes in newborn kittens was dependent on the duration of oxygen exposure, and (ii) that vaso-proliferation only happens when constriction is followed by the total obliteration of retinal vessels.

Ashton's results were convincing but only if they could be extrapolated to the human situation. Animal models, in his studies, kittens, develop a form of disease that closely resembles that seen in infants with aROP. However, in the animal models, the disease does not progress to cicatricial damage: in human infants, it does. If this observed difference reflects an intrinsic difference between species, then the animal forms of the disease are not analogous to human ROP and the extent to which observations can be extrapolated is open to conjecture. On the other hand, if the observed differences are a function of the circumstances in which the human and animal forms of the disease develop, there is nothing to preclude the

extrapolation of observations from one species to another. It is possible and in fact, probable, that the strictly controlled conditions imposed in the animal experiments create a situation that is fundamentally different from that faced by premature infants struggling to survive. If factors other than oxygen are responsible for the induction of blindness, then the absence of blindness in the animal models is more a reflection of the absence of this second group of risk factors than it is a reflection of true differences between the various forms of the disease.

Since the early 1970's, only a few studies have focused on the mechanisms involved in oxygen-induced damage. The results of one of these are particularly interesting. In this study[181], which was done to assess the relationship between prostaglandins and ROP, newborn beagle puppies were randomly allocated to two groups. Puppies in the first group were given an aqueous suspension of aspirin which inhibits the prostaglandin system* while those in the second group received a placebo. When aspirin-treated and the control puppies were exposed to 95-100% oxygen for 72 hours, the treated puppies were found to have retinopathy of significantly greater severity than their untreated littermates. More importantly, Grade III cROP was seen in puppies exposed to both aspirin and oxygen. This was an important observation because it suggested, for the first time, that there was an experimental model that develops both the active and cicatricial form of ROP.

After a second set of experiments, Flower et. al.[181] concluded (i) that retinopathy could not be induced by aspirin alone, and (ii) that the aspirin treatment was simply exacerbating the inhibitory effect of oxygen on the

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* i.e.., it interferes with the conversion of arachidonic acid to prostacyclin, a vasodilator, and thromboxane, a vasoconstrictor

prostaglandin system. Additional experiments showed that the retinal vessels in the aspirin-treated puppies were significantly dilated compared to those seen in their weight-matched controls. This was a particularly interesting observation since it threatens the sanctity of many accepted views. For years, vaso-constriction was thought to be an early sign of onset. This changed when Ashton identified vaso-obliteration as the pathophysiological trigger for ROP, but it changed only to the extent that constriction was no longer seen as the first sign. What was required was prolonged constriction leading to irreversible obliteration of the retinal vessels. Flower's observations suggest a scenario that is not only different but exactly the opposite. Rather than being an early sign of ROP, he argued that constriction is simply a normal physiological response to hyperoxic conditions. It is the inhibition of this normal response that is causal and leads to the onset of symptoms[181].

Flower's observations raise an interesting question: can so many observers have been so wrong for so long? The answer to this question is, of course, yes. The history of ROP is fraught with instances of competent observers being wrong. Ashton may have been misled by what is a normal response. However, his observations are strengthened by the fact that they were made repeatedly by different investigators working in different conditions, often with different experimental animals. Flower's observations have yet to stand this test. Substantially more evidence, other than the observation of cicatricial damage, is needed to substantiate the idea that beagles develop a more human-like form of ROP. There are numerous reports describing induced retinal detachments in dogs[182-184], but none showing that canine detachments occur via the same process as detachments in infants with ROP. Until this is shown, it can't be taken for granted that the

development of cicatricial damage in beagle puppies is analogous to the damage seen in the human form of the disease.

III.4 PROBLEMS WITH THE 40% POLICY

III.4.1 FAILURE OF ROP TO DISAPPEAR

In the decade following the imposition of the 40% policy, it became obvious that, although less frequent, ROP was continuing to occur. Proof came both from published case reports and from the surveys that were done to confirm the decline in incidence. Figure III.1 shows that 3 children born in 1955, supposedly the year after the epidemic ended in New York State, were blinded by ROP[169]. In California, the same was true of 7 children born in 1956 and one born in 1957[170]. The series from the Boston Lying-In Hospital (Table III.1)[160], Sweden (Figure III.3)[172], and the United Kingdom (Figure III.2)[171] also showed a trend toward reduced but definitely not null incidence.

Individual case reports also showed that ROP had not been eradicated. Unfortunately, it is quite possible that these reports were also a factor contributing to the belief that ROP was no longer a problem. In hindsight, it is clear that physicians were reluctant to describe the disease in infants who were treated with any level of supplemental oxygen. Part of this reluctance may have been due to the fact that ROP was no longer considered an interesting, hence a reportable disease. However, it is also likely that physician's were hesitant to publicly admit to having such patients. Whatever the reason - a lack of interest or the fear of litigation that resulted from the perception that ROP was the 'fault' of the attending physician - the net effect was clear. The case reports were heavily weighted to descriptions of the disease in infants who were not exposed to supplemental oxygen or who, for one reason or another, could not be regarded as treatment failures.

III.4.2 EXCEPTIONS TO THE 'OXYGEN AS CAUSE' THEORY

Affected infants not exposed to excessive amounts of oxygen called into question yet another theory formulated in the 1950's, that of 'oxygen as the sole and sufficient cause for ROP'. The infants fell into three main categories: (a) those who were not exposed, (b) those with congenital ROP, and (c) those who were exposed but could not have had elevated arterial oxygen levels. In addition, there was a fourth category that was tangentially related. Infants in this category were exposed to oxygen, were known to have bouts of sometimes severe hyperoxia and yet, failed to develop the signs of the disease[185,186].

III.4.2A ROP IN INFANTS NOT EXPOSED TO OXYGEN

When the hypothesis was first formulated[126], there were people who argued that oxygen could not be causally related to ROP because they had seen the disease develop in infants who were not exposed to oxygen in excess of that found in room air. Although they received some attention at the time, these reports[46,80,115,187,188] were soon discredited by the evidence implicating oxygen as a cause. With the disappearance of reports fitting the oxygen theory, the new reports describing the disease in unexposed infants became more difficult to ignore. Some described ROP in full term infants[169,172,188-199], others, premature infants not exposed to supplemental oxygen[164,190-192,197,199-202]. Some of the infants were blind[164,169,189,200,203], some had only the early signs of aROP[164,187,190].

Symptoms in unexposed full term infants were particularly problematic because they also challenged the dogma that ROP was unique to the premature retina[197]. While some infants were exposed for a brief period of time[172,193,195], most were not. The idea that the disease could occur in

these infants without seriously undermining the association with immature vascular development became easier to accept once Cogan[175], Ashton[176-178], and others[204-206] showed that, even in infants born at term, vascular development was incomplete. However, this did not explain how the disease could develop in infants in the absence of supplemental oxygen.

III.4.2B CONGENITAL ROP

A few reports described ROP that could not have been caused by supplemental oxygen or any other postnatal factor. Affected infants were either stillbirths or livebirths who died within hours or days of birth. Most of these infants were anencephalic. Addison, Font and Manschot[207] reported 9 of 73 eyes taken from anencephalic babies had signs of ROP. In another series of 21 anencephalic infants[208], one infant was affected and another had signs suggestive of the disease. Other anencephalic babies and at least 3 babies with congenital anomalies other than anencephaly also showed signs of ROP at or shortly after birth[191,209-211].

III.4.2C ROP AND CONGENITAL HEART DISEASE

The 'oxygen as the sole and sufficient cause' theory was further undermined by the appearance of ROP in infants suffering from cyanotic congenital heart disease. Because of their complex anomalies, it was thought that many of these infants were incapable of transmitting highly oxygenated blood to their retinas[210,212,213]. In one, PO_2* in blood routinely taken from the descending thoracic artery never rose above 94 mm Hg even though FiO_2** rose above 30 to 60%. Because this infant had a severely hypoplastic

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* oxygen pressure

** fraction of oxygen in inspired air

pulmonary artery and a rudimentary valve, the blood from the thoracic aorta had to have been similar to that found in the retinal vessels. Thus, if the PO_2 levels in the aorta were not elevated, it was unlikely that the levels in the retinal vessels could have been elevated[213].

III.4.2D POSSIBLE EXPLANATIONS

A number of possibilities were offered to explain the occurrence of ROP in infants who should not have been affected. The most popular of these centered on the observation that, at birth, when neonates begin to absorb oxygen through their lungs rather than via their umbilicus, there is a dramatic increase in arterial oxygen saturation levels*. It was suggested that, in some infants, even this normal increase may be all that is required to set in motion the process of vasoconstriction leading to the obliteration of retinal vessels[148,192,203,204]. Flower[181] included a variation of this theme in his hypothesis that ROP was caused by the failure of the retinal vessels to constrict in the presence of oxygen. He noted that, in utero, venous-like blood, with its low oxygen saturation level, flows into the retina at low arterial pressure. With the arterialization of the blood flow at birth, both the saturation level and the infant's blood pressure rise. He argued that these increases result in some degree of vasoconstriction in the perinatal period and that this constriction, coupled with the increase in pressure, establishes the normal level of retinal vasotonia. If this scenario is true, then ROP in infants not exposed to supplemental oxygen might be a consequence of retinal vasotonia that is inadequate to protect the structurally immature retinal vessels from the sudden rise in arterial tension and pressure at birth.

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* from 50% in utero to 90% at birth

Addison, Font and Manschot[207] had a different theory to explain ROP in anencephalic babies. They argued that, because of the reduced number of cells in the eyes and because the eyes are non-functional, anencephalics have a reduced retinal requirement for oxygen. If the intrauterine blood levels of oxygen are not reduced, the retina may become hyperoxic enough, relative to its needs, to induce the development of the disease in utero. Foos[210] also invoked the notion of relative hyperoxia to explain symptoms in an infant with a PDA that was surgically corrected. The Foos hypothesis held that the reversal of any condition that interferes with the oxygen-carrying capacity of the blood or that causes tissue hypoxia may result in relative hyperoxia that is sufficient to initiate the vascular changes characteristic of ROP.

A number of other theories have also been suggested. Bruckner[203] suggested that symptoms may have been due to severe intrauterine anoxia. Others argued that the exceptions to the oxygen theory were probably evidence that the disease could be caused by another, non-oxygen related mechanism[148,164,191,194]. It was also suggested that, in at least some exceptions, particularly those in which prematurity was not a factor, the explanation might be simply that the diagnoses were wrong, that the infants had one or another of the conditions that can be confused with cROP[189,192].

Infants undermining the 'oxygen as the sole and sufficient cause' theory should not have come as a surprise. None of the studies establishing oxygen as 'a' cause[48,52,102,106,148-150,153-157,161] established it as 'the' cause. Nevertheless, this idea was so strong that, for years, exceptions were viewed with a great deal of skepticism. There was even one school that held that ROP should be defined such that the exceptions were excluded[189,214]. Although some found this solution acceptable[188], most appear to have withstood the temptation to redefine the diagnosis so the disease would

fit the theory rather than the theory, the disease.

III.4.3 FAILURE OF THE 40% POLICY

III.4.3A INCREASED MORTALITY

The continued occurrence of ROP was not enough to bring about the demise of the 40% oxygen policy. Since they usually developed symptoms in the absence of supplemental oxygen, the reported cases pointed more to a failure of the theory of causation than to a failure of the policy itself. The first evidence pointing to this latter failure came from an observed association between oxygen restriction and neonatal death. In a comparison of pre- and post-policy mortality rates from hyaline membrane disease (HMD), Avery and Oppenheimer[215] showed an increase in the proportion of infants dying from HMD following the imposition of the 40% policy. More substantive evidence came from Cross[171] and Bolton and Cross[216] in 1973 and 1974 respectively. In the first study, Cross[171] showed that, in England and Wales, the rates of death in the first 30 minutes of life and on days 1 through 6 decreased continuously from 1935 to the early 1950's. Thereafter, in the period usually associated with oxygen restriction, the decrease in rates arrested. When the same pattern was observed in the United States, Cross concluded "... it is highly credible that the restriction of oxygen administration on day 0 and the plateau of the death rate from day 0 from 1950 onward are related."[171]

Cross's observations, which he used to estimate that each case of blindness prevented cost some 16 infants their lives, were ecological. Although they suggested that death rates and oxygen policies were related, they fell short of establishing a causal relationship. Furthermore, they failed to identify the babies who were being adversely affected. If the 40% policy was

having a detrimental effect on survival in the first few days of life, one could reasonably expect that the effects would be trivial in full term infants, smaller babies would be at increased risk, and death rates would be more adversely affected in areas where, before the policies were introduced, the use of high oxygen concentrations was commonplace. In 1974, Boulton and Cross[216] reported the results of a study done to examine these predictions. The data showed that, in New York State, the death rate in full term infants with normal birth weights improved continuously from 1935 to 1970. In lower weight infants, rates improved in the period 1945-1950, then plateaued for the decade coinciding with restriction. In addition, in New York City, where the use of high concentrations had been common, the death rates in the first day of life were higher than they were in the rest of the state.

Boulton and Cross[216] briefly considered a number of alternative hypotheses that might explain their New York observations. One of these, that some environmental factor had induced genetic changes that increased the number of non-viable conceptions, was particularly interesting. In rejecting the hypothesis, it was argued that it was unlikely that an environmental factor would increase the number of neonatal deaths in England and Wales and in the United States at approximately the same time. What makes this rationale interesting is that it was used with regard to supplemental oxygen, for what is this if not an environmental factor? Had oxygen been a mutagen rather than iatrogen, the ROP story itself would have proved that just such an occurrence could occur.

After rejecting their alternative hypotheses, Boulton and Cross concluded their results were consistent with the hypothesis that oxygen restriction was increasing neonatal mortality. With this in mind, they reanalyzed the death rates and, noting what appeared to be an exponential

decrease, they predicted that, in the period 1951-1969, 20,000 babies in England and 150,000 in the U.S.A. had died of hypoxia because adherence to the policy had led to their being inadequately oxygenated. This prediction was surprising in view of Cross's earlier assertion that "it is not possible with statistical respectability to project the relatively smooth curve between 1935 (1937 in U.S.A.) and 1950..."[171]. The same can be said for the fact that they used the discrepancy between the projected and the observed number of deaths to conclude that the number of infants who died as a result of restriction far exceeded the number who would have been blinded had oxygen been administered more liberally. There wasn't, and still isn't, any evidence to suggest that oxygen does anything other than obliterate retinal vessels. While it is true that this obliteration leads to the changes that are clinically characterized as aROP, it is not true that blindness is the inexorable consequence of those changes. Thus the reference to the blinding of babies, casually made and not questioned, couldn't be substantiated then any more than it could be now.

On the surface, the increases in mortality appeared to contradict the results of the National Cooperative Study[150]. However, it must be remembered that the Cooperative Study related only to infants who survived the first 48 hours of life. Unfortunately, when the oxygen policies were imposed, they were applied to infants from the moment of birth onwards. This created an anomalous situation: the effects of curtailment after the age of 48 hours were known[150] but under the age of 48 hours, the most susceptible period in the life of a premature newborn, the effects were unknown. What Cross pointed to when he suggested the failure of the 40% policy were deaths in this undefined period.

III.4.3B INCREASED MORBIDITY

Additional data suggesting the failure of the policy came from a follow-up study on a cohort of infants born in the period 1951-1953. This study[217] showed that the highest rates of cerebral palsy (CP) were found in infants with a history of cyanotic attacks. Furthermore, 57% of children who were born at less than 31 weeks gestation, had attacks of cyanosis, and were exposed to oxygen for less than 11 days, were diplegic compared to 0% of similar children exposed to oxygen for longer periods. When premature care units were ranked according to their respective median lengths of time for oxygen administration, there was a reverse correlation between CP and ROP[218]. The rates of the former were lowest in units that administered oxygen for the longest periods of time and highest in units where exposures were the shortest. For ROP, the opposite was true.

These results were later cited as proof that oxygen restriction was increasing the incidence of spastic diplegia in premature infants[165,197]. In many ways, this was reminiscent of the situation that occurred after the first Cooperative Study. Then too, popular perception had transformed a duration variable, i.e., length of exposure, into a concentration variable. On the basis of the published evidence, it is difficult to explain why the medical profession unquestioningly accepted either transformation. However, condemning the profession for doing so with respect to the 40% policy is itself hard to justify for it overlooks what was alluded to but seldom explicitly stated: the growing frustration within the profession as physicians tried to grapple with the problem of treating severely cyanotic infants with strictly curtailed levels of oxygen.

III.5 LIBERALIZATION OF THE 40% POLICY

III.5.1 BLOOD GAS MONITORING AND INDIRECT OPHTHALMOSCOPY

By the mid 1960's, it was known that, in some infants, limiting exposure was not enough to ensure that the oxygen tension in the blood reaching the eyes did not exceed normal limits[219]. In other infants, limiting exposures resulted in there being too little oxygen to success-fully treat bouts of cyanosis and/or apnea. One of the problems associated with the decision to administer supplemental oxygen and hence, one of the reasons why a fixed limit had been put on exposures, was that, with the available technology, it was difficult to assess hypo- or hyperoxemia in newborns. Prior to the mid 1960's, most assessments were clinical. However, with the advent of methods to measure PaO_2* in micro amounts of blood, it was soon recognized that clinical assessments were often unreliable. Newborns could appear cyanotic when blood leaving the heart was well oxygenated or they could present with the pink skin color associated with normoxemia when they were actually hypoxemic. As measurement techniques were refined, the use of serial blood gas measurements to diagnose states of hypo- and hyperoxemia became more routine[220]. This raised the specter of physicians being able to increase ambient oxygen concentrations without concomitantly increasing the risk that PaO_2 would exceed normal limits.

At approximately the same time, new ophthalmological screening techniques were being introduced. The most important of these, indirect ophthalmoscopy, allowed for a much more extensive examination of the retina** than was previously possible[194,221-227]. With the introduction of

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* arterial oxygen pressure

** the new technique allowed for better illumination, a stereoscopic rather than a monocular image and visualization of an area that was up to four times greater than that observable using the old method of direct ophthalmoscopy

this technique and the PaO_2 monitoring techniques, the stage was set for the liberalization of the oxygen exposure policy. Serial blood gas measurements carried with them the promise of there being a way to reduce the risks associated with the 40% policy without increasing the risk for ROP. In infants who were affected, indirect ophthalmoscopy promised a more efficacious way of diagnosing the early active stages of the disease.

III.5.2 LIBERALIZATION

By the mid to late 1960's, tertiary care centres had taken advantage of the new techniques and were using a more deterministic or liberalized approach to administer oxygen. These changes culminated in a new set of recommendations by the American Academy of Pediatrics. In the 1971 revision of the manual Standards and Recommendations for Hospital Care of Newborns, the recommendations were as follows[147]:

1. in newborn infants exposed to supplemental oxygen, the oxygen tension of arterial blood should be kept close to the normal range of 60 to 100 mm Hg,

2. inspired oxygen in relatively high concentrations may be needed to maintain arterial tension in the normal range, and

3. premature infants requiring oxygen in concentrations greater than 40% for more than brief periods of time should be treated in hospitals equipped to do serial blood gas measurements.

From the reference to concentrations greater than 40%, it is clear that the new policies were not aimed at clearing up the entrenched confusion between risk and the concentration of oxygen versus risk and duration of exposure. It is equally clear that the recommendations were predicated on the assumption that it was possible to maximize survival without causing brain

damage and, at the same time, minimize the risk for ROP[197,228]. What wasn't clear was the validity of this assumption.

III.6 POST-LIBERALIZATION INCIDENCE: A NEW EPIDEMIC?

The idea that the policy could be changed without increasing the risk for ROP was not universally accepted[165,166]. Many hospitals were not equipped to do routine, serial oxygen measurements. In those that were, there was still the possibility that infants might be exposed to prolonged periods of undetected hyperoxia[165]. Since the monitoring techniques allowed for only for point rather than continuous measure-ments, infants treated with high concentrations of ambient oxygen for HMD[166] or episodic bouts of cyanosis or apnea[219] were vulnerable to periods of hyperoxygenation should their conditions suddenly improve.

Concern was also expressed about the fact, in the first few days of life, blood samples usually came from an indwelling catheter in the umbilical artery. Since this blood is derived from the abdominal aorta below the ductus arteriosus, the PaO_2 being measured may be lower than that found in the retina[166]. The use of umbilical catheters was problematic in another sense. Because of the risks involved, these devices can't be left in situ for long periods of time. At some point, the sampling site has to change from the umbilical to the temporal or radial artery. This creates an additional set of problems, and did so particularly in the late 1960's and early 1970's, because there was considerable disagreement as to the interpretation of PaO_2 measurements from these various sites[165,186]. Values defining the normal range for one site did not necessarily define the normal range for another. Moreover, the critical levels, i.e., those associated with an increased risk for ROP, had not been established for any of the possible sites[194,212].

For a time, it was thought that these problems could be minimized by ophthalmoscopic monitoring for vasoconstriction[229-231]. Later it would be shown that, because of hazy media in very young infants, the method was not a reliable alternative to routine PaO_2 assessments. Furthermore, the reliability, even when the media weren't hazy, was questionable. Often, the observed vasoconstriction did not correspond with concomitantly taken PaO_2 measurements. The vessels could appear constricted when PaO_2 levels were well within normal limits or could appear normal when PaO_2 was two times higher than the upper limit defined for the normal range[220,221,232,233].

In the context of the increasing incidence of ROP following liberalization, the failure of ophthalmological monitoring is irrelevant. What is important is that the promise that it might be useful was not enough to quell the concern that an increase might occur. Given what was believed to be true of oxygen and ROP (that incidence correlated with concentration) rather than what was true (that it correlated with duration), it was logical to assume that if the concentrations increased, so too would the incidence. This was particularly true since there could be no guarantee that the increase in ambient oxygen concentrations would not result in infants being exposed to prolonged periods of high PaO_2. Thus, the concerns were quite valid. Unfortunately, the fact that they were voiced is also problematic. Before liberalization, there was little interest in defining the incidence of ROP. After liberalization, concern that the incidence would change prompted people to look for an increase thereby setting the stage for there to be a new epidemic, but one of 'interest' rather than 'disease'.

III.6.1 INCREASING INCIDENCE OF ROP

The early data relating incidence to the new exposure policies were

confusing. In 1968, Seedorff[200,234] published data showing that, in Denmark, the incidence of ROP was unaffected by the discovery that oxygen was a cause. A year later, Lindstedt[235] noted that, in Sweden, the incidence had increased in the early 1960's. These results led to a survey of Swedish children who were born and developed ROP in the period 1945-1966[172]. These data suggested that the incidence peaked around 1952 or 1953, fell dramatically until 1960 and thereafter, had gradually increased.

The Swedish results conflicted with a study that surveyed 1,117 American hospitals to determine the impact of liberalization on incidence[166]. This study, which used 1967 as the representative year for the liberalized policy, suggested that incidence "... was not too different from the estimated experience over the previous (sic) 10 years" when the restrictive policy was in place. This observation created a conflict. Taken at face value, the Swedish results suggested an increase in incidence independent of the oxygen policy while the American results suggested incidence had not increased even after the liberalized policy was introduced.

In hindsight, it is likely that neither study accurately reflected reality. As had many of the studies that defined the original epidemic, the Swedish study defined incidence in terms of incident cases rather than incidence rates. In addition, there were other factors such as a 15% increase in premature births and a 25% decrease in 6 month mortality in the period 1960 - 1966 that might have led to the observed increase in the number of cases[172]. The American data were no more convincing. Only 36% of the hospitals had responded to the initial inquiry[166]. In addition, in some hospitals 1967 was likely to have been a transition year from the old policy to the new rather than a representative year for liberalization.

Throughout the 1970's and early 1980's, interest in the incidence of

ROP continued to grow. In some reports, the authors admitted that their interest was sparked by the change in the exposure policies. In others, interest was attributed to a variety of reasons: the fact that the disease hadn't disappeared after strict monitoring of PaO_2 was introduced, other reports purportedly showing that the incidence was increasing, etc.. Two studies made no such claim. In the first, which was a follow up to the Seedorf study[200,234], incidence in Denmark was again found to be the same before and after 1952[236]. In the second, Tarkkanen and Mustonen[237] looked at the 31 cases diagnosed at the Helsinki University Eye Hospital in the years 1956-1974. When the cases were subdivided into four 5-year birth intervals, it was found that twice as many case were born in the last two intervals (1965-1974). Again, the Helsinki data are difficult to interpret because they relate incident cases rather than incidence rates. In addition, since 22 of the cases were blind, it is clear that, although included, the less severe forms of the disease were substantially under-ascertained.

If the Helsinki results were indicative of an increase, it too occurred independently of the changes in the oxygen policy. All of the cases received supplemental oxygen but at concentrations of less than 40%[237]. This was not the case for other reported increases. For example, McCormick[221] reported the results of indirect ophthalmoscopic examinations of 2,031 infants admitted to the intensive care nursery of the Vancouver General Hospital in the period 1968-1976. This survey was noteworthy for two reasons: (i) the results suggested that the post-epidemic incidence of ROP was higher than previously thought* and (ii) beginning in 1974, there was a substantial increase in the number of infants who were being diagnosed. In the 6 years

* McCormick found signs of aROP in 144 or 7% of the infants examined

prior to 1974, there were 3, 7, 11, 6, 7 and 12 cases diagnosed respectively. From 1974 to 1976, these numbers jumped to 29, 39 and 30. Although he alluded to it, McCormick did not attribute his results to the change in the oxygen exposure policy. Rather, he noted[221]:

> The great increase in numbers of ocularly damaged babies since 1974 is partially explained by the increasing survival rate... of very low birth weight infants; a general increase in the number of admissions to the nursery; and a great increase in the number of small newborns transported to the nursery from hospitals not equipped to care for sick newborn infants. These reasons may not account for the whole of the increase, and it may be that we are producing more retinopathy than before.

A year later, Gunn, Aranda and Little described a study that was done at the Montreal Children's Hospital[238]. Infants weighing 500-1000 grams at birth were subdivided into two groups: those admitted between 1962 and 1971 and those admitted 1972-1976. Only two of 18 infants (11%) admitted in the earlier period had cROP compared to 15 of 35 (43%) admitted in the later period (Table III.2). Since both infants in the early period had grade 5 cROP compared to only one infant in the later period, Gunn concluded that the increase was due to an increased number of infants with aROP. Although they paid lip service to the possibility that their results were confounded by the introduction of indirect ophthalmoscopy and routine post-discharge follow-up, Gunn and her colleagues clearly believed their results were indicative of a true increase in rate.

III.6.2 CURRENT INCIDENCE

Most of the renewed interest in ROP translated into studies to define the point rather than the changing incidence of the disease. These studies were done with different populations of infants, different diagnostic techniques and examination schedules, and different classification systems.

TABLE III.2
SURVIVAL AND OPHTHALMOLOGICAL OUTCOME OF CHILDREN BORN WEIGHING 500 - 1000 GRAMS AT THE MONTREAL CHILDREN'S HOSPITAL

	BIRTH PERIOD	
	1962-1971	1972-1976
Total admissions	218	134
Infants surviving to discharge	54 (25%)	36 (27%)
Children followed-up	42	35
Children with eye exam <1 yr. of age	18	35
Children with ROP (cicatricial)*	2 (11%)	15 (43%)
Children with high myopia	10	10
Esotropia (operative correction)	9	2

* of those with eye exam < 1 year or age
** from Gunn, Aranda and Little[238]

Some included only aROP, some differentiated active and cROP and others combined the forms and referred to 'total' ROP. In a few of the studies, incidence was defined in terms of infants who survived the early neonatal period. In most, it was defined in terms of cruder rates that related to infants who were liveborn in, or admitted to, a particular hospital. Although the differentiation was usually made, only a few studies were standardized in terms of the groupings used to define the birth weight-specific rates.

At the risk of creating a sense of comparability between the studies that simply isn't there, the data have been summarized (Table III.3). As can be seen, the incidence of aROP ranged from 20%[239] to 53%[240] in infants weighing <1301 grams and 8%[241] to 65%[242] in infants weighing <1501 grams. For infants weighing >1500 grams, the incidence fell to less than 1%[243]. The importance of birth weight with this form of the disease is underscored when attention is focused on infants who weighed <1001 grams at birth. For these infants, aROP ranged from a high of 77%[240] to a low of 16%[241]. There was also considerable variation in the incidence of cROP. In one study[250], incidence was 39% in infants weighing <1001 grams while in another, the comparable rate was only 9%[243].

Table III.3 also shows the relationship between birth weight and cROP is not as clear-cut as the relationship between weight and aROP. In the study by Yu et. al.[249], the rate of cROP in infants weighing 501-1000 grams was 13.3% while the rate was only 2.5% in infants weighing 1001-1500 grams. In the Campbell study[243], this correlation was not observed. Once aROP was diagnosed, the frequency of cROP did not vary with weight. The importance of differentiating incidence rates defined in terms of survivors from the cruder rates defined in terms of livebirths is also clearly demonstrated in Table III.3. For example, Pomerance[241] found that in infants born weighing

TABLE III.3
SUMMARY REVIEW OF STUDIES DEFINING CURRENT INCIDENCE OF ROP

STUDY PERIOD	STUDY LOCATION AND INCLUSION CRITERIA	FORM ROP*	B. WT. CATEGORY	INCIDENCE %	INCIDENCE NO.	REFERENCE
Sept 1978-	Edmonton; born Royal Alexandra	A	750-1249	33%	8/24	
April 1981	Hospital; admitted to neonatal ICU;					Finer[244]
	b.wt. 750-1500 gms; b.wt. appropriate	A	1250-1500	15%	4/27	
	for g.age; assigned control group for					
	vitamin E trial					
1968-1974	Vancouver; admitted to premature	A	< 2100	13%	55/418	
	nursery; survived					McCormick[240]
	small because of prematurity only	A	< 1300	53%	38/72	
		A	< 1000	77%		
1974-1978	Oregon; required intensive care	A	< 1700	40%	59/149	
						Palmer[245]
	examined in 6th-7th week of life	A	< 1700	85%	23/27	
1975-1980	San Francisco; birth weight 1500 gms	A	< 1501	11%	34/303	
	or less; survived to discharge; had eye	A	< 1001	24%	19/79	Sniderman[246]
	examination	A	1001-1500	7%	15/224	
1979-1980	Tel Aviv; admitted to neonatal ICU	A	501-1000	65%	31/48	
		A	1001-1250	37%	28/76	Shohat[247]
		A	1251-1500	20%	21/106	
1978-1980	Los Angeles; b.wt. less than 1500	A	< 1500	8%	19/225	
	gm; received oxygen supplementation;	A	< 1001	16%	16/101	Pomerance[241]
	routine eye examination	A	1001-1500	2%	3/124	
	survived	A	< 1001	24%	12/51	
		A	1001-1500	3%	3/105	
1979-1981	admitted to National Collaborative	A	500-749	43%	23/54	
	Study on PDA in Premature Infants;	A	750-999	26%	105/403	Purohit[239]
	born in or admitted to 1 of 13	A	1000-1249	15%	109/718	
	participating hospitals	A	1250-1499	7%	59/808	
		A	1500-1750	3%	31/1042	
		A	Total	11%	327/3025	

Nov. 1979- Dec. 1980	Houston, Texas; b.wt. 1500 gms or less; admitted to neonatal ICU within 24 hrs of birth; received supplemental oxygen; survived; assigned to control group for vitamin E trial	A	< 1501	65%	33/51	Hittner[242]
	Connecticut; had respiratory distress syndrome; assigned to control group for vitamin E trial	A		22%	8/37	Puklin[248]
1977-1980	Melbourne, Australia; admitted to neonatal ICU with one or more conditions that would lead to routine examinations	C C	501-1000 1001-1500	7.5% 2%	8/107 6/268	Yu[249]
	-survived	C C	501-1000 1001-1500	13% 2.5%	8/60 6/237	
1976-1978	Syracuse, New York; b. wt. 1000 gms or less; admitted to neonatal ICU; available for follow-up at 8 and 15 months of age	C	< 1001	39%	15/38	Ruiz[250]
1976- June 1978	Houston; admitted to neonatal ICU in 1st 24 hrs. of life; b.wt. 1500 gms. or less; g.age 32 wks. or less; b.wt. appropriate for g.age; had PDA; survived 1st month of life	A C	< 1501 < 1501	48% 15%	23/48 7/48	Procianoy[251]
1972-1976	Nashville; admitted neonatal ICU; had hyaline membrane disease; survived	C	< 1750	2%	3/144	Stahlman[252]
1965-1970	Seattle; admitted neonatal ICU; survived neonatal period		< 1000	23%	5/22	Alden[253]
1976-1979	Indianapolis; all surviving premi's who received oxygen; in last two years of study, all surviving neonates < 35 weeks gestational age	A A A A A A C C	< 751 751-1000 1001-1250 1251-1500 1501-2000 > 2000 < 750 751-1000	13% 30% 12% 7% 3% <1% 0% 10%	1/8 24/81 19/163 16/182 10/373 2/1908 0/8 8/81	Campbell[243]

		C	1001-1250	2%	4/163	
		C	1251-1500	4%	7/182	
		C	1501-2000	0%	0/373	
		C	> 2000	<1%	1/1908	
1975-1980	Seattle; admitted neonatal ICU; b. wt. less than 2000 gms; survived	A	< 751	40%	4/10	Kalina[228]
		A	751-1000	42%	32/76	
		A	1001-1250	14%	25/185	
		A	1251-1500	4%	10/282	
		A	> 1500	<1%	9/1782	
		C	< 751	10%	1/10	
		C	751-1000	12%	9/76	
		C	1001-1250	1%	6/185	
		C	1251-1500	<1%	2/282	
		C	> 1500	0%	0/1782	
1955-1958	Boston; born in Boston Lying-In Hospital; b. wt. 1814 gms or less	A	< 1815	9%	19/205	Zacharias[164]
		C	< 1815	3%	6/205	

* A = active ROP C = cicatricial ROP

<1001 grams, the crude rate of aROP was 16% while the survivor-specific rate was 24%. In the study by Campbell et. al.[243], the crude rate in the same weight category was 13% and the survivor-specific rate, 28%. Similar differences in the cROP rates were also described by Yu et. al.[249].

Zacharias's data[164] on the incidence of ROP in the Boston Lying-In Hospital in the late 1950's is also included in Table III.3. This was done because there are those who point to these data to substantiate the allegation that the incidence is increasing. At first glance, it would appear that the data supports this allegation. In reality, there is very little inter-period comparability in terms of either the crude or the more refined rates. Although the comparisons are interesting, the fact that they cannot be supported by a ceterus paribus argument* renders them useless in defining the current situation.

III.6.3 INCREASING INCIDENCE REVISITED

The data supporting the allegation that incidence is increasing is, at best, minimal. There was even one large case series from the neonatal intensive care unit at the University Hospital in Seattle that purportedly showed that rates of active and cROP were unchanged over the 13 year period 1968-1980. The results of this study[228], which looked at birth weight-specific rates in two birth periods, 1968-1974 and 1975-1980, are summarized in Table III.4. Unfortunately, although they went to the trouble of calculating weight-specific incidence, the investigators based their conclusions on the total rather than the weight-specific rates. Had they focused on the latter, their conclusions might have been quite different. For infants weighing <1000

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* i.e.., it cannot be assumed that all other factors have been equal over time

TABLE III.4
BIRTH WEIGHT-SPECIFIC INCIDENCE RATES IN INFANTS RECEIVING NEONATAL INTENSIVE CARE (UNIVERSITY HOSPITAL, SEATTLE, WASHINGTON), 1968-1980

BIRTH WEIGHT CATEGORY	1968-1974 BIRTHS			1975-1980 BIRTHS		
	NO. SURVIVORS	NO. ROP	% ROP	NO. SURVIVORS	NO. ROP	% ROP
1. ACTIVE ROP						
< 751 grams	3	3	100%	10	4	40%
751-1000 grams	40	12	30%	76	32	42%
1001-1250 grams	111	21	19%	185	25	13.5%
1251-1500 grams	175	15	9%	282	10	3.5%
1501-1750 grams	187	7	4%	276	7	2.5%
1751-2000 grams	169	1	<1%	335	2	<1%
Total	685	59	9%	1164	80	7%
2. CICATRICIAL ROP						
< 751 grams	3	0	0%	10	1	10%
751-1000 grams	40	2	5%	76	9	12%
1001-1250 grams	111	5	4.5%	185	6	3%
1251-1500 grams	175	1	<1%	282	2	<1%
1501-1750 grams	187	1	<1%	276	0	0%
1751-2000 grams	169	1	<1%	335	0	0%
Total	685	10	1.5%	1164	18	1.5%

* modified from Kalina and Karr[228]

grams at birth, weight-standardized incidence ratios, calculated using rates from the early period to estimate the expected number of cases in the later period, result in values of 1.5 and 2.5 for active and cROP respectively. Since the lower 95% confidence limits for these ratios do not include the number '1', the ratios suggest that the incidence for very low weight infants did increase even though the overall incidence did not.

The fact that the idea is poorly substantiated and in some cases, supposedly refuted, has done little to curb the impression that incidence is increasing. For some time, the literature has been pervaded with this idea. Often it is referred to as fact with no supporting evidence presented or cited[185,254-257]. To clarify this problem, Phelps[258] even went so far as to estimate of the number of children affected by severe ROP in the 1979 U.S. birth cohort. According to these estimates, 397 to 883 infants were probably blinded by the disease and approximately 2100 were probably affected by at least some type of cicatricial sequelae. On the basis of these estimates, Phelps concluded the "... annual accrual of new ROP blind ... is close to the estimated number of cases that occurred during the 'epidemic' years of 1943 to 1953."[258]

The Phelps estimates, and hence her conclusions, are vulnerable to a number of criticisms. There were no published birth weight distribution statistics for 1979. To compensate, the distribution in 1974 livebirths was projected to the 1979 cohort. Because of changes that occurred in the interim[259-260], this estimation of the population at risk has to be viewed with some skepticism. In addition, since birth weight-specific survival rates were not available at the national or state level, Phelps had to extrapolate rates from individual hospitals. Unfortunately, these rates are often biased by differences in regional services and in the ethnic and socioeconomic mix of the populations being served. The fact that the hospitals publishing birth

weight-survival statistics are usually those that offer neonatal intensive care introduces another, potentially more serious, bias. By 1979, transport services for high risk infants were widespread throughout the United States. However, to assume that all high risk infants would have been transported to a tertiary care unit is unrealistic. Similarly, most if not all of the data defining the percentage of blinding or severe cROP are generated in large neonatal intensive care units. This is problematic because, by 1979, oxygen administration was no longer limited to these centres. Again, it does not seem reasonable to assume that all the secondary care centres equipped to administer oxygen were equipped to do the sophisticated, and presumably costly, blood gas monitoring that is routine in tertiary care units.

In spite of the limitations, the Phelps estimates are now routinely cited as proof that ROP is again a problem. In 1982, Lucey[261] cited only these estimates to substantiate the allegation that "(w)e are now experiencing a second epidemic of this dread disease." While a few cautionary voices are being raised[15,262], indications are they are not being heard. Although Lucey, obviously an ardent supporter of the increased incidence theory, has been quoted as saying "I don't believe there are any (population-wide) figures that allow us to establish the epidemic we all think we are seeing"[263], the overwhelming perception seems to be that ROP is a disease that has returned with a vengeance[264].

III.7 REIMERGENCE OF INTEREST IN ROP

With the suspected increase in incidence and the new screening techniques, ROP again became a disease worthy of attention. Much of this attention translated into attempts to modernize the clinical description, to define the optimum time for diagnosis and to develop new ways for

categorizing the clinical signs. In addition, interest has again focused on the problem of defining the etiological factors, and the treatment and prophylactic modalities that might be effective in combating the disease.

III.7.1 MODERNIZING THE CLINICAL AND PATHOLOGICAL DESCRIPTION

The decades between the onset of the first epidemic and the concern about a second epidemic were marked by dramatic improvements in the diagnostic and histopathological techniques used to describe ROP and other ocular disorders. The most notable of these improvements relates to the description of the events that occur at the end-point reached by the developing vessels as they move outward toward the periphery of the retina. Most of the more recent descriptions refer to a proliferation and accumulation of mesenchymal cells in this area[226,262,265,296]. Clinically, these changes, which are indicative of a developing arteriovenous shunt, appear as a white line dividing the vascular from the avascular retina[206,226,265,266]. Posterior to the shunt, the major vessels are dilated and tortuous[206,226]; within the shunt, new vessels appear as multi-branched tufts[206,226,262], which, as the disease progresses, pierce the internal limiting membrane and grow into the vitreous behind the crystalline lens[206,265].

It is now thought that the appearance of the demarcation line between the vascular and avascular retina is the first sign diagnostic of early aROP[265]. This line also figures prominently in the contemporary view of when and how regression and cicatrization occur. Clinically, when regression is about to occur, the shunt loses its whitish appearance. Normal capillary buds within the shunt eventually push into the avascular retina obscuring the demarcation line and bringing about its eventual disappearance[226]. If these

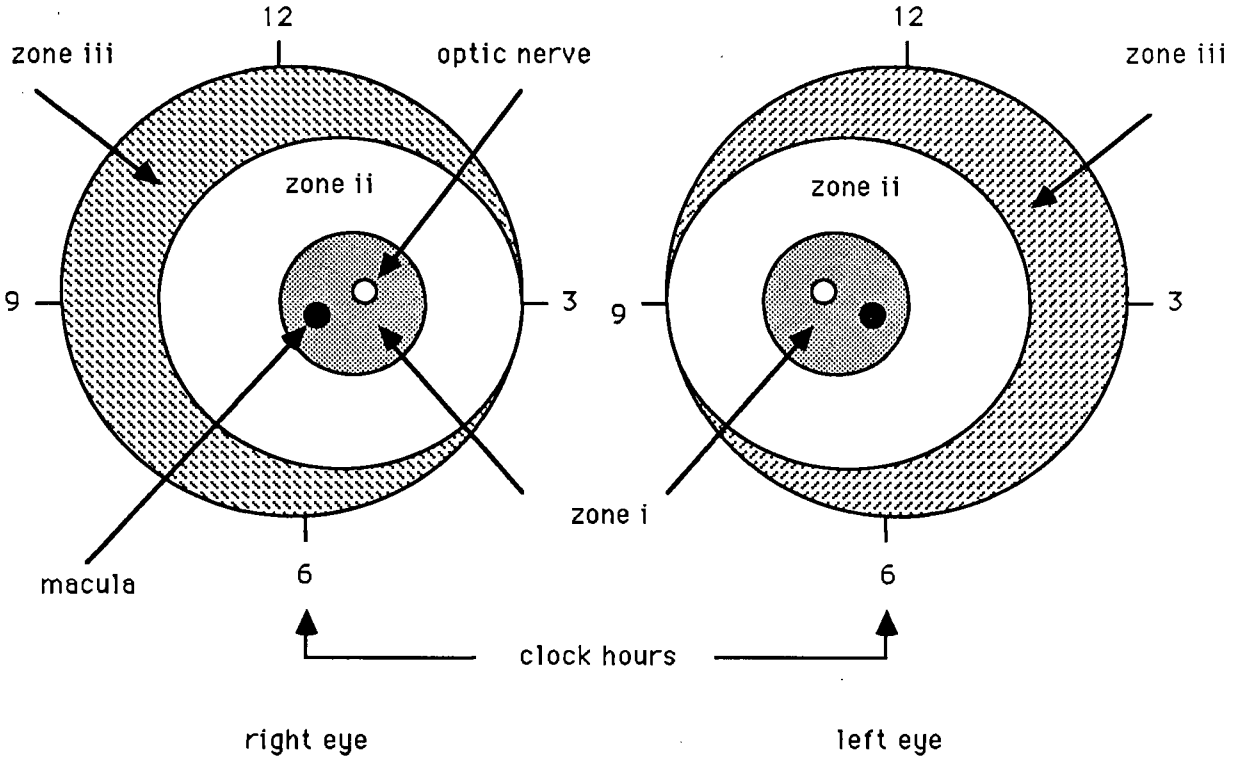
regressive changes fail to occur, the capillary buds do not form, the shunt with its microvascular anomalies, persists[266] and the result is cicatrization.

There are two interesting but seldom referred to observations that should be mentioned with regard to regression and cicatrization. The first is that these two processes often occur simultaneously in different parts of the same retina. This is important because it suggests that these processes are influenced by as yet unknown microfocal factors[266]. The second is that the processes do not represent all or nothing phenomena. Even after regression, infants usually continue to show some signs of having had the disease[267]. What really regresses to normal is the infant's potential for visual acuity. It is this fact, i.e., the observation that some infants undergo this process while others do not, that makes the active form of ROP such an enigma. There is not, and never has been, a satisfactory answer to explain why the disease "... result(s) in a little abnormal peripheral retinal vascularization in some infants, become(s) more florid before settling down ... in others, and yet show(s) a relentless progression to blindness in still other infants."[221]

III.7.2 CURRENT CLASSIFICATION SYSTEMS

The delineation of the arteriovenous shunt and the development of the techniques that made its description possible resulted in a proliferation of the classification systems that are used to categorize the disease[221,227,248,268,269]. In 1984, an international committee, responding to the problems caused by this proliferation, devised a new system that incorporated the contemporary descriptions of the active form of the disease. This system differs from those preceding it by the specification of two parameters: the location of the disease in the retina and the extent of the vascular involvement. Figure III.4 outlines the schematic that was devised to

FIGURE III.4
NEW INTERNATIONAL CLASSIFICATION:
SCHEMATIC SHOWING ZONE BORDERS AND CLOCK HOURS
TO DESCRIBE LOCATION AND EXTENT OF ROP



localize the disease. As can be seen, the retina is subdivided into three zones and the extent of the disease within each zone is specified as are the hours on a clock[15].

In the new system, the staging for aROP is defined as follows:[15]

STAGE 1

-marked by the appearance of a relatively flat demarcation line separating the avascular from the vascularized retina*

STAGE 2

-reached when the demarcation line exhibits both height and width

STAGE 3

-reached when the ridge defining stage 2 has with it, extra-retinal fibrovascular proliferative tissue

STAGE 4

-characterized by 'unequivocal' retinal detachment

A categorization known as 'plus' disease was also defined. This designation is to be invoked if, and only if, the vascular changes are so marked that the posterior veins are enlarged and the arterioles tortuous. To use the example devised by the committee[15], the occurrence of a stage 2 ridge in an infant showing marked posterior dilation and tortuosity warrants the designation of stage 2+ disease.

It is too early to tell if the recommendations made by the inter-national committee will be adopted. The system, which at the present time relates only to aROP, comes complete with its own set of problems. Because of the difficulties inherent in attempting to identify anatomic landmarks in premature eyes, the boundaries of the zones defining location are only

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* vascular changes may be apparent prior to the development of this line but alone, they do not constitute sufficient evidence to justify the diagnosis of stage 1 ROP

approximate. Furthermore, to make the system prognostically significant, the committee subdivided stage 3 aROP to reflect the amount of fibrovascular proliferative tissue present. If only limited amounts of tissue are observed, the signs are classified as 'mild' stage 3. More tissue signifies 'moderate' stage 3 and massive infiltration of the tissues surrounding the ridge is considered 'severe'. Unfortunately, this raises the specter of there being 6 subdivisions for a single stage (mild stage 3, mild stage 3+, etc.). This may be problematic because, if the subdivisions are difficult to assign, physicians may opt to continue the practice of developing new or modifying old systems to meet their particular needs[15].

III.7.3 SCREENING FOR ACTIVE ROP

By the end of the first epidemic, it was known that ophthalmological examinations had to be done before regression obscured the signs diagnostic of the disease. Unfortunately, it was also known that the specter of under-ascertainment was not limited to examinations that were done too late. Since ROP doesn't usually occur until some time after birth, screening had to be postponed until the early signs could develop.

In 1977, McCormick[221] detailed other reasons for delaying the time of the initial examination. He pointed out that the use of indirect ophthalmoscopy could result in over-ascertainment if infants are examined at too young an age. This conclusion was based on the observation that visible iris vessels, which are often seen in infants with aROP, are not uncommon in newborns. More importantly, in the immediate postnatal period, even mature infants who are not at high risk can present with dilation and tortuosity of the retinal vessels. In normal infants, the iris vessels and the distorted retinal vessels disappear, usually in the first few days

of life. However, if screening is done too early, these anomalies could result in the appearance of ROP in infants who are not affected. This possibility is minimized if the telltale demarcation line between the vascular and avascular retina is used as a diagnostic criteria. Unfortunately, even in the 1980's, there are still those who argued that dilation and tortuosity are diagnostic of onset[270].

Since premature infants are usually in hospital for prolonged periods of time, the recommendations made by the American Academy of Pediatrics at the time of liberalization (that screening be done at discharge and again at 3 to 6 months of age) minimized the chances of under- or over-ascertainment as a result of examinations done too early. However, the recommendations left open the possibility that some infants would be screened too late. In 1981, Palmer[245] reported results suggesting the extent to which this could happen. These results (Table III.5) suggested that incidence reached a maximum during the 8th week of life. Furthermore, since only 4% of the cases were diagnosed at less than 5 weeks of age, the data suggested there was a clear cut minimum age for the initial screening examination. However, since he didn't do routine serial examinations, Palmer couldn't estimate the age of onset in infants who were diagnosed later in the first year of life nor could he exclude the possibility of regression in the infants who were examined later and appeared normal. Nevertheless, he did show that the early signs of aROP could occur in older infants. This observation led to the recommendation that screening be done twice, at 6 weeks and again at 10 weeks of age, before infants are considered normal. If only done once, he recommended that the screening examination be done in the 7th to 9th week of life[245].

Palmer's results suggest that the American Academy of Pediatrics

TABLE III.5
FREQUENCY OF ACTIVE ROP DETECTED BY AGE AT FIRST EXAMINATION
WITH INDIRECT OPHTHALMOSCOPY

AGE AT (WEEKS)	NO. EXAM.	NO. EXAMINED	% aROP aROP	CUMULATIVE % aROP
0 - 1	2	0		
1 - 2	8	0		
2 - 3	11	0		
3 - 4	11	0		
4 - 5	6	2	33.3%	5.3%
5 - 6	9	3	33.3%	10.6%
6 - 7	11	9	81.8%	24.1%
7 - 8	16	14	87.5%	37.8%
8 - 9	9	41	44.4%	38.6%
9 - 10	3	2	66.7%	39.5%
10 - 11	3	2	66.7%	40.4%
11 - 12	2	1	50.0%	40.7%
12 - 13	5	3	60.0%	41.7%
13 - 14	3	0		
14 - 15	0	0		
15 - 16	4	1	25.0%	39.8%
16 - 20	9	2	22.2%	38.4%
20 - 24	7	2	28.6%	37.8%
24 - 28	6	2	33.3%	37.6%
28 - 32	4	2	50.0%	38.0%
32 - 36	5	0		
36 - 40	2	1	50.0%	36.0%
40 - 44	4	0	----	35.7%
Total	140	50	35.7%	

* modified from Palmer[245]

recommendations may have resulted in substantial under-ascertainment. To make this point, he cited data showing that, for infants weighing 751-1000 grams, the overall length of stay in intensive care is 61 days[245]. This suggests that affected infants in this weight group would be detected by initial examinations done at discharge. However, for infants weighing >1000 grams, the median length of stay was considerably lower raising the possibility that discharge examinations might precede the onset of the disease.

III.7.4 LATE EFFECTS

In 1975, Hatfield[271] reported that 24% of the blind school age population in the United States in the 1968-69 school year had ROP. Of these, two thirds were 15 to 19 years of age, victims of the first epidemic. An additional 26% were 10 to 14 years of age while the remaining 8% were 5 to 9 years. This showed that, even after the end of the original epidemic, ROP was continuing to exact a price. Unfortunately, that price wasn't limited simply to the provision of educational services. Over the years, the devastating impact of blindness on a child's psychological, intellectual and physical development[272,273] had become increasingly clear. In addition, there was evidence suggesting that ex-premature children with ROP were at higher risk for emotional and behavioral problems than were children with non-ROP forms of blindness[256].

The psycho-social impact of the disease, and the possibility of emotional and behavioral consequences beyond those caused by prematurity and blindness, underscored the importance of detecting the changes that could lead to severe visual impairment. In the early years, when ROP was being defined as a disease, there were a few reports suggesting that retinal detachment could occur years after the disease was supposedly arrested[57] As

the population of children affected during the first epidemic aged, it became apparent that late detachments were not uncommon[190,274,275]. Moreover, even minor cicatricial changes could lead to some, although not necessarily severe, impairment. Numerous authors noted an association between ROP and myopia[28,186], retinal degeneration, retinal schisis, strabismus, acute angle-closure glaucoma and other conditions that could impact directly on visual acuity[262].

III.7.5 THE NEW SEARCH FOR ETIOLOGICAL FACTORS

III.7.5A ARTERIAL OXYGEN (PO_2)

As mentioned previously, the idea that the oxygen exposure policy could be liberalized was predicated on the idea that restricting arterial rather than ambient oxygen would minimize the risks for neonatal mortality, neurological damage and ROP. Inherent in this was the assumption that there is a threshold level below which the risk for ROP is minimal, above which it is increased. In 1969, five major neonatal care centres undertook a prospective analytical study to determine this level[276]. Infants were enrolled if they were admitted to the intensive care unit of one of the participating hospitals in the period 1969-1972 and if they had a respiratory disorder severe enough to necessitate exposure to supplemental oxygen.

In the 3 year study period, 1,373 infants meeting the inclusion criteria were identified. Of these, 654 (47.6%) were excluded, 208 (15.1%) because they died within 40 days of birth, 446 (32.5%) because their respiratory disorders were not treated with oxygen or because the information pertinent to the study was not recorded. The remaining 719 were included although ten, all with ROP, were later excluded because their blood gases had not been measured. In the initial analyses, low birth weight was so highly correlated

with ROP that it masked the effect of all other variables. When the data were stratified into three birth weight categories, no association between PaO_2 and ROP was detected. What was detected was the association identified by the first cooperative study[150], namely the correlation between incidence and the duration of exposure.

There are numerous possible explanations for the failure of the second study to establish a threshold PaO_2 level. The report suggests that the sampling frequency was not well standardized across hospitals. In addition, the elapsed time from one PaO_2 measurement to the next was sufficiently large to allow for substantial undetected variation. Another possible explanation lies in the large number of infants who were excluded either because the relevant tests weren't done or the information wasn't recorded. As mentioned, there were 10 infants with ROP who were excluded from the analyses because their blood gases weren't measured. The fact that these infants were eliminated after the exclusion phase of the study raises the possibility that there were other infants who should have been excluded because there was no or only minimal blood gas information available.

It may also be that the study failed to find a threshold level because there is no threshold to find. The idea that there should be a critical level comes from the reasoning that, if ambient oxygen is associated with ROP, arterial oxygen should also be associated. In 1964, Ashton[227] produced experimental evidence that substantiated this idea. Newborn kittens were subdivided into two groups: in the first, pure oxygen was passed through a cup attached to one eye; in the second, it was inhaled. After three days of treatment, animals in the second group showed retinal abnormalities typical of early ROP. In the first group, the eyes exposed to pure oxygen did not differ from those exposed to room air.

While they implicated arterial rather than ambient oxygen, Ashton's observations didn't identify the particular aspect of arterial oxygen that was implicated. That aspect could have been, but was not necessarily, a critically high level. It is possible that the factor of concern was simply duration, perhaps to even minimal increases in tension. Alternatively, there may be other factors (i.e., cofactors) that have to be present before induction of the disease by high PO_2 occurs. If either alternative is true, then the second cooperative study was doomed to failure by the assumptions on which it was based.

The idea that more than just a simple threshold level is involved gains credence when subsequent studies are taken into account. Most of these studies fall into one of two categories: those that attempted to find a correlation between PaO_2 and ROP and those that looked at the PaO_2 levels that could be attained without inducing the disease. In recent years, there have been several studies that fall into the first category[186,197,214,249,276]. These studies are noteworthy because they failed to detect a correlation between ROP and PaO_2 or, in some cases, between ROP and the duration of oxygen therapy[186,214,247,249]. In one of the first studies falling into the second category, Baum and Bulpitt[279] showed that when infants had high PaO_2 levels for short periods of time, the retinal vessels constricted but showed no signs of vaso-spasm or obliteration. Another study[185] showed that infants could have increased PaO_2 (>150 mm Hg for 7 to 43 hours) without developing the early signs of aROP. While they appeared to corroborate the results of the second cooperative study, none of these later studies eliminate the possibility that there is an undetected level above which risk increases. All were done with small populations so that, in each, the power to detect small but potentially important differences in PaO_2 was minimal.

One of the few things the various studies had in common was the fact that, without exception, PaO_2 determinations were made from blood samples that were intermittently drawn. In the late 1970's, a new technique, transcutaneous oxygen monitoring ($TcPO_2$), was introduced in many intensive care nurseries. The technique had two distinct advantages over the earlier method: it allowed for continuous, noninvasive PO_2 measurements and it eliminated the necessity of switching from arterial to capillary measurements*. Unfortunately, the new method was not without problems. Its use resulted in a massive accumulation of data that was difficult to analyze and store. In addition, most of the measuring devices were equipped for either a digital display or paper readout. Since the digital display necessitated the reading and recording of values at specific points in time, these alternate readout mechanisms raised the possibility that, while monitoring was continuous, recording was not[280].

These problems, which in some centres are being overcome with automated data processing techniques[280,281], have not precluded the widespread use of the new technique. In some nurseries, it has been used to show that there are wide variations in oxygen tension[282]. In others, it has been used to show that hypoxemic and hyperoxemic episodes are often of short duration, hence not amenable to detection by intermittent measurements[280,281,283]. Unfortunately, there is also evidence showing that, even when $TcPO_2$ monitoring is used, cases with ROP continue to occur[244,246,247,249,284,332]. Thus it may be that the use of new technique will be important not in establishing a threshold level but in showing that no such level exists.

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* oxygen levels in capillary blood are much lower than the levels in arterial blood

III.7.5B OTHER OXYGEN RELATED FACTORS

Most of the studies sparked by the renewed interest in ROP include variables that relate more to oxygen in general than PO_2 in particular[186,214,239,247,249,250,276]. As was the case during the original search for etiological factors, the studies were done using different classification systems and inclusion criteria. In many, variables, although ostensibly similar, were different enough to make comparisons difficult. In addition, in most of the studies making use of multiple variables, each variable was analyzed separately. In one such study, Gunn et. al.[186] examined 35 oxygen and non-oxygen related variables using only univariate techniques. The use of these techniques without concomitant adjustments to the levels defining statistical significance, and the methodological differences between the studies may explain why the results often differed either from one study and the next or between the more recent studies and those done earlier. For example, some of the recent studies failed to find an association between ROP and the duration of oxygen therapy[186,214,247,249,276]. Similarly, some[186,214,239,250] found a significant association between the duration of, or the need for, assisted ventilation while others did not[247,249].

Perhaps the only definitive statement that can be made about the new results is that, when combined, they point to an association between oxygen and ROP that is no longer as clear as it was once thought to be. Since the sample sizes in the the more recent studies were much smaller that those used of the first and second collaborative studies, the fact that some failed to associate onset with the duration of oxygen exposure in no way eliminates duration as a variable. Likewise, the fact that some studies implicated assisted ventilation does not necessarily mean that they implicated oxygen. It could

be that infants who require assisted ventilation - presumably because they are smaller and/or sicker than their non-ventilated counterparts - are more prone to the development of the disease.

III.7.5C OTHER FACTORS

The observation that ROP was continuing to occur, sometimes in the absence of supplemental oxygen exposure, in the later years, almost always in spite of restricted exposure and the use of arterial and/or capillary monitoring, led a number of investigators to reconsider the role of non-oxygen related factors as possible etiological agents. This is interesting when one takes into account the fact that, only a few years ago, such suggestions would have been untenable. The renewed interest in etiological factors is interesting from another perspective. Even a cursory comparison of the variables considered in the 1970's and early 1980's (Appendix II) with those considered in the 1940's and early 1950's (Appendix I) reveals the extent to which the search for factors has come full circle[254]. Variables once eliminated as possible causes are being reexamined. The most noteworthy of these, in the sense that they close the circle, are 'premature exposure to light'[285] and 'persistence of the hyaloid artery'[333], the first two factors postulated by Terry[2,141] to explain the original epidemic.

Although extensive, the list of factors in Appendix II is by no means exhaustive. As pointed out by Teberg et. al.[286], there are numerous factors that have never been evaluated in spite of their known association with the group at highest risk (i.e., low birthweight infants). Most of the variables that are included in the Appendix II were examined from the perspective of their being 'direct' etiological agents. While this is in keeping with the theory that suggests that any factor contributing to retinal vaso-constriction is a potential

cause for ROP[287], there are suggestions that the relationship may not be so straightforward. It has been suggested that non oxygen-related factors may modify the association between oxygen and immature retinal vessels[185,186,204,221,285]. Others have suggested that, in addition to the factors associated with onset, there are non oxygen-related factors that are specifically associated with the severity of the disease[242].

In Appendix II, there are no non oxygen-related variables, with the exception of low birth weight, that stand out as major etiological factors. This observation, coupled with those made in the studies that failed to associate PO_2 with the onset of the disease, have led to suggestions that:

1. the disease is multifactorial[197,239],

2. the more recent cases are developing ROP by pathogenic processes different than those involved in the first epidemic[197], and/or

3. the etiology of ROP is, in fact, unknown[288].

III.7.6 SEARCH FOR TREATMENT AND PREVENTION MODALITIES

III.7.6A TREATMENT

Terry's 1942 attempt to minimize the consequences of ROP with roentgen irradiation[2] marked the beginning a long and frustrating search for an effective treatment. During the original epidemic, numerous attempts were made: surgery[36], diathermy[2], ACTH or cortisone[14,42,46,75,98,125,136,139,140], high concentrations of ambient oxygen[31,55,56], or mydriatics and miotics[6-8,22,115]. None of the attempts stopped the progression of the disease or minimized its consequences. With the imposition of the 40% policy, the perceived need for an effective treatment disappeared. When interest in ROP revived, interest in finding an effective intervention followed suit. Unfortunately, the new attempts - cryotherapy[221,261,262,264,312-

[316], photocoagulation[317], and scleral buckling[262,264,269,318] - have been equally unsuccessful.

III.7.6B PREVENTION/PROPHYLAXIS

In more recent years, the attempts to find an agent prophylactic for ROP have focused on dl-a-tocopherol or vitamin E, a factor considered and rejected during the original epidemic[17,25,27,51]. The rationale for assuming that vitamin E might be efficacious in reducing risk centres on its role as an antioxidant or scavenger of the free oxygen radicals that damage cell membranes[319-323].

The revived interest in vitamin E has sparked a new round of clinical trials. In one trial, the vitamin reduced both incidence and severity[291,293]. In others, it either reduced severity but not incidence[242,244,294] or it was totally ineffective[248,334]. In yet another trial, there was no difference in incidence or severity when different supplementation schedules were compared[313]. When kittens were exposed to oxygen and vitamin E, the vitamin reduced but didn't eliminate oxygen-induced retinopathy[295,324]. In other experiments, a hyperoxia-induced fall in the levels of superoxide dismutase, which some people suggest is associated with ROP, was partially prevented when kittens were pretreated with large doses of vitamin E[305].

Many authors have accepted the idea of vitamin E as an efficacious prophylactic, some even going so far as to suggest the possible mechanisms whereby it exerts it protective effect[254,294,325]. However, others argue that the evidence is far from conclusive. For example, Phelps and Rosenbaum[324] point out, with human ROP, it has not been possible to correlate the severity of the acute changes with damage in the cicatricial phase. Therefore, the experimental data, which suggests that vitamin E might be protective in the

acute phase, can't be extrapolated to the human situation. The human trials are no less problematic because the results are extremely difficult to compare. None of the studies were standardized in terms of patient selection, dose schedules, vitamin preparations or routes of administration. As a result, there is a wide spectrum in the serum levels found in the various case/control groups. In addition, there have been specific criticisms leveled against many of the studies. For example, in one trial done by Hittner, the overall incidence of ROP was 65%[242]. Comparable rates have been described in infants weighing <1000 grams but only 39% of the infants included in the Hittner trial fell into this category. This led to the suggestion that the trial was done using an unusual population[326]. Other criticisms relating to the same trial focused on: (i) the lack of information on inter-observer reliability, (ii) the fact that infants who might have undergone spontaneous regression were withdrawn before regression could take place, and (iii) the fact that Hittner recommended the prophylactic use of vitamin E on the basis of 5 infants who developed Grade III cROP[326]. It was also noted that the significance of the difference between the case and control groups hinged on the inclusion of infants who died after 4 weeks of age. When these deaths were eliminated, the protective effect of the vitamin disappeared[327].

The most serious criticism levelled against the new trials relates to the fact that they were done with extremely small numbers[328]. Numerous studies[329,330] have raised the possibility of deleterious side-effects in infants treated with high doses of supplemental vitamin E. Although the reports of many of the trials claim there were no side-effects or increases in mortality, none were large enough to ensure that the treatment was, in fact, safe. This is of some consequence since, in order to be effective as a prophylactic, vitamin E would have to be administered to all low birth weight infants. In the

United States, this would mean treating approximately 22,000 infants per year. According to one estimate, if untreated, approximately 2,000 of these infants would develop cROP and approximately 500 would progress to blindness[326]. Thus, 20,000 infants not destined to have ROP would have been treated unnecessarily. If the treatment increases mortality by as little as 10%*, the prevention of 2,000 cases would be paid for by 2,000 deaths[328]. Concern that this might happen, coupled with the conflicting results of the clinical trials, has led the American Academy of Pediatrics to reject the widespread use of vitamin E as an agent prophylactic for ROP[331].

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* in most of the trials that made reference to mortality, the sample sizes were such that only increases in mortality in the neighborhood of 25-30% could have been detected with 90% confidence[328]

CHAPTER IV
ROP IN BRITISH COLUMBIA, 1952-1983: RATIONALE AND METHODS

IV.1 RATIONALE

In 1983, data from the B.C. Health Surveillance Registry (the Registry) was reviewed. The data, which related to children with selected conditions who were liveborn in the Province of British Columbia (B.C.) between 1952 and 1981, were stratified to 3 birth weight categories: <1501, 1501-2500, and >2500 grams. The review specific for ROP (ICD9 362.2) showed that, in the mid 1950's, the incidence of the disease dropped dramatically: in infants weighing <1501 grams, from 292.5 per 10,000 livebirths in the period 1952-1954 to 35.7 per 10,000 in the period 1955-1957. A similar, but less dramatic decrease was also observed in infants weighing 1501 to 2500 grams (from 33.3 to 0 per 10,000). In infants weighing >2500 grams, the incidence in both time periods was negligible.

Since ROP is rare in heavier infants and since the observed decrease in incidence occurred concomitant with the period usually associated with the end of the original epidemic, these results were not unexpected. However, the data also indicated that, in more recent years, the rates in low weight infants were showing the substantial increases suspected but not confirmed in other jurisdictions[172,237,238]. These increases contrasted with what appeared to be stable rates for 'congenital anomalies of the eye' (ICD 743.0-743.9) over the 30 year study period. This latter observation was important because it minimized the potential for there being major ascertainment biases underlying the changing rates of ROP.

IV. 2 METHODS

IV.2.1 OBJECTIVES

Since the preliminary study was done without reference to the visual status of the infants who were affected and since the diagnoses of ROP were not substantiated, a more detailed investigation was undertaken. The objectives of the new study were:

1. to determine if the observed increases in the incidence of ROP were 'real' and if so, to identify the infants at increased risk, and

2. to identify the cofactors that differentiate infants who are blinded by the disease from those who are not.

IV.2.2 DATA SOURCES

Data for the study were collected from 3 sources. Cases were identified from an updated version of the Registry master file. Additional information was then collected from (i) the Registry's machine-readable and hard-copy records, (ii) the Ministry of Health's Physician's Notices of Livebirth records, and (iii) the patient records from the Vancouver General Hospital.

IV.2.2A BRITISH COLUMBIA HEALTH SURVEILLANCE REGISTRY

The B.C. Health Surveillance Registry is a population-based data collection system designed to ascertain handicapped children and adults who are born in (i.e., incident cases), or are resident in (prevalent cases), the Province of British Columbia[335-337]. Since its inception in 1952, the system has been operated by the Division of Vital Statistics, B.C. Ministry of Health. To be included, individuals have to have a physical, mental or emotional problem that is likely to be permanently disabling, to interfere with his or her ability to obtain an education, or to prevent full and open employment, or

they have to have a familial condition or congenital malformation[338]. Organizations registering cases that meet these criteria do so voluntarily. Since this raises the specter of under-ascertainment, the system registers cases from numerous sources*.

Individuals can become known to the Registry at any age. Original information is continually updated as new information is received. For example, it was estimated that in 1982, the system processed 7,000 to 10,000 new registrations and updated information on roughly the same number of individuals[336]. Once received, the information is transcribed, first to a paper record and then, if compatible with the format, to a machine-readable record. If it does not meet Registry standards, the information is flagged and held until it can be assessed either through normal channels or through queries sent to the registering agencies.

Originally, all diagnostic information was recorded on the paper record but only 4 diagnoses were coded and transcribed to the machine-readable record. In 1983, the operating procedures were revised so that 20 different diagnoses could be included in the computerized database. These additional diagnoses were added prospectively for new cases and retrospectively for historical cases. Since there were paper records for more than 150,000 incident or prevalent cases, the retrospective addition of diagnostic information was done when the historical paper records were reviewed, either to update the information that was recorded or to include the case in a study or administrative review.

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* including provincial and municipal health units, hospital admission-separation notices, live and stillbirth registrations, childhood death registrations, the Canadian National Institute for the Blind, the Jericho Hill School for the Blind and various other diagnostic, treatment and special interest organizations

Diagnoses are coded according to the most recent edition of the International Classification of Disease (ICD)[339]. When new editions of this manual are issued (the latest being ICD, Edition 9), the entire database is recoded[340] so that diagnostic information recorded for one birth cohort is directly comparable to that recorded for another. Two additional coding systems, one for genetic anomalies[341], the other for the etiology of registered conditions, are also included.

IV.2.2B PHYSICIAN'S NOTICES OF BIRTH

Physician's Notices of Birth (PNOBs), documents which physicians must complete within 48 hours of attending at a birth, have been in use in B.C. since 1951. The forms, which relate to more than 99% of the infants liveborn in the province, have been redesigned on numerous occasions. Although the specific information requested differs from one version of the form to the next, all have requested details pertaining to maternal factors, complications of pregnancy, labour and delivery, the condition of the infant at birth, and the presence or absence of birth injuries and/or congenital malformations.

IV.2.2C VANCOUVER GENERAL HOSPITAL

The Vancouver General Hospital (VGH) is the largest tertiary, acute care facility in B.C.. Throughout the study period, the VGH was the major provincial resource providing diagnostic services and the only resource providing tertiary care services designed specifically for newborns, infants and older children. In 1984, paediatric services were transferred to a new facility, the B.C. Children's Hospital. Since that time, the records of patients admitted

to the VGH as children have remained the responsibility of the VGH*.

IV.2.3 DESIGN AND METHODOLOGY

IV.2.3A INCIDENCE STUDY

The machine-readable Registry master file current to May 1985 was searched and a subfile of records pertaining to cases who were born in the province between 01 Jan. 1952 and 31 Dec. 1983 and who were registered as having ROP (ICD9 - 362.2) was created. The paper records for these cases were located and reviewed to recover pertinent information that is not routinely transcribe to machine-readable form**. The machine-readable records were also computer-linked to their corresponding PNOB records so that birth weight information, which is not recorded on either Registry record, could be recovered.

Listings detailing the identifying information for cases with ROP were then presented to the Medical Records Department of the VGH. The patient index for admissions from 1952 onwards was manually searched to identify cases born in the VGH or admitted at any time after birth. When these cases were identified, their medical records were reviewed*** for information that would substantiate the diagnoses of ROP and indicate the degree of visual loss.

The criteria used to substantiate the diagnoses were as follows: (i) there were clinical and/or pathological descriptions that were compatible with the

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* if needed, the VGH patient records can be temporarily transferred to the Children's Hospital

** for example, details specifying the level of disability resulting from a given diagnosis, information identifying the individuals or organizations responsible for making the diagnoses, etc.

*** in some cases, the medical records had been transferred to and hence were reviewed at, the B.C. Children's Hospital

diagnosis of ROP, or (ii) there was evidence that the diagnosis was made by an ophthalmologist, or (iii) the diagnosis was forwarded to the Registry from the Canadian National Institute for the Blind or the Jericho Hill School for the Blind.

Cases accepted into the study were classified as 'ROP blind' if the details specifying visual acuity were compatible with the legal definition of blindness*, the Registry or the VGH had information specifically stating that the case was blind, or the case was made known to the Registry by the Canadian National Institute for the Blind or the Jericho Hill School for the Blind. Cases not fitting one or more of these criteria were categorized as 'ROP not blind'.

The analyses pertaining to cases who were blind or not blind were done with two variables: birth year in single year intervals and birth weight in grams. Data for the period 1952-1954 were excluded so that changes in incidence after the end of the original epidemic could be determined. For infants born in the period 1955-1983, birth weight was categorized as: < 500 grams, 500-749, 750-999, 1000-1249, 1250-1499, ... > 2500. These categories were chosen a priori because they conform with recommendations made by the World Health Organization and with evidence that suggests that rates may be under-estimated if weight-specific categories are defined as 501-750 grams, 751-1000, etc.[342].

The machine-readable PNOB files were used to generate a birth weight-specific census of the livebirths who were born in B.C. in the period 1952-1983. When it was completed, the census was used to determine the annual weight-specific incidence of ROP blind and not blind throughout the study

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* visual acuity of 20/200 or worse in the better eye with the best correction with spectacles or visual fields less than 20º with fixation

period. In the first set of analyses, incidence rates, specific for four weight categories (<1000 grams, 1000-1249, 1250-1499, and 1500 grams or more), were calculated as follows:

$$\text{rate ROP: blind (not blind)} = \frac{[(\text{no. cases/birth weight category/birth year}) \times 10^4]}{[\text{no. livebirths/birth weight category/birth year}]}$$

Simple linear regression lines for each visual (blind and not blind) and birth weight category were then fitted to the rates for the 29 year period 1955-1983. In infants weighing the less than 1000 grams, the relationship between incidence and birth year was not linear. To compensate, this category was subjected to a second analysis which was done by subdividing the 29 year period 1955-1983 into two shorter periods. These sub-periods were defined as: (i) the period from 1955 to the last year when the incidence was zero and (ii) the period from the year immediately following the end of the first period (i.e., the first year when the incidence was greater than zero) to the end of 1983. For the blind category, the sub-periods defined were 1955-1964 and 1965-1983. For the not blind category, they were defined as 1955-1971 and 1972-1983. Within each visual category, the sub-periods were then fitted with separate linear regression lines.

To confirm the results of the linear regressions and to refine the data further, the birth year and weight-specific rates were then amalgamated into two birth intervals (1955-1964 and 1965-1983) and single crude rates for each of 5 weight categories (500-749 grams, 750-999, 1000-1249, 1250-1499, and >1501) were calculated. The rates for the earlier period, 1955-1964, were used to define the baseline incidence of ROP in the years immediately following the end of the original epidemic. When there were no cases in the baseline period, the rates were estimated using the 'rule of 3's'[344]. This is a simple

rule that allows one to estimate, with 95% confidence, the maximum rate that is compatible with an observation of zero cases in a population of a given size.

When they were calculated, the observed and estimated baseline rates were used to determine the number of cases that would be expected in each visual and weight category if the rates for the baseline period continued to apply in the later period (1965-1983). The expected and observed numbers of cases in the later period were then used to calculate visual and weight-specific standardized incidence ratios (SIR's) (number observed/number expected) and 95% confidence limits.

IV.2.3B COFACTOR STUDY

Since ROP is a rare disease, the search for cofactors that differentiate infants who are blinded by the disease from those who are not was done using a case-control study design. Infants designated 'blind' and 'not blind' in the incidence study were included as cases (blind) and controls (not blind) in the cofactor study if they were born in or were admitted to the VGH within 28 days of birth*. When infants fitting these criteria were identified, their medical records were reviewed and details pertaining to the diagnostic and therapeutic information listed in Table IV.1 were recovered.

In the initial analyses, variables were dichotomized and analyzed using the univariate techniques included in the statistical package SAS (Statistical Analysis System)[345]. For all but two of the continuous variables, the dicotomizations were done using the median value to define the exposure in terms of 'high' (greater than or equal to the median) or 'low' (less than the

* within 28 days defined as any time from birth (day 0) to the end of the 27th day of life

median). For the two exceptions, 'age at first exposure to an oxygen-supplemented isolette' and 'age at first exposure to a respirator with oxygen concentrations greater than room air', the dicotomizations were defined as 'exposed on day born' or 'exposed after day born'. The diagnostic variables were dichotomized 'yes' if the diagnosis appeared on a Registry or VGH record and 'no' if it did not.

In the first set of analyses, which related to the period 1955-1983, chi-square values, odds ratios and 95% confidence limits were calculated for all of the dichotomized variables. The data were then stratified into 3 birth periods (1955-1964, 1965-1974 and 1975-1983) and odds ratios, 95% confidence limits, measures of general association and the Breslow-Day chi-square for homogeneity were calculated using the Cochran-Mantel-Haenszel procedures in SAS.

Since dichotomization can reduce sensitivity, a second set of analyses were done. Variables that could be analyzed in continuous form were tested using t-test and logistic regression procedures. These procedures were applied to two data sets, the first relating to the ROP-affected infants born between 1955 and 1983; the second, to the infants born between 1970 and 1983. Because of the limited number of infants who were ROP blind and not blind in each of the data sets, the logistic regressions were done using separate models for each variable.

TABLE IV.1
VARIABLES INCLUDED IN ROP COFACTOR STUDY

VARIABLE	SOURCE	RECORDING
patent ductus arteriosus	VGH & HSR	ICD 747.0
agenesis of lung	VGH & HSR	ICD 748.5
respiratory distress*	VGH & HSR	ICD 769
respiratory disease	VGH & HSR	ICD 770.7
intraventricular hemorrhage	VGH & HSR	ICD 772.1
necrotizing enterocolitis	VGH & HSR	ICD 777.5
gestational age	PNOB	weeks
birth weight	PNOB	grams
birth year	PNOB	single years
total days in hospital	VGH	days
neonatal weight loss	VGH	grams
parenteral nutrition	VGH	days
exchange/replacement transfusions	VGH	number
pH < 7.2**	VGH	hours
pH > 7.5**	VGH	hours
pCO_2 < 35 mm Hg**	VGH	hours
pCO_2 > 45 mm Hg**	VGH	hours
pO_2 < 40 mm Hg**	VGH	hours
pO_2 > 100 mm Hg**	VGH	hours
supplemented isolette	VGH	total days
supplemented isolette**	VGH	half days
respirator at 0_2 > room air	VGH	total days
respirator at 0_2 > room air**	VGH	half days
age at 1st exposure to supplemented isolette	VGH	days
age at 1st exposure to respirator (0_2 > RA)	VGH	days
weighted oxygen score***	VGH	score

* including hyaline membrane
** in 1st 28 days of life
*** O_2 score = [(0.2)(# 1/2 days FiO2 21-30%) + (0.3)(# 1/2 days FiO2 31-40%) + (0.4)(# 1/2 days FiO2 41-50%) ... + (0.9)(# 1/2 days FiO2 91-100%)]

CHAPTER V
ROP IN BRITISH COLUMBIA, 1952-1983: RESULTS

V.1 INCIDENCE STUDY

As of May 1985, there were 180,000 individuals known to the Registry. Of these, 168 fit the criteria for inclusion in the incidence study, 167 (99.4%) had records that linked to a PNOB and 83 (49.4%), records that linked to a VGH patient record.

Annual crude incidence rates* were determined using the 167 cases whose Registry records linked to a PNOB. Six of the 167 were subsequently excluded from the birth weight-specific analyses either because they weren't weighed at the time of birth or because their weight wasn't recorded. Of those who were included in the weight-specific analyses, 91 (56.5%) were designated as 'ROP blind' and 70 (43.5%), as 'ROP not blind'. The annual numbers and crude rates for cases designated blind and not blind for each of 4 birth weight categories (0-999, 1000-1249, 1250-1499, and 1500+ grams) are shown in Table V.1 and Figure V.1 and Table V.2 and Figure V.2 respectively.

Since the incidence study was designed to look at changes in birth weight-specific rates after the end of the original epidemic, cases who were born during the epidemic, i.e., in the period 1952-1954, were excluded. This left a final study population of 53 cases who were blind and 68 who were not blind. When these data were compared to those in an earlier study by McCormick[221], it was obvious that there was substantial under-ascertainment of cases in the not blind category. In his study, McCormick found that only 5% of infants developing the early signs of ROP subsequently progressed to blindness[221]. Since this 5% was defined for children who were born in B.C.,

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* crude incidence rate = $\frac{\text{no. affected/birth weight category/year}}{\text{no. livebirths/birth weight category/year}}$

TABLE V.1
ROP: BLIND - RATE PER 10,000 LIVEBIRTHS BY BIRTH WEIGHT CATEGORY

BIRTH YEAR	BIRTH WEIGHT CATEGORY (IN GRAMS) 0-999 GMS. NO.	RATE	1000-1249 GMS. NO.	RATE	1250-1499 GMS. NO.	RATE	1500+ GMS. NO.	RATE
1952	1	109.89	2	322.58	5	609.76	5	1.74
1953	2	215.05			3	394.74	8	2.61
1954	2	217.39	3	400.00	1	111.11	6	1.87
1955			1	151.52			1	0.30
1956					1	94.34		
1957			1	109.89				
1958					1	85.47		
1959			1	126.58				
1960					1	102.04		
1961			1	101.01				
1962								
1963			1	109.89	1	89.29		
1964					1	91.74	1	0.28
1965	1	73.53	1	133.33				
1966			1	102.04				
1967					1	71.94		
1968	2	136.99	1	104.17				
1969								
1970	1	78.74			1	83.33		
1971	1	87.72	1	103.09	1	76.34		
1972								
1973								
1974							2	0.57
1975	1	78.13			1	105.26		
1976	3	240.00	1	125.00				
1977	3	201.34						
1978	2	127.39					1	0.27
1979	1	72.99			1	104.17		
1980			1	121.95				
1981	3	180.72						
1982	4	220.99	1	109.89				
1983	2	133.33	1	116.28			1	0.23
TOTAL	29	70.27	18	66.13	19	56.72	25	0.22

Figure V.1 (a)
Incidence of ROP: Blind by Birth Year for Birth Weight Category 0-999 Grams

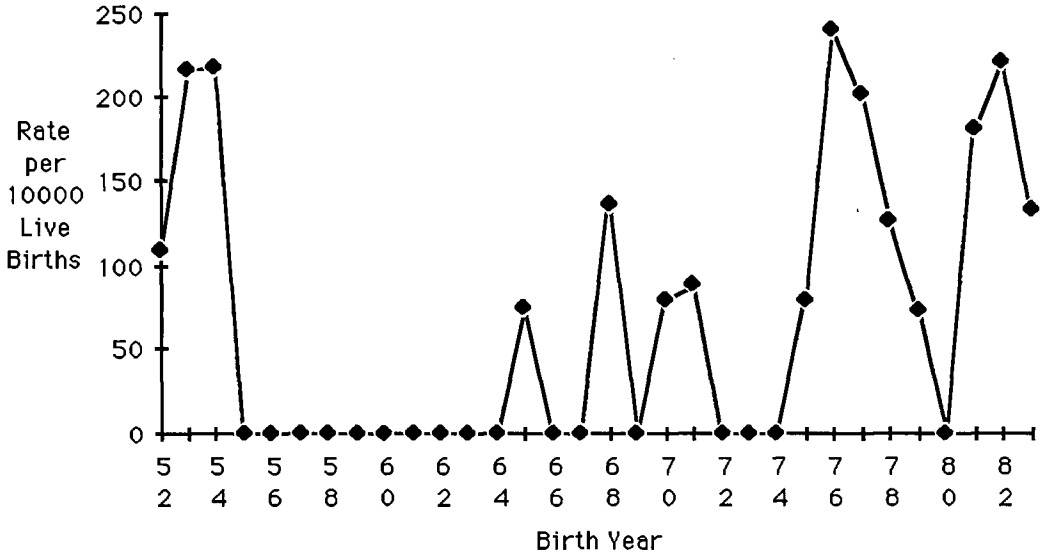


Figure V.1 (b)
Incidence of ROP: Blind by Birth Year for Birth Weight Categories
1000-1249, 1250-1499 and 1500 Plus Grams

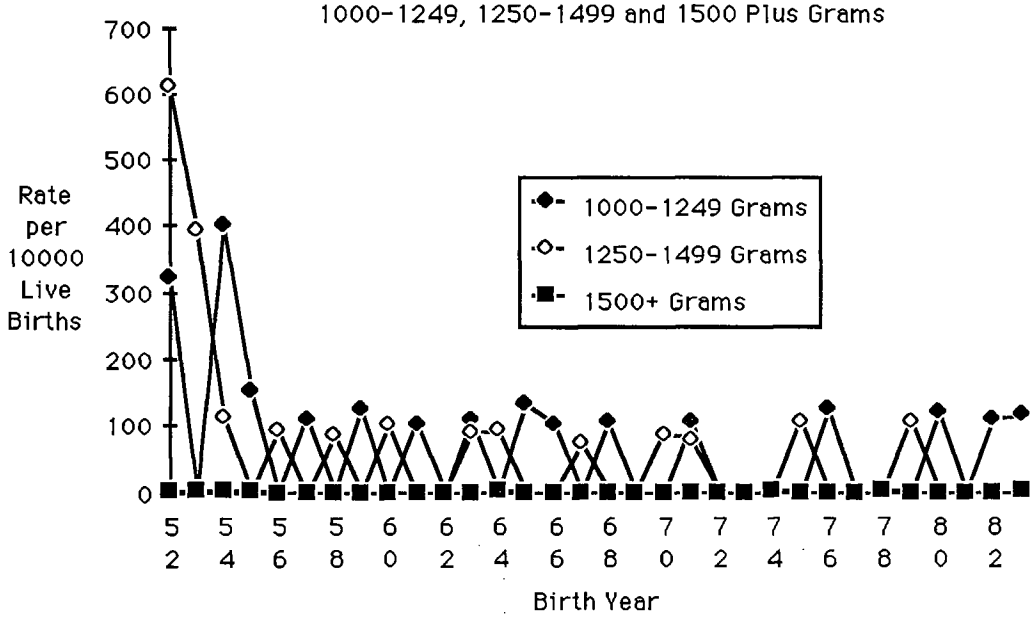


TABLE V.2
ROP: NOT BLIND - RATE PER 10,000 LIVEBIRTHS BY BIRTH WEIGHT CATEGORY

BIRTH WEIGHT CATEGORY (IN GRAMS)

BIRTH YEAR	0-999 GMS. NO.	RATE	1000-1249 GMS. NO.	RATE	1250-1499 GMS. NO.	RATE	1500+ GMS. NO.	RATE
1952	1	109.89	0		0		0	
1953	0		0		1	131.58	0	
1954	0		0		0		0	
1955	0		0		0		0	
1956	0		0		0		0	
1957	0		0		0		0	
1958	0		0		0		0	
1959	0		0		1	85.47	0	
1960	0		0		0		0	
1961	0		0		0		0	
1962	0		0		1	81.30	0	
1963	0		0		0		0	
1964	0		0		0		0	
1965	0		0		0		0	
1966	0		0		0		0	
1967	0		0		0		0	
1968	0		0		0		0	
1969	0		0		1	98.04	0	
1970	0		0		0		0	
1971	0		1	103.09	0		0	
1972	1	90.91	0		0		0	
1973	0		0		0		0	
1974	1	71.43	1	111.11	0		1	0.28
1975	1	78.13	1	138.89	0		0	
1976	1	80.00	2	250.00	0		0	
1977	4	268.46	0		0		0	
1978	5	318.47	3	389.61	1	105.26	1	0.27
1979	2	145.99	1	119.05	2	208.33	1	0.26
1980	2	158.73	2	243.90	0		2	0.50
1981	5	301.20	1	108.70	0		1	0.24
1982	7	386.74	1	109.89	1	91.74	1	0.24
1983	11	733.33	1	116.28	0	00.00	0	0.00
Total	41	99.35	14	51.43	8	23.88	7	0.06

Figure V.2 (a)
Incidence of ROP: Not Blind by Birth Year for Birth Weight Category 0-999 Grams

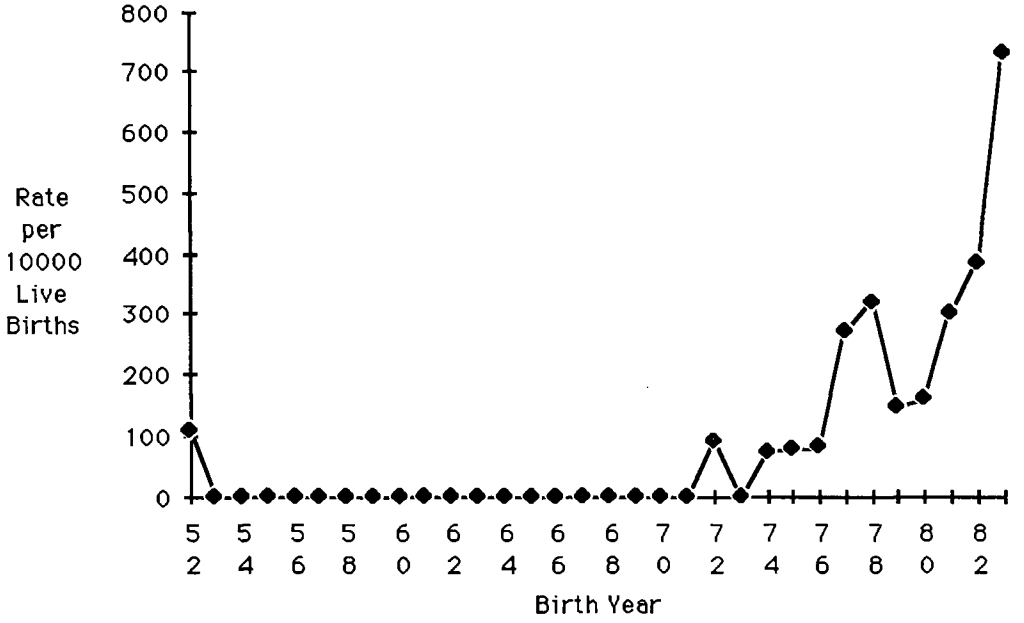
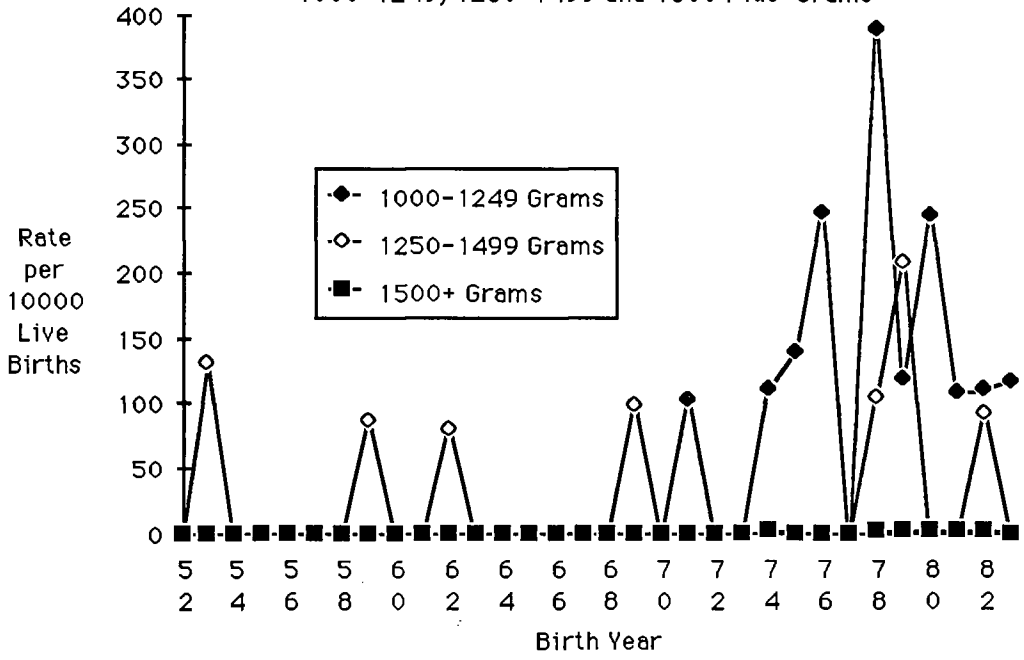


Figure V.2 (b)
Incidence of ROP: Not Blind by Birth Year for Birth Weight Category
1000-1249, 1250-1499 and 1500 Plus Grams



there should have been more than a thousand infants in the not blind category to correspond to the 53 infants who were blinded by the disease in the period 1955-1983. Since the Registry knew of only 68 infants who were 'ROP not blind' in this period, it was decided that this category should be excluded.

The results of the birth weight-specific linear regression and SIR analyses for infants who were blinded by ROP in the 1955-1983 B.C. livebirth cohorts are outlined in Tables V.3 and V.4 respectively. As can be seen, both analyses showed a significant increase in incidence over time. With the linear regressions, the increase in the non weight-specific incidence over the period 1955-1983 was significant at $P > 0.0001$. A similar but less dramatic result was obtained from the analysis done using standardized incidence ratios (SIR's). In these analyses, the non weight-specific SIR was 1.63 and the lower 2-sided 95% confidence limit equaled but did not include the number '1'.

When the weight-specific results were examined, the linear regression and SIR analyses indicated that the increase in the incidence of ROP-induced blindness was limited to a single birth weight category. For the regressions, this category was defined as <1000 grams ($P < 0.001$). In the SIR analyses, the <1000 gram category was subdivided into 2 smaller categories: 500-749 grams and 750-999 grams. Again, there was only one category that showed a significant increase. Infants in the 750-999 gram category in the period 1965-1983 were 3.07 times more likely to be blinded by ROP than their equal weight counterparts in the period 1955-1964. Since the upper and lower 95% confidence limits were 11.06 and 1.26 respectively, this represented a significant increase in incidence in the later period. In contrast, infants in the

TABLE V.3
RESULTS OF BIRTH WEIGHT-SPECIFIC LINEAR REGRESSION ANALYSES FOR INFANTS ROP: BLIND IN PERIOD 1955-1983

BIRTH WEIGHT(GMS)	B*	SE B**	T	SIG T
0-999	6.092	1.323	4.604	0.0001
1000-1249	-0.807	1.341	-0.601	0.5527
1250-1499	-1.140	0.975	-1.169	0.2524
1500 +	0.001	0.003	0.463	0.6468
TOTAL ROP: BLIND	0.018	0.006	2.842	0.0084

* estimated beta weight = slope of regression line
** standard error of beta

TABLE V.4
B.C. BIRTH WEIGHT-STANDARDIZED INCIDENCE RATIOS - ROP: BLIND

BIRTH WT. (GMS) SIR	1955-1964 BASELINE CONF. LIMITS RATE[1]	1965-1983 OBSERVED NUMBER	1965-1983 EXPECTED NUMBER[2]	
500- 749	71.43[4]	6	6.91	0.87
750- 999	43.60[4]	18	5.87	3.07
1000-1249	58.00	8	9.67	0.83
1250-1499	46.17	5	9.32	0.54
1500+	0.05	4	3.46	1.16
TOTAL	0.37	42	25.82	1.63

1 per 10,000 livebirths
2 calculated by applying rate (1955-64) to birth weight-specific census of livebirths 1965-83
3 upper and lower 2-sided 95% confidence limits
4 calculated using "rule of 3's"[31]

smallest weight category, 500-749 grams, did not appear to be at increased risk in the period 1965-1983 as compared to earlier period, 1955-1964.

V.2 COFACTOR STUDY

As stated, the identifying information* submitted to the Medical Records Department of the VGH was sufficient to identify 83 (49.4%) cases who were admitted to the hospital at some point in their lives. Of these, 55 (25 blind, 30 not blind) were admitted within 28 days of birth and were eligible for inclusion in the cofactor study. Thirty six (36) of the 55 were born in the VGH, 14 were born elsewhere in the province but admitted on the day of birth, and 4 were born in B.C. and admitted the day after birth. One infant in the not blind category was not admitted until the age of 24 days. Table V.5 details the number of affected individuals who were admitted (i) at any time and (ii) within 28 days of birth for the birth years 1952 to 1983 inclusive.

The results of the univariate analyses done using dichotomized variables, and dichotomized variables stratified by birth interval, are summarized in Tables I and II of Appendix III. When the data were not stratified (Appendix III: Table I), there were 2 variables that showed a difference significant at the P = 0.05 level. Both variables, respiratory distress syndrome and neonatal weight loss, appeared to exert a protective effect. Infants who had ROP and respiratory distress (and/or hyaline membrane disease) were only 0.13 times as likely to be blind as infants with ROP but not respiratory distress. Similarly, ROP-affected infants who lost 141 grams or less in the first 28 days of life were only 0.28 times as likely to be blind as those who lost more than 141 grams. When the dichotomized variables were

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* child's surname, given names, and birth date; mother's surname, given names and maiden name

TABLE V.5
NUMBER BLIND AND NOT BLIND ADMITTED TO VGH BY BIRTH YEAR

BIRTH YEAR	ADMITTED TO VGH AT ANY TIME		ADMITTED TO VGH WITHIN 28 DAYS[1]	
	BLIND	NOT BLIND	BLIND	NOT BLIND
1952	6	2	3	1
1953	6		3	
1954	4	1		1
1955	2		1	
1956				
1957	2		1	
1958	1			
1959				
1960	1			
1961	1			
1962		1		
1963				
1964	1			
1965	1			
1966	1		1	
1967	1		1	
1968	1		1	
1969		2		2
1970	1			
1971	1	1		
1972				
1973	1			
1974	2	3	1	3
1975	1	1		1
1976	3	2	3	1
1977	3	4	3	4
1978	3	4	3	4
1979	1	4	1	3
1980		4		4
1981	1	4	1	4
1982	2	2	2	2
1983	1			
TOTAL	48	35	25	30

1 within 28 days of birth

stratified to 3 birth intervals, 1955-1964, 1965-1974 and 1975-1983, the protective effect of respiratory distress disappeared (Appendix III: Table II).

The results showed other interesting but statistically insignificant differences. For example, in the univariate analyses not stratified for birth period:

(i) 67% of the infants who had routine blood gas measurements and were ROP blind and only 46% of comparable infants who were not blind had blood pH measurements greater than 7.50,

(ii) 62% of the infants who were blind spent more than 351 hours at $pCO_2 > 45$ mm Hg compared to only 42% of the infants who were not blind, and

(iii) 39% of the ROP blind and 58% of the ROP not blind had weighted oxygen scores greater than 15.7.

It is likely that this last observation was confounded by time. When the data were stratified, 54% of the cases who were blind and 58% who were not blind had weighted oxygen scores of more than 15.7. Two additional observations worthy of mention were made when the stratified data pertaining to the other variables were examined. In the most recent birth period (1975-1983), 31% of the infants who were blind and 48% who were not blind weighed less than 992 grams at birth. In addition, 69% of the blind and only 50% of the not blind were on respirators at oxygen concentrations greater than room air for more than 35 half days in the first 28 days of life.

The t-test results for the continuous variables relating to affected infants born in the periods 1955-1983 and 1970-1983 are summarized in Appendix IV. When the blind and not blind groups were compared using values based on pooled variance estimates, none of the variables differed

significantly at the 0.05 level. When the homogeneity of the variances were tested for the two time periods (1955-1983, 1970-1983), two variables, hours pH above 7.50 mm Hg and number of half days in a supplemented isolette in the first 28 days of life, were significantly different indicating that, for each time period, the variances for the blind and not blind groups were unequal. When these two variables were reanalyzed using t-tests based on separate variance estimates, the results were again insignificant.

The logistic regression analyses also produced negative results (Appendix V: Tables I and II). Because of the small number of infants in each time period, no attempt was made to identify interactions between, or the possible confounding effects of, different variables. When the logistic regression models were used to determine if ROP-induced blindness could be predicted from the single effects of any of the variables that were included, none were significant at the 0.05 level.

CHAPTER VI
ROP IN BRITISH COLUMBIA, 1955-1983: CONCLUSIONS AND DISCUSSION

VI.1 DISCUSSION: INCIDENCE OF ROP IN BRITISH COLUMBIA

In recent years, concern that the increased use of supplemental oxygen could lead to a new epidemic of ROP has led to the largely unsubstantiated idea that there is a new epidemic. This makes the current study unique since it reveals, for the first time at a population-level, that the incidence of ROP-induced blindness has increased significantly since the end of the original epidemic. The study also demonstrates:

1. that the epidemic is limited to infants weighing less than 1000 grams at birth, and

2. that since the mid 1960's, there has been a definite shift in the weight groups at greatest risk for blindness as a result of the disease.

In the first epidemic, the infants at greatest risk for ROP were those weighing 1000 to 1500 grams at birth[21,22,35,37,38,43,57,76,122,123]. More recently, hospital-based, hence potentially biased data, have suggested that this is no longer true[228,239-241,243,244,246,247,249,251]. The current study has confirmed this suggestion at the population level. In the period 1952-1954, the last three years of the original epidemic in B.C., the crude incidence* of ROP progressing to blindness was 163.0 per 10,000 livebirths weighing less than 1000 grams at birth. In the highest risk group, 1000-1499 grams, the incidence was 362.3 per 10,000, and in the lowest risk group, 1500 grams or more, it was 2.2 per 10,000. In the period 1965-1983, the order of the birth weight categories ranked highest to lowest in terms of risk changed. Crude incidence was

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* incidence defined in terms of livebirths, not survivors

highest in infants weighing less than 1000 grams (90.6 per 10,000), lower in those weighing 1000-1499 grams (35.3 per 10,000), and negligible in infants weighing 1500 grams or more (0.06 per 10,000).

The current study shows, quite clearly, that infants weighing more than 1000 grams are still being blinded by ROP. However, in the weight categories defined for these infants, the rates of blindness are not significantly higher than those observed in the period immediately following the end of the original epidemic (1955-1964). This is not true for infants weighing less than 1000 grams. Regression lines fitted to crude annual birth weight-specific incidence rates over the period 1955-1983 show that an increase in the overall incidence of ROP-induced blindness results from an increase in this lower weight group.

Had the "rule of 3's"[344] not been used to estimate the maximum rates compatible with the observation of zero cases in the baseline period (1955-1964), both sub-categories defined for infants weighing less than 1000 grams (500-749 and 750-999 grams) would have shown an infinite increase in incidence when the data were expressed as standardized incidence ratios (SIR's). With the rule, only one sub-category, 750-999 grams, showed an increased risk for ROP-induced blindness. However, since the baseline rates for both sub-categories were estimated, it is not unreasonable to assume that the observed results are a conservative estimate of the changes that actually took place. If the true rate in the baseline period was lower than the estimated maximum rate*, there may have been a significant but undetected increase in the incidence of ROP-induced blindness in the 500-749 gram

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* i.e.. the upper 95% confidence limit compatible with the observation of zero cases in the 500-749 gram category in the baseline period

category. Similarly, the observation that infants in the 750-999 gram category were 3.07 times more likely to be ROP: blind in the period 1965-1983 compared to the earlier period, 1955-1964, is likely to be a minimal estimate of the increase that actually occurred.

VI.2 ALTERNATE EXPLANATIONS FOR INCREASED RATE

The results of the incidence study suggest that there is a new epidemic of ROP-induced blindness in B.C.. However, there are factors other than a true increase in rate that may explain the observed changes in incidence. For example:

1. The study may have included infants who should have been excluded because their ocular problems were due to conditions other than ROP.

None of the infants known to the Registry as ROP: blind were excluded from the incidence study because of misdiagnosis or misclassification. However, the review of the VGH patient records was not particularly helpful in substantiating the diagnoses. For many cases, particularly those not severely affected, there was a paucity of recorded clinical and pathological detail. Patient records, especially those relating to mildly affected cases whose first admission occurred several years after birth and was the result of conditions unrelated to ROP, often made no reference to the case ever having had the disease. This was less true for cases who were severely affected. For most of the infants in the ROP: blind category, there were clinical descriptions, either at the VGH or the Registry, to support the diagnoses of

ROP. Therefore, if there were cases who should have been excluded, it is likely they were preferentially included in the 'not blind' category.

2. There may have been changes in the Registry's ascertainment of cases who were ROP: blind over time.

Although it cannot be eliminated with certainty, it is unlikely that this possibility led to an apparent, but not true increase in the incidence of ROP-induced blindness. In 1964, the Registry did introduce 'admission-separation notices' from all publically funded hospitals in the province as an ascertainment source for anomalies in children under the age of 10 years. However, the major source for ascertaining blindness, the Canadian National Institute for the Blind, had been registering children since the system started in 1952. Therefore, if the introduction of hospital admission-separation notices had an effect, it is likely that effect would have:

(i) been most pronounced for infants who were ROP: not blind,

(ii) applied equally to all birth weight groups, and

(iii) been noticeable for anomalies of the eye other than ROP.

Two of these predictions were not born out (1) because the increase in the incidence of ROP-induced blindness was birth weight-specific, and (ii) because in the preliminary study*, the rates for 'congenital anomalies of the eye' in low birth weight infants were constant while the rates for ROP increased. The third prediction, that the effect would have been most pronounced in infants who had ROP but were not blind, was not relevant since cases who were ROP: not blind were excluded from the analyses.

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* see Chapter IV

3. It could be that the more recent cases have a disease that is similar to but not the same as the ROP that occurred during and immediately after the original epidemic.

Again, this possibility can't be eliminated with certainty. However, there is no conclusive evidence to support the idea that the more recent cases have anything other than classical ROP. After the mid 1950's, the idea that a new disease might be occurring was usually invoked to explain symptoms in infants who were not exposed to supplemental oxygen[164,190-192,197,199,202]. In the past decade, improvements in the clinical description and changes in the signs considered diagnostic for the disease have led to descriptions that differ slightly from those published earlier. However, in the absence of evidence to the contrary, it is reasonable to assume that these descriptive differences are more likely due (i) to changes in the terminology used to describe the disease, (ii) to the introduction of routine screening and indirect ophthalmoscopy, and (iii) to the increased incidence of ROP in infants weighing less than 1000 grams.

4. The results may have been confounded by changes in weight-specific survival over time.

Decreased mortality, or the converse, increased survival, cannot be readily eliminated as a possible explanation for the new epidemic. In the current study, incidence was defined in terms of crude rates that related incident cases who were ROP: blind to the total population of infants liveborn in B.C. throughout the study period. In actual fact, the liveborn population

provides only a rough estimate of the population that is actually at risk. Some livebirths will have survived long enough to be blinded by ROP while others did not.

It is known that, over the 29 year study period, there have been substantial reductions in neonatal mortality, particularly in very low birth weight infants[259,260]. Since the observed increase in incidence is limited to these infants, it is likely that at least some proportion of the increase can be attributed to concomitantly occurring changes in birth weight-specific mortality. If this is true, adjusting the population at risk so it includes only infants who survived the early neonatal period may eliminate some or all of the increases observed in this study.

VI.3 DISCUSSION: COFACTORS IN ROP-INDUCED BLINDNESS

In the majority of infants with ROP, the early proliferative changes arrest and the retinopathy heals. This raises what has always been, a most puzzling question: why do ostensibly similar proliferative changes regress to the norm in some cases but progress to severe cicatricial damage and blindness in others?

In 1956, the National Cooperative Study showed (i) that there is a direct correlation between the incidence of active and cROP and the duration of exposure to supplemental oxygen, and (ii) that the severity of cROP is not dependent on the duration of the exposure or the concentration of the oxygen administered[150]. In the intervening years, there has been no credible evidence to contradict these findings. This raises the possibility that ROP-induced blindness results from a two-step process. In the first step, exposure to factors causal for ROP (for example, oxygen) obliterate the developing capillaries in the retina and set the disease process in motion. In the second

step, other factors (i.e., cofactors) determine the progression of the disease to cicatricial damage, retinal detachment and severe or total visual impairment.

The idea of a two-step disease process gains credence from, or at least may partially explain, the results of the animal experiments done to date. In these experiments, non-human species, particularly kittens and mice, developed oxygen-induced lesions similar to those seen in infants with aROP[48,106,156,157]. However, with the possible exception of beagle puppies[255], none of the species progressed to a level of damage suggestive of cROP. This raises questions about the appropriateness of using these species to study the human form of the disease. However, if there are cofactors involved, the absence of blindness in animals with aROP can be readily explained. In all of the experiments to date, these animals were exposed to strictly controlled laboratory conditions. If these conditions eliminated or even minimized one or more of the cofactors, it would not be unreasonable to assume that the absence of cicatricial damage and blindness is a function of the environment and the lack of comorbid conditions in the newborn animals rather than a reflection of fundamental biological differences between animal retinopathy and human ROP.

Unfortunately, the study to identify the cofactors leading to blindness in infants with ROP was inconclusive. Two factors, neonatal weight loss and respiratory distress syndrome (RDS), appeared to be protective when the data were dichotomized and analyzed using univariate techniques. However, the protective effect of one of these variables, RDS, disappeared when the dichotomized data were stratified to 3 birth intervals. This suggests that, for this variable, the observed relationship was confounded by time and hence, by the epidemic itself.

The protective effect of neonatal weight loss did not disappear when the dichotomized data were stratified. However, it must be remembered that, in the univariate analyses, 25 variables were dichotomized and analyzed separately. Since significance was defined at the 0.05 level, at least one of these variables could have shown a statistically significant association due to chance alone. Whether this suffices to explain the observed protective effect of neonatal weight loss is open to conjecture. Certainly, the idea gains credence from the observations that: (i) the association was not observed when the data were analyzed using t-test and logistic regression procedures, and (ii) there are no data in the literature specifically associating weight loss with blindness. Unfortunately, the lack of substantiating evidence may itself be fortuitous since only a few studies have looked for factors associated with the severity rather than onset.

Before the correlation between weight loss and visual outcome can be considered anything other than hypothetical, the possibility of a chance association has to be eliminated and the biological plausibility of the protective effect has to be established. It is difficult to imagine a mechanism whereby weight loss itself could protect the retina from the blinding effects of ROP. Therefore, if the effect is real, it is likely indicative of other factors more directly related. For example, although indirect, there are data that could be used to support the idea of a correlation between the severity of ROP and the condition of infants in the early neonatal period. In the National Cooperative Study*, all but one of the infants in the 'routine' oxygen exposure group received supplemental oxygen for 15 days or more.

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* see Section II.2.4C

Coincidentally, in the 'curtailed group, the same number of infants were exposed to oxygen for a comparable length of time. Since the duration of exposure in the 'routine' group was determined by the protocol of the study, it was assumed that this group contained the same proportion of sick infants as the study population as a whole. Therefore, for analytical purposes, infants in this group were considered to be 'well'. In contrast, infants receiving supplemental oxygen for 15 days in the 'curtailed' group were assumed to be 'sick' since, in this group, oxygen was administered only when there were clinical indications suggesting it was necessary. When the 'sick' and 'well' infants were compared, the results showed that while the duration of exposure to supplemental oxygen was the same, the incidence of cROP was not. In the 'well' group, the rates of cROP were approximately double those in the 'sick' group. To substantiate the alleged difference in the health status between the 'sick' and the 'well' group, the study team cited data pertaining to the amount of weight gained in the first 40 days of life. In the group at lowest risk for cicatricial damage from ROP, i.e., the 'sick' group, the mean weight gained by infants who were the products of a single birth was 200 grams. In the products of a multiple birth, the comparable gain was 250 grams. In the 'well' group, the group with twice the incidence of cicatricial disease, the mean weight gain in single and multiple births was 490 and 500 grams respectively[150]. Since infants who gained the least weight in the first 40 days of life probably also lost the most, this observation at least does not contradict the idea that weight loss is directly or indirectly protective for the damaging effect of ROP.

It is not surprising that the cofactor study failed to detect differences in variables other than neonatal weight loss. For at least two variables, 'hours

pH above 7.50 mm Hg' and 'number half days in an oxygen- supplemented isolette', the use of t-tests to detect differences between infants in the ROP: blind and ROP: not blind category was inappropriate. When the tests were done using pooled variance estimates, the homogeneity of the variances between the two groups were significantly different. When the tests were repeated using separate variance estimates, the small number of cases in each birth interval precluded there being meaningful results.

Of even greater importance was the fact that, with the infants that were available, the power of the study to detect even substantial differences between infants who were 'ROP blind' and 'ROP not blind' was negligible. For example, 1099 infants who were 'ROP blind' and a comparable number who were 'ROP not blind' would have been needed to detect a 100 gram difference in mean birth weight with a power of 80%. Since the study was done with only 25 infants in the 'ROP blind' group, the power to detect this difference at the a = 0.05 level was only 7%. This means that mean weight would have had to differ by 663 grams in order for the difference to have been detected. Since this represents half the mean birth weight of the infants who were blinded by ROP, it is almost certain that, for this variable, the observed results were vulnerable to a Type II error. Similar calculations for the variable 'half days on a respirator at oxygen concentrations greater than room air', are no more reassuring. To detect a difference of 5 half days, the study would have needed 304 infants in each visual group. With the difference that was observed, 2.7 half days, eliminating the possibility of an undetected association with either the blind or the not blind group would have necessitated the inclusion of 1041 infants in each group. Since there was data for only 19 infants who were 'ROP blind', the power of the current study to

detect a significant difference in the number of half days on a respirator was at most, 6%.

VI.4 CONCLUSIONS: WHERE DO WE GO FROM HERE?

The implications of the population-based incidence and the case-control cofactor studies done in the Province of British Columbia are far from clear. The observed increase of ROP-induced blindness suggests the occurrence of a new epidemic. However, because of the possible confounding effect of increased survival, it can't be assumed the epidemic reflects the introduction or the increased use of factors causal for ROP or ROP-induced blindness. Similarly, because of the low power, hence the high possibility of Type II errors, it can't be assumed the variables in the cofactor study are etiologically unrelated to the induction of blindness in infants with ROP.

Since B.C. appears to be a unique jurisdiction in which to study the incidence of ROP-induced blindness, a second study designed to clarify the occurrence of a new epidemic has recently been undertaken. The Health Surveillance Registry database current to mid 1987 will be used to identify incident cases of ROP-induced blindness in the extended period 1952-1985. Machine-readable birth registration records for the extended study period will be used (i) to determine the birth weights and gestational ages for all cases, and (ii) to generate a birth year, birth weight and gestational age-specific census of all infants liveborn in the province in the extended study period. A third source, death registration records for the period 1952-1986, will be used to identify B.C. livebirths who died in the province in the first year of life.

When the records from these three sources have been linked (Registry to birth registration records, birth registrations to infant death records) and

the necessary tabulations have been generated, the data will be used (i) to substantiate the continued occurrence of the new epidemic and (ii) to test the following hypotheses:

a) the incidence of ROP-induced blindness, when defined in terms of survivor-specific (#ROP: blind /#surviving livebirths) rather than crude rates (#ROP: blind/#livebirths), has not changed significantly in any birth weight category since 1954,

b) since the mid 1970's, improvements in the annual survival rates amongst infants weighing 500-749 and 750-999 grams have been greater than the improvements in the other birth weight categories, and

c) during the period when oxygen was restricted to concentrations of less than 40% (1955 to the mid 1970's), the annual survival rates in infants weighing 500-749 and 750-999 grams decreased to a greater degree than the rates observed in the heavier weight categories, and the rates observed amongst comparable weight infants in the period when oxygen was not restricted (i.e., 1952-1954).

VI.5 POLICY IMPLICATIONS

Since the incidence study was done without specific reference to the oxygen exposure policies used in B.C. throughout the study period, there is no way to implicate the liberalization of the 40% policy with the observed increases in incidence. If the hypothesized relationship between incidence and survival is true, liberalization may, in fact, confound the relationship between incidence and survival. If survival is an intervening variable between oxygen and ROP (i.e., if liberalization led to an increase in birth weight-specific survival which, in turn, led to the observed increase in ROP), what will be called into question is the policy of active intervention to

resuscitate or otherwise ensure survival in prematurely born or very low weight infants. Until survival-specific rates for blindness due to the ROP are available, policy responses to the new epidemic are inappropriate. Before it can be assumed that the epidemic points to a failure of the active intervention or the liberalized oxygen policy, it needs to be shown that one or both of these policies result in the blinding of an inordinate number of infants. If this can't be shown, the blinding of a minority of very low weight infants may be the price that has to be paid for the survival of the majority.

If survival is not a factor in the new epidemic, the possibility of endogenous or exogenous factors contributing to the increase in incidence will have to be entertained. Unfortunately, this means that the etiological relationships underlying the epidemic will have to be determined. It can't be assumed that, because oxygen was a major factor in the original epidemic, it is responsible for the latest increases in incidence. It is now clear that oxygen need not be 'the sole and sufficient cause' for ROP. Therefore, other factors that obliterate developing vessels in an incompletely differentiated retina may be contributing to, or in fact may be responsible for, the increase in the incidence of the disease. Furthermore, since the increase in the incidence of blindness from ROP does not necessarily mean there has an increase in the incidence of the milder forms of the disease, it is possible that the rates of active ROP were unchanged while the incidence of blindness increased.

Even if oxygen is implicated in the new epidemic, changing exposure policies may be difficult. The original epidemic ended when the 40% policy eliminated the practice of routinely exposing newborn infants to high concentrations of oxygen for long periods of time. In the new epidemic, such an obvious and easy policy solution is unlikely. Infants are not exposed unless their clinical conditions suggest it is necessary; those who are exposed

are returned to room air in the shortest possible time. The increased incidence of neonatal mortality and morbidity after the implementation of the 40% policy suggests that a strictly curtailed, deterministic exposure policy is not a feasible option. Lastly, because there is no evidence conclusively associating ROP and PO_2, there is no rational basis on which to revise the liberalized policy now in place.

Whatever the reason for the new epidemic, it is sure to impact on the policies governing and the facilities providing medical, educational and support services for the severely visually impaired. In the last epidemic, which blinded an estimated 10,000 children, the facilities and support services for blind children were taxed to the limit. In the new epidemic, the downward shift in the weight groups at risk for ROP-induced blindness will minimize the impact. However, the fact that there is a smaller population at risk does not negate the fact that there will be an increased demand for services to cope with the increased prevalence of infants blinded by the disease. Therefore, if the epidemic continues, policies aimed at increasing the current level of support services may have to be implemented.

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APPENDIX I

ETIOLOGICAL RELATIONSHIPS CONSIDERED IN PERIOD 1942 TO MID 1950'S

Appendix I
Factors Suspected of Being Etiologically Related to ROP: 1942 to mid 1950's

Factor	Theoretical and Observed Correlations	References
I. Parental Factors		
1. Race	In some series, no correlation; in some, incidence higher in whites than blacks (USA) or natives (Australia); in many hospitals servicing blacks, disease unknown or incidence low.	10, 19, 27, 28, 36, 38, 76, 81
2. Parental Age	not correlated with either mother's or father's age.	10, 19, 35, 38, 71, 76, 111
3. Social/Economic Status	not correlated	10, 111
4. Place of Conception	not correlated	35
5. Parity of Mother	In most reports, no correlation; in some, incidence higher in primiparous vs multiparous mothers; in others, converse true.	10, 19, 35, 38, 68, 71, 76, 107, 112
6. Blood Type (Rh)	not correlated	5, 22, 24, 35, 71, 76, 111, 112
II. Pregnancy Related Factors		
1. Causes of Premature Birth		
a. Multiple Birth	In some reports, higher incidence in twins; when multiple births reported, disease usually concordant; usually assumed correlated with ROP only insofar as both correlated with prematurity.	10, 22, 35, 50, 68, 71
b. Other Causes of premature birth	No evidence linking ROP to various causes of premature delivery (eg. toxemia of pregnancy, etc.)	5, 10, 19, 35, 38, 71, 76, 111
2. Maternal Infection	No correlations noted with infections or smallpox vacinnations during pregnancy.	1, 5, 19, 21, 22, 111

3. Nausea of Pregnancy	not correlated	77
4. Attempted Abortion	not correlated	77
5. Diet During Pregnancy	not correlated	35, 36, 111
6. Medications	No evidence of drug used uniformly by mothers of affected infants.	5, 22, 111
7. X-Ray Examinations	not correlated	35, 71
8. Weight Gain	not correlated	35,71
9. Chronic Illness	Evidence of toxoplasmosis found in one mother and affected infant; no evidence of cranial calcifications in other infants with ROP; in other studies, no correlations with other chronic illness during pregnancy noted.	19, 22, 35, 38, 50, 71, 76, 112
10. Endocrine Disturbances		5
11. Place of Residence During Pregnancy	not correlated	35
12. Type or Condition of Placenta	In some studies, no correlation; in others, placental deformities appeared related.	35, 56, 76, 113 114
13. Uterine Bleeding	In some studies, mother's with high incidence of uterine bleeding during pregnancy; in others, ante partum bleeding not implicated	5, 12, 19, 22 34, 35, 56, 68, 71, 76, 113, 114
III. Labour/Delivery Related Factors		
1. Onset of Labour	not correlated	19, 35
2. Length of Labour	not correlated	38
3. Presentation of Fetus	not correlated	35, 71, 111
4. Type of Delivery	not correlated	19, 35, 38, 71 76, 111
5. Type of Anesthesia or Analgesia	not correlated	35, 38, 71
IV. Infant Factors		
1. Season: Conception or Birth	In one series, cases born in clusters throughout spring, summer, and autum; in others, no correlation with season of birth	10, 38, 68, 69 76, 111, 112

2. Month of Occurrence	In one series, disease occurred in 'batches'; in others, observation not confirmed	84
3. Sex	Occasional report of preponderance in males; in some, sex ratio skewed in favor of affected females; in most studies, disease equally distributed between sexes.	10, 19, 22, 35, 38, 67, 68, 71, 80, 81
4. Birth Injuries	not correlated	35
5. Malformations and Associated Conditions	Except for the conditions listed below, no correlation with specific malformations or malformations in general.	5, 10, 22, 35, 59, 71
a. Skin Hemangiomas	High incidence of skin hemangiomas in some series; not noted in others; in some studies, no difference in incidence in infants with and without hemangiomas; in one report, incidence of hemangiomas constant while incidence of ROP fluxuated from year to year.	10, 21, 22, 25, 26, 31, 35, 54, 59, 63, 70, 71, 75, 76, 80,
b. Intra-Cranial Disorders	Reports that ROP rare without associated intra-cranial involvement; not confirmed in other studies.	10, 19, 55, 76, 118
c. Ocular Hypertension		119
d. Mental Retardation	In some series, high frequency of mental retardation in affected; in others, incidence not significantly increased compared to premature children in general.	22, 33, 55, 68, 70, 76, 84, 87, 116-118
6. Hereditary Factors	In B.C., ROP in one set of siblings born 2 years apart; in other reports, multiple occurrences within families limited to products of multiple conception.	2, 5, 10, 22 35, 38, 70, 76, 111, 113, 120, 121
7. Condition of Infant		
a. Birth Weight	Almost universal agreement for correlation between ROP and preterm, hence low birth weight infants; few cases born weighing >1985 grams.	21, 22, 35, 37, 38, 43, 57, 76, 122, 123
	Some argued incidence inversely proportional to birth weight, others disagreed; in some hospitals, increased incidence limited to infants weighing 3-4 lbs.; some authors argued was inverse relation between b. wt. and time of onset.	37, 38, 71, 76, 78, 80, 112-124, 125
	In some studies, severity varied inversely with b. wt; in others, it did not.	80, 103

b. Gestational Age	Few attempts made to correlate ROP with g. age; in studies where correlation correlation noted, majority of cases born 8 or more weeks pre term; occassional reports of ROP in term infants.	21, 22, 35, 38, 60, 122
	Suggestion that g. age, unrelated to weight, important factor; a few argued was more important; some reported g. age not related.	43, 80, 81, 103, 126
c. Need for Resuscitation	not correlated	38
d. Cyanosis or Asphyxia	not correlated	10, 35, 38
e. Chest Wall Retractions	not correlated	35
f. Jaundice	not correlated	10, 35, 111
g. Diarrhea	not correlated	35
h. Body Temperature	not correlated	5, 35, 71
i. Anemia of Prematurity	not correlated	5, 18, 21, 111
j. Rh Incompatibility with Mother	not correlated	5, 22, 24, 35, 71, 76, 111, 112
k. Rate of Weight Gain	not correlated	35
l. Intra-Atrial Blood Pressure	not correlated	5, 8, 36, 79, 127
m. Calcium, Phosphorous & Phosphatase Levels	not correlated	36
n. RBC Resistance to Breakdown	Correlation between resistance of erythrocytes to hemolysis with dialuric acid and ROP suggested but not substantiated.	128
o. Neonatal Infections	Numerous suggestions that ROP caused by microorganism, probably a virus. No evidence to correlate ROP with postnatal infection.	5, 10, 21, 34, 69, 80, 84, 87, 111, 124
p. Limited Kidney Function		111
q. General Health	In one study, observation that babies with ROP in nursery and in oxygen longer taken as sign their general health not as good as babies with no ROP; not confirmed by other studies	38, 71
r. Inability to Digest or Assimilate Food		5

s. Vitamin A Deficiency	Theory grew out of fact that eye defects similar to ROP were produced in offspring of vitamin A-deficient mothers; theory discredited by experimental evidence and observation that, in some series, was positive correlation between increased incidence increased use of water-miscible vitamin A; in other series, prophylactic use of vitamin A did not reduce incidence.	5, 17, 19, 78, 129-132
t. Vitamin K Deficiency	Thought vitamin K deficiency leading to intraocular hemorrhage might give rise to the lesions characteristic of ROP; later noted that several infants receiving supplemental vitamin K later developed ROP; in another series, was no difference in amount of vitamin K given infants who did and didn't develop disease.	5, 19
u. Vitamin E Deficiency	Hypothesized that, because were numerous factors in diets of premature infants that might lead to a vitamin E deficiency, such a deficiency might be implicated in etiology; results of first clinical trial seemed to substantiate idea; theory abandoned when subsequent studies failed to confirm early results; one trial raised possibility that prophylaxis with vitamin might be harmful.	5, 17, 26, 27, 38, 50, 63, 75, 112, 133, 134
v. Uveitis		39, 63
w. Lack of Inhibiting Factors From Endocrine Sources		5, 13
x. Adrenal Cortical Steroid Deficiency	The idea used as rationale for unsuccessful attempts to treat ROP with ACTH.	25, 42, 74, 98, 125, 135-140
y. Deficency of Maternal Factors Due to Preterm Birth	In one study, weekly transfusions of whole blood from women in the third trimester of pregnancy not prophylactically effective in preventing ROP; in another, incidence in premature infants given estrogen therapy did not differ from incidence in controls.	36, 102
8. Medical Management		
a. Prenatal Exposure to X-Rays	not correlated	35, 71
b. Exposure to Light	Terry first to suggest exposure of immature light was causally related; number of hospitals reported their policies re exposure unchanged in periods when incidence was increasing; some reports suggested incidence unaffected when premature infants subjected to the added illumination of biweekly ophthalmological examinations; issue considered resolved when the results of clinical trials failed to implicate light.	5, 7, 36, 38, 70, 78, 111, 141, 142

c. Initial Thirsting & Starving	Idea grew out of observation that, in some hospitals with high incidence of ROP, food and fluids were routinely withheld for first 2-3 days of life; other hospitals that initiated feedings within hours of births reported ROP not seen.	31, 35, 50, 64, 69, 78, 143
d. Feedings	Were suggested when was noticed that incidence appeared highest in hospitals only cow's milk; others noted period of increasing incidence occurred comcomitant with increasing use of prepared formulae; one trial showed incidence reported correlated with sodium content of formula; in some hospitals, disease not known in infants fed cow's milk or common in infants fed breast milk.	19, 26, 36, 50, 68, 69, 71, 79, 101, 111
e. Use of Antibiotics	not correlated	69
f. Other Medications	not correlated	111
g. Blood Transfusions	In some series, high frequency of affected infants with earlyn and repeated blood transfusions; in other studies, no correlations with transfusions found; some reports that transfusions given to infants with early signs of aROP exacerbated progression of disease.	11, 23, 35, 38, 69, 79, 80, 84, 105, 112, 127, 143
h. Use of Water-Miscible Vitamins and Iron	In early study, was positive correlation between increase in incidence and increased use of water-miscible vitamins; later studies showed incidence did not drop when water-miscible multivitamins and iron excluded from diet; attempts to correlate homogenizing and emulsifying agents also unsuccessful.	35, 36, 51, 71, 78, 122
i. Careless Use of Substances Influencing Growth		144

APPENDIX II

ETIOLOGICAL RELATIONSHIPS CONSIDERED AFTER END OF FIRST EPIDEMIC (MID 1950'S TO PRESENT)

Appendix II.
Factors Suspected of Being Etiologically Related to ROP: 1970's-1980's

Factors	Theoretical and Observed Correlations	References
I. Parental Factors		
1. Race	not correlated	239, 242
2. Maternal Gravidity	not correlated	242
II. Pregnancy Related Factors		
1. Causes of Premature Birth		
a. Multiplicity	not correlated	214, 239, 247, 249, 276
b. Toxemia of Pregnancy	In one study, toxemia included in set of 'pregnancy complications' associated with increased risk; in another, not associated with onset or severity.	199, 239, 242
2. Threatened Abortion	not correlated	239
3. Use of Medications	In one study, no association with beta-methasone during pregnancy; in another, association with antihistamines but not with aspirin in last 2 wks. of pregnancy.	239, 246
4. Chronic Illness	In one study, maternal anemia associated with decreased risk and maternal diabetes, with increased risk; another associated diabetes or severity.	199, 239, 242
5. Other Complications of Pregnancy	Some reports linked ROP to antecedent complications of pregnancy, esp. those than might result in fetal exposure to chronic hypoxemia.	189, 199, 210
6. Exposure to Noxious Substances	One study suggested maternal smoking associated with increased risk; another failed to associate smoking or alcohol use during pregnancy.	199, 239
III. Labour and Delivery Related Factors		
1. Hospital of Birth	not correlated	246, 247
2. Medications During Delivery	not correlated	239

3. Prolonged Duration of Ruptured Membranes	not correlated	239
IV. Infant Factors		
1. Sex	not correlated	186, 239, 242 246, 247, 249
2. Birth Order	not correlated	242
3. Malformations and Associated Conditions		
a. Patent Ductus Arteriosus	In most studies, either was no correlation or was a correlation that disappeared when confounders controlled	186, 214, 239, 242, 246, 249, 251, 289, 290
b. Intraventricular Hemorrhage	In a number of studies, IVH a possible risk factor for aROP or cROP; in another study, association disappeared when confounders controlled;	197, 239, 242, 289, 290
c. Persistent Hyaloid Artery	In one report, two classes of persistent hyaloid artery were identified: in the first class, the persistent artery was unrelated to ROP; in the other, the artery was an integral component of the retrolental membrane and hence, was thought thought to be related.	333
d. Other Anomalies	ROP described in infants with variety of conditions (trisomy 18, cri-du-chat, meningomyelocele, hydrocephalus, microcephaly, adrenal hypoplasia, multiple congenital anomalies	191, 210
4. Condition of the Infant		
a. Birth Weight	Most studies report inverse relationship between b. wt. and incidence; in Second Cooperative Study, birth weight so highly correlated that it masked the effect of other variables; in some studies specific for VLBW infants, was no difference in weights of infants who did and did not develop ROP.	150, 186, 240, 241, 242, 246, 247, 276
b. Gestational Age	Some studies report association between gestational age and either incidence or severity; results not confirmed by studies that controlled for birth weight; several studies failed to correlate incidence with 'small for g. age'.	186, 239, 242, 247, 249, 276
c. Asphyxia or Cyanosis	not correlated	186, 247

d. Hyperbilirubinemia	not correlated	214
e. Anemia or Low Hematocrit	One study linked low hematocrit, hemoglobin and red cell count to ROP; others found no association.	239, 242
f. Weight Loss	One report suggested 'maximum weight loss in early neonatal period' associated with increased risk .	186
g. Hypotension	not correlated	239
h. Sepsis/Septicemia	Some reports of correlation between ROP and sepsis or septicemia; others found no association.	186, 239, 242, 247, 249, 284
i. Apgar Score	Most studies failed to correlate Apgar scores with ROP; one study found association that disappeared when confounders controlled.	239, 242, 249
j. Vitamin E Deficiency	Most evidence implicating vitamin E deficiency as an etiological factor came from studies done to test efficacy of vitamin E as a prophylaxis; results mixed.	242, 244, 248, 291-297
k. Lactic Acidosis	In experiment using kittens, Imre concluded neovascularization due specifically to the increased concentration of lactic acid in eye.	298, 299
l. Acidosis and Alkalosis (pH)	Data conflicting; in one study, ROP not linked to lowest pH measured; in another, (i) severe acidosis occurred more often in control group and (ii) number of episodes of alkolosis correlated with ROP but correlation disappeared when confounders controlled	239, 247, 249, 300
m. Hyper/Hypocarbia (pCO2)	Some studies report no association between PCO_2 and ROP; one reported onset associated with increased frequency of hypocarbia; several report disease associated with hypercarbia; reviews of medical records from 2 institutions showed: (a) infants with severe ROP had higher peak PCO_2 levels than infants less severely affected, (b) duration of exposure to $PCO_2 > 50$ torr associated with cROP, and (c) was association between ROP and $PCO_2 > 50$ torr occurring simultaneously with PO_2 levels > 100 torr.	197, 247, 276, 301-304
	Flower et. al showed when hyperoxia and hypercarbia coincide in puppies, hypercarbic effect predominates in retinal circulation and leads to vaso-dilation and capillary leaks; similar results reported by Spalter et. al.;	156, 181, 204

	conflicting results produced in experiments with kittens.	
n. Apnea	In some studies, positive association between ROP and apnea; in others, relationship not observed.	186, 214, 239, 242, 247, 289
o. Respiratory Distress Syndrome	One study reported incidence of 'chronic lung disease' higher in infants with ROP; in same study, no correlation with 'hyaline membrane disease'; in another study, 'respiratory distress syndrome' not associated with cROP.	186, 246
p. Bradycardia	not correlated	239
q. Convulsions	not correlated	247
r. Bronchopulmonary Dysplasia	In some studies, increased frequency of BPD in affected infants; in others, no association.	239, 242, 244, 246, 249, 250 295
s. Superoxide Dismutase	Bougle et. al. showed that there was a marked reduction in SOD activity in retinas of kittens exposed to sufficient oxygen to produce irreversible lesions;	305-307
t. Hypocalcemia	not correlated	214
u. Pneumothorax	not correlated	214, 242
5. Medical Management		
a. Exposure to Light	In 1985 study, infants who were not protected from illumination had higher incidence of ROP than did infants with protected eyes; in protected group, more more infants who developed ROP in cribs situated near a window.	285
b. Phototherapy	not correlated	186, 247, 300
c. Parenteral Nutrition	Two studies found significant association between incidence and duration of parenteral nutrition in newborn period	186, 247
d. Feedings	One study found significant association with 'days without oral feeding'.	186
e. Blood Transfusions	A number of studies suggest a positive correlation between ROP and exchange and/or replacement transfusions; other studies failed to find association; in some studies, blood transfusions appeared to confounding rather than causally related.	186, 201, 210, 214, 239, 247, 249, 276, 300, 308-311

f. Medications	Two studies reported high incidence of ROP in infants treated with indomethacin, a drug used to induce the closure of PDA's; other studies failed to correlate drug with ROP	239, 249, 251, 303

APPENDIX III

ROP COFACTOR STUDY: RESULTS
UNIVARIATE ANALYSES OF DICHOTOMIZED VARIABLES
(STRATIFIED AND UNSTRATIFIED)

APPENDIX III: TABLE 1
RESULTS OF UNIVARIATE ANALYSES OF DICHOTOMIZED VARIABLES
NOT STRATIFIED BY BIRTH PERIOD

VARIABLE NAME	CATEGORIES[1]	#BLIND/NOT BLIND BLIND	NOT BLIND	ODDS RATIO [95% C. LIMITS]
patent ductus arteriosus	yes	10	16	0.83
	no	9	12	[0.26 - 2.69]
agenesis of lung	yes	6	10	0.83
	no	13	18	[0.24 - 2.87]
respiratory distress, hyaline membrane disease	yes	12	26	0.13
	no	7	2	[0.02 - 0.73]
respiratory disease	yes	9	15	0.78
	no	10	13	[0.24 - 2.51]
intraventricular hemorrhage	yes	1	1	1.50
	no	18	27	[0.09 - 25.55]
necrotizing enterocolitis	yes	0	1	----
	no	19	27	
gestational age (weeks)	LE 28	10	17	1.39
	GT 28	9	11	[0.43 - 4.52]
birth weight (grams)	LE 992	10	13	0.74
	GT 992	8	14	[0.22 - 2.46]
days stay in hospital	LE 86	10	14	0.90
	GT 86	9	14	[0.28 - 2.89]
neonatal weight loss	LE 141	13	9	0.28
	GT 141	6	15	[0.08 - 0.99]
days parenteral nutrition	LE 32	10	14	0.90
	GT 32	9	14	[0.28 - 2.89]
number of transfusions	LE 8	10	15	1.04
	GT 8	9	13	[0.32 - 3.34]
hours at pH < 7.20	LE 25	5	15	2.18
	GT 25	8	11	[0.56 - 8.51]
hours at pH > 7.50	LE 0	9	14	0.52
	GT 0	4	12	[0.13 - 2.12]

1. LE = less than or equal to median value; GT = greater than median value

VARIABLE NAME	CATEGORIES[1]	#BLIND/NOT BLIND BLIND	NOT BLIND	ODDS RATIO [95% C. LIMITS]
hours at pCO2 < 35	LE 74	7	13	0.86
	GT 74	6	13	[0.23 - 3.25]
hours at pCO2 > 45	LE 351	5	15	2.18
	GT 351	8	11	[0.56 - 8.51]
hours at pO2 < 40	LE 121	6	14	1.36
	GT 121	7	12	[0.36 - 5.18]
hours at pO2 > 100	LE 17	6	14	1.36
	GT 17	7	12	[0.36 - 5.18]
days in isolette[2]	LE 52	11	13	0.68
	GT 52	8	14	[0.21 - 2.20]
1/2 days in isolette[3]	LE 55.5	10	13	0.84
	GT 55.5	9	14	[0.26 - 2.71]
days on respirator[2]	LE 23.5	11	12	0.58
	GT 23.5	8	15	[0.18 - 1.90]
1/2 days on respirator[3]	LE 35	10	14	0.97
	GT 35	9	13	[0.30 - 3.14]
1st exposure to isolette	day born	13	17	0.71
	day after	6	11	[0.21 - 2.44]
1st exposure to respirator	day born	13	22	0.85
	day after	2	4	[0.14 - 5.28]
weighted oxygen score[4]	LE 15.7	11	10	0.46
	GT 15.7	7	14	[0.13 - 1.58]

1. LE = less than or equal to median value; GT = greater than median value
2. at oxygen concentrations greater than room air
3. number of half-days exposure in first 28 days of life
4. O_2 score = [0.2][# .5 days FiO_2 21-30%] + [0.3][.5 d. FiO_2 31-40%] ... + [0.9][.5 d. FiO_2 91-100%]

APPENDIX III: TABLE 2
RESULTS OF UNIVARIATE ANALYSES STRATIFIED TO 3 BIRTH INTERVALS:
1955-1964, 1965-1974, 1975-1983

VARIABLE NAME	CATEGORIES[1]	NUMBER BLIND(B) & NOT BLIND(NB) 1955-64		1965-74		1975-83		ODDS RATIO [95% CONF. LIMITS]
		B	NB	B	NB	B	NB	
patent ductus arteriosus	yes	0	0	0	1	10	15	1.31
	no	2	0	4	4	3	8	[0.31 - 5.56]
agenesis of lung	yes	0	0	0	1	6	9	1.06
	no	2	0	4	4	7	14	[0.28 - 3.98]
respiratory distress, hyaline membrane disease	yes	0	0	0	5	12	21	0.24
	no	2	0	4	0	1	2	[0.05 - 1.05]
respiratory disease	yes	0	0	0	1	9	14	1.13
	no	2	0	4	4	4	9	[0.28 - 4.45]
intraventricular hemorrhage	yes	0	0	0	0	1	1	1.83
	no	2	0	4	5	12	22	[0.11 - 32.12]
necrotizing enterocolitis	yes	0	0	0	0	0	1	----
	no	2	0	4	5	13	22	
gestational age (weeks)	LE 28	0	0	1	2	9	15	1.00
	GT 28	2	0	3	3	4	8	
birth weight (grams)	LE 992	0	0	1	1	9	12	0.55
	GT 992	1	0	3	3	4	11	[0.15 - 2.05]
days stay in hospital	LE 86	2	0	2	2	6	12	1.11
	GT 86	0	0	2	3	7	11	[0.32 - 3.82]

1. LE = less than or equal to the median value; GT = greater than the median value

VARIABLE NAME	CATEGORIES	NUMBER BLIND(B) & NOT BLIND(NB) 1955-64		1965-74		1975-83		ODDS RATIO [95% CONF. LIMITS]
		B	NB	B	NB	B	NB	
neonatal weight loss	LE 141	1	0	3	3	9	6	0.25
	GT 141	1	0	1	2	4	13	[0.07 - 0.95]
days parenteral nutrition	LE 32	2	0	4	5	4	9	1.45
	GT 32	0	0	0	0	9	14	[0.34 - 6.24]
number of transfusions	LE 8	2	0	4	4	4	11	1.55
	GT 8	0	0	0	1	9	12	[0.41 - 5.91]
hours at pH < 7.20	LE 25	-	-	0	3	5	12	1.92
	GT 25	-	-	0	1	8	10	[0.47 - 7.87]
hours at pH > 7.50	LE 0	-	-	0	2	9	12	0.53
	GT 0	-	-	0	2	4	10	[0.12 - 2.94]
hours at pCO2 < 35	LE 74	-	-	0	1	7	12	1.03
	GT 74	-	-	0	3	6	10	[0.26 - 4.16]
hours at pCO2 > 45	LE 351	-	-	0	2	5	13	2.31
	GT 351	-	-	0	2	8	9	[0.56 - 9.48]
hours at pO2 < 40	LE 121	-	-	0	4	6	10	0.97
	GT 121	-	-	0	0	7	12	[0.24 - 3.93]
hours at pO2 > 100	LE 17	-	-	0	1	6	13	1.69
	GT 17	-	-	0	3	7	9	[0.42 - 6.82]
days in isolette[2]	LE 52	2	0	4	2	5	11	0.87
	GT 52	0	0	0	3	8	11	[0.27 - 2.81]

2. at concentrations greater than room air

VARIABLE NAME	CATEGORIES	NUMBER BLIND(B) & NOT BLIND(NB) 1955-64 B	1955-64 NB	1965-74 B	1965-74 NB	1975-83 B	1975-83 NB	ODDS RATIO [95% CONF. LIMITS]
1/2 days in isolette[3]	LE 55.5	2	0	3	3	5	10	1.10
	GT 55.5	0	0	1	2	8	12	[0.31 - 3.91]
days on respirator[2]	LE 23.5	2	0	4	4	5	8	0.75
	GT 23.5	0	0	0	1	8	14	[0.19 - 2.95]
1/2 days on respirator[3]	LE 35	2	0	4	3	4	11	1.32
	GT 35	0	0	0	2	9	11	[0.38 - 4.61]
1st exposure to isolette	day born	2	0	3	3	8	14	0.85
	day after	0	0	1	2	5	9	[0.24 - 3.06]
1st exposure to respirator	day born	-	-	2	4	11	18	0.84
	day after	-	-	0	1	2	3	[0.13 - 5.59]
weighted oxygen score[4]	LE 15.7	1	0	4	2	6	8	0.52
	GT 15.7	0	0	0	3	7	11	[0.15 - 1.80]

3. number of half-days exposure in first 28 days of life
4. O2 score = [0.2][# .5 days FiO2 21-30%] + [0.3][.5 d. FiO2 31-40%] ... + [0.9][.5 d. FiO2 91-100%]

APPENDIX IV

ROP COFACTOR STUDY: RESULTS
T-TESTS ON CONTINUOUS VARIABLES OVER TWO TIME PERIODS
(1955-1983 AND 1970-1983)

APPENDIX IV

RESULTS OF T-TEST ANALYSES USING VARIABLES COLLECTED FOR CASES ROP: BLIND AND NOT BLIND IN THE PERIODS 1955-1983 AND 1970-1983

	1955-1983			1970-1983		
VARIABLE	MEAN	S.D.	P[1]	MEAN	S.D.	P[1]
gestation in weeks						
blind	28.6	3.76	0.99	28.4	3.69	0.90
not blind	28.6	4.25		28.2	4.74	
birth weight in grams						
blind	1302.3	877.93	0.67	1303.3	895.30	0.75
not blind	1190.5	801.85		1208.6	911.18	
total days in hospital						
blind	93.8	56.05	0.75	94.4	57.80	0.52
not blind	99.4	61.54		107.9	69.84	
neonatal weight loss						
blind	152.8	60.14	0.09	156.9	61.10	0.11
not blind	122.7	52.40		124.6	49.79	
total days in parenteral nutrition						
blind	41.7	31.54	1.00	43.8	31.72	0.38
not blind	41.6	35.33		53.4	33.98	
number of transfusions						
blind	9.0	6.34	0.98	9.4	6.37	0.29
not blind	8.9	8.24		11.9	7.67	
hours pH below 7.20[2]						
blind	34.2	57.62	0.55	35.2	58.61	0.59
not blind	45.1	40.3		45.1	40.29	
hours pH above 7.50[2]						
blind	7.5	12.51	0.17	7.8	12.67	0.15
not blind	2.5	5.32		2.5	5.32	
hours PCO_2 below 35 mmHg[2]						
blind	92.0	76.01	0.88	87.7	74.19	0.74
not blind	95.8	62.27		95.8	62.27	

1. two tailed probability for t-values based on pooled variance estimate
2. in first 28 days of life

VARIABLE	1955-1983 MEAN	1955-1983 S.D.	1955-1983 P	1970-1983 MEAN	1970-1983 S.D.	1970-1983 P
hours PCO_2 above 45 mmHg[2]						
blind	314.1	177.45	0.35	323.0	175.05	0.44
not blind	367.2	140.22		367.2	140.22	
hours PO_2below 40 mmHg[2]						
blind	125.5	106.53	0.19	130.5	105.54	0.24
not blind	182.1	157.41		182.1	157.41	
hours PO_2 above 100 mmHg[2]						
blind	18.1	16.18	0.63	17.0	15.60	0.50
not blind	20.7	15.27		20.7	15.27	
total days in supplemented isolette						
blind	61.4	46.71	0.99	63.6	47.57	0.51
not blind	61.5	51.22		74.6	53.50	
half days in supplemented isolette[2]						
blind	43.4	20.03	0.44	43.6	20.44	0.28
not blind	47.4	10.66		50.0	9.55	
total days on respirator						
blind	35.9	29.48	0.89	37.6	30.03	0.42
not blind	34.5	38.44		46.6	37.94	
half days on respirator[2]						
blind	33.5	19.15	0.67	33.9	19.87	0.24
not blind	30.8	23.78		41.5	17.68	
weighted oxygen score[3]						
blind	13.8	7.87	0.93	13.8	8.13	0.41
not blind	14.0	7.84		16.0	7.40	

3. for oxygen exposures in first 28 days of life

APPENDIX V

ROP COFACTOR STUDY: RESULTS
LOGISTIC REGRESSIONS ON CONTINUOUS VARIABLES OVER TWO PERIODS
(1955-1983 AND 1970-1983)

APPENDIX V: TABLE 1
RESULTS OF LOGISTIC REGRESSION ANALYSES USING VARIABLES COLLECTED FOR CASES ROP: BLIND AND NOT BLIND IN THE PERIOD 1955-1983

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
gestational age					
intercept	-0.3663	2.2154	0.03	0.87	
variable	-0.0008	0.0767	0.00	0.99	0.000
birth weight					
intercept	-0.1897	0.5745	0.11	0.74	
variable	-0.0002	0.0004	0.19	0.66	0.000
days in hospital					
intercept	-0.5521	0.5843	0.89	0.34	
variable	0.0017	0.0052	0.11	0.74	0.000
neonatal weight loss					
intercept	1.0963	0.8634	1.61	0.20	
variable	-0.0096	0.0058	2.72	0.10	-0.110
days parenteral nutrition					
intercept	-0.3859	0.4842	0.64	0.43	
variable	< -0.0001	0.0092	0.00	1.00	0.000
number of transfusions					
intercept	-0.3781	0.4831	0.61	0.43	
variable	-0.0011	0.0425	0.00	1.00	0.000
hours pH below 7.20[1]					
intercept	-0.8437	0.4251	3.94	0.05	
variable	0.0039	0.0064	0.37	0.54	0.000
hours pH above 7.50[1]					
intercept	-0.3896	0.3880	1.01	0.32	
variable	-0.0698	0.0551	1.60	0.21	0.000
hours PCO_2 below 35 mmHg[1]					
intercept	-0.7642	0.5688	1.81	0.18	
variable	0.0008	0.0048	0.02	0.87	0.000
hours PCO_2 above 45 mmHg[1]					
intercept	-1.3982	0.8407	2.77	0.10	
variable	0.0021	0.0022	0.89	0.34	0.000
hours PO_2 below 40 mmHg[1]					
intercept	-1.2326	0.5537	4.96	0.03	
variable	0.0036	0.0027	1.68	0.20	0.000
hours PO_2 above 100 mmHg[1]					
intercept	-0.9004	0.5468	2.71	0.10	
variable	0.0107	0.0217	0.24	0.62	0.000
days in supplemented isolette					
intercept	-0.3546	0.4895	0.52	0.47	
variable	< 0.0001	0.0063	0.00	0.99	0.000

1. in first 28 days of life

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
half days in supplemented isolette[1]					
intercept	-1.0383	0.9297	1.25	0.26	
variable	0.0151	0.0191	0.62	0.43	0.000
total days on respirator					
intercept	-0.3035	0.4399	0.48	0.49	
variable	-0.0014	0.0092	0.02	0.88	0.000
half days on respirator[1]					
intercept	-0.1478	0.5500	0.07	0.79	
variable	-0.0063	0.0144	0.19	0.66	0.000
weighted oxygen score[1]					
intercept	-0.3415	0.6455	0.28	0.60	
variable	0.0039	0.0407	0.01	0.92	0.000

APPENDIX V: TABLE 2
RESULTS OF LOGISTIC REGRESSION ANALYSES USING VARIABLES COLLECTED FOR CASES ROP: BLIND AND NOT BLIND IN THE PERIOD 1970-1983

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
gestational age					
intercept	-0.3120	2.3980	0.02	0.90	
variable	-0.0108	0.0840	0.02	0.90	0.000
birth weight					
intercept	-0.4549	0.6011	0.57	0.45	
variable	-0.0001	0.0004	0.10	0.75	0.000
days in hospital					
intercept	-0.9814	0.6479	2.29	0.13	
variable	0.0035	0.0054	0.44	0.51	0.000
neonatal weight loss					
intercept	0.9890	0.9686	1.04	0.31	
variable	-0.0102	0.0064	2.48	0.12	-0.100
days parenteral nutrition					
intercept	-1.0673	0.6137	3.02	0.08	
variable	0.0092	0.0103	0.80	0.37	0.000
number of transfusions					
intercept	-1.1817	0.6361	3.45	0.06	
variable	0.0531	0.0495	1.15	0.28	0.000
hours pH below 7.20[1]					
intercept	-0.7920	0.4286	3.41	0.06	
variable	0.0035	0.0064	0.30	0.58	0.000
hours pH above 7.50[1]					
intercept	-0.3268	0.3936	0.69	0.41	
variable	-0.0737	0.0562	1.72	0.19	0.000
hours PCO_2 below 35 mmHg[1]					
intercept	-0.8094	0.5717	2.00	0.16	
variable	0.0017	0.0049	0.12	0.73	0.000
hours PCO_2 above 45 mmHg[1]					
intercept	-1.2634	0.8553	2.18	0.14	
variable	0.0018	0.0022	0.63	0.43	0.000
hours PO_2 below 40 mmHg[1]					
intercept	-1.1604	0.5620	4.26	0.04	
variable	0.0033	0.0028	1.40	0.24	0.000
hours PO_2 above 100 mmHg[1]					
intercept	-0.9474	0.5512	2.95	0.09	
variable	0.0156	0.0223	0.49	0.48	0.000
days in supplemented isolette					
intercept	-0.8929	0.5820	2.35	0.13	
variable	0.0045	0.0068	0.45	0.50	0.000

1. in first 28 days of life

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
half days in supplemented isolette[1]					
intercept	-1.7486	1.1645	2.25	0.13	
variable	0.0248	0.0300	1.17	0.28	0.000
total days on respirator					
intercept	-0.9368	0.5555	2.84	0.09	
variable	-0.0085	0.0103	0.69	0.41	0.000
half days on respirator[1]					
intercept	-0.4342	0.8254	3.02	0.08	
variable	-0.0225	0.0192	1.38	0.24	0.000
weighted oxygen score[1]					
intercept	-1.0254	0.7739	1.76	0.19	
variable	0.0385	0.0457	0.71	0.40	0.000