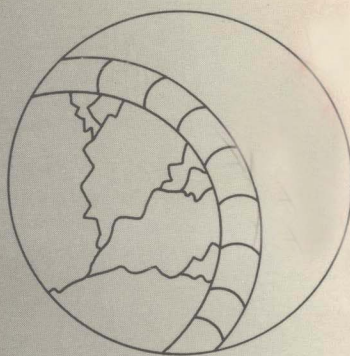
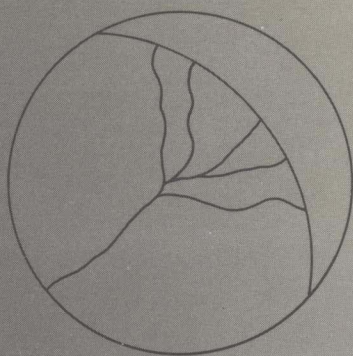


# TREATMENT OF RETINOPATHY OF PREMATURITY



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# Treatment of Retinopathy of Prematurity

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# INTRODUCTION

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Over the last 44 years a plethora of literature has emerged on retrolental fibroplasia (RLF) and retinopathy of prematurity (ROP). There appears to have been an “oxygen epidemic” from the late 1940s through the mid 1950s. During this period ROP was the leading cause of blindness in neonates. This resulted in the mid 1950s in three prospective, controlled studies and one large retrospective review of the use of oxygen in nurseries. Although the percentage of arterial oxygen delivered per se could not be incriminated, the duration of oxygen administration was found to be of significance. However, most centers developed guidelines in neonatal oxygen therapy that differed from the conclusions of the large multicenter, cooperative controlled studies.

Over the next 25 years a number of factors, including phototoxicity, ischemia, elevated oxygen levels, low oxygen levels, adrenocortical deficiency, elevated and low carbon dioxide levels, vitamin E or A deficiency, iron deficiency, maternal factors, multiple gestation, poor nutrition, cyanotic congenital heart disease, anencephaly, exchange and replacement transfusion, complications of pregnancy, congenital anomalies, intraventricular hemorrhage, septicemia, and prematurity itself, were advanced as possible causes of the disease. Despite meticulous attention to oxygen use, however, the disease is increasingly prevalent at this writing; in fact, it has occurred in term infants who have never been given supplemental oxygen as well as in the hypoxic infant.

Court awards, mostly based on excessive oxygen therapy, have run into the millions of dollars. However, the disease of fibrovascular proliferation in the neonatal retina, or ROP, remains an enigma.

**Joseph W. Eichenbaum, M.D.**

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## FOREWORD

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In the epidemic of Retinopathy of Prematurity (ROP) in the early 1950s, overuse of oxygen was identified as the major cause of the disorder. It is significant that during the epidemic, very low birth weight infants, those with markedly immature retinal vessels and hence greater susceptibility to ROP, rarely survived. With modern neonatal intensive care, including arterial blood-gas monitoring and other sophisticated measures, a significant population of these infants with very immature retinas and high risk for ROP are surviving. ROP is occurring in this new population of high risk, small premature infants in spite of the most meticulous monitoring of oxygen.

Recognizing that a significant number of new cases of ROP are developing, the authors present a useful update on treatment and address several key aspects of ROP. These include a historical overview by Dr. Joseph Eichenbaum and a special chapter on medicolegal aspects by Dr. Alfred Mamelok.

Dr. John Flynn, who has contributed so greatly to the modern understanding of ROP, has written a chapter on the clinical overview of the disorder. Current concepts on the natural history, suggested pathogenesis, and the new international classification are included.

Drs. Harvey Topilow and Albert Ackerman have provided chapters on the rationale for cryotherapy and present their experiences in the use of cryotherapy for advanced stage 3 ROP.

For the first time since Terry's original identification of ROP in the early 1940s, a successful form of treatment has been conclusively documented. The multicenter national clinical trial on cryotherapy provided the large sample size necessary to confirm the studies of several individual investigators who reported on this method of treatment. Cryotherapy reduced the incidence of adverse outcome from severe ROP by approximately 50% in the collaborative study. Dr. Rand Spencer, a principal investigator in the study,

has summarized the findings and recommendations from this collaborative effort.

Dr. Rainer Mittl has provided an update on vitrectomy surgery, which permits the treatment of the more advanced stages of ROP. Dr. Juan Orrellana has presented chapters describing scleral buckling for stages 4 and 5 ROP and the "open-sky" vitrectomy technique for stage 5 disease.

The authors are to be congratulated on this useful contribution to the contemporary management of ROP.

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## PREFACE

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Retinopathy of prematurity (ROP), or retrolental fibroplasia as it was originally named, has had a most curious life span as a twentieth century disease. The enigmatic findings of the disease, with scar tissue behind the neonate lens associated with retinal detachment, have been responsible for the two largest “epidemics” of blindness in neonates in modern times. These outbreaks of the disease occurred approximately 25 years apart, in the mid 1950s and late 1970s. Initially, excessive oxygen use in the newborn nurseries was implicated as the cause of the disease. However, just as the directives against hyperoxic therapy were known to have been enforced, a new ROP epidemic in the late 1970s surfaced. Restricting oxygen in neonates was also shown to result in increased brain damage in infants. Neonatologists, pediatricians, obstetricians, and ophthalmologists have recently attempted to view the disease as a problem of prematurity itself. Nonetheless, the literature is replete with exceptions. Many reports cite ROP in full-term infants. Certain studies suggest the efficacy of vitamin E in treating the disease; others deny any statistically significant role of the vitamin. Retinal buckling, drainage of subretinal fluid, and cryotherapy seem to offer hope. Their application, timing and relationship to the mechanisms of the disease, however, remain controversial. Thus in the last 45 years, although much has been written about the cause and therapy of ROP, little is actually understood.

Despite this woefully puzzling predicament over the state of our medical knowledge, malpractice suits relative to administration of oxygen in infants over the last 25 years have been legion, with awards into the millions of dollars. Cases are still being brought to trial regarding optimal therapy. Yet many of our newer concepts of understanding, managing, and treating ROP have barely achieved clinical recognition and acceptance.

It was with the concept of our uncertainty as clinicians and the lack of clear understanding of the cause and management of ROP that the editors



met to discuss the contents of this text. The medical as well as the legal literature was reviewed to highlight what has been learned from medical research and what telescoped into the courtroom. Experts in vitrectomy, retinal buckling, and cryotherapy were asked to write on their experiences and strategies in ROP. *Therapy of Retinopathy of Prematurity* presents the history of ROP, the frustrating medicolegal implications, and the controversial management of this disabling disease, along with hope of providing a stepping stone to further understanding.

**Joseph W. Eichenbaum, M.D.**

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*I wish to acknowledge my gratitude to Ms. Belinda Daniel for her typing of many portions of the text and for her careful and considerate suggestions, perseverance, and devotion.*

*Many thanks to my wife, Dr. Annette Eichenbaum, for her understanding, patience, and support as well as timely review of statistical material.*

*Many thanks to my co-editors, Drs. Mamelok, Mittl, and Orellana, whose insights and judgments made this text possible.*

*I wish to express my sincere gratitude to Dr. Arnall Patz for reviewing large portions of this manuscript and for providing additional historical information as well as suggestions on various chapters of the text. I thank Dr. Richard Green for providing didactic photomicrographs from his work on ROP. Special thanks to Dr. Steven Podos for reviewing the entire manuscript.*

*Last, but not least, I would like to express my appreciation to my children, Kenny and Gary, whose simple but loving and gentle support of the project helped make it all worthwhile.*

**Joseph W. Eichenbaum, M.D.**

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## Medicolegal Aspects of Retinopathy of Prematurity

Alfred E. Mamelok, M.D.

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Since the mid-1950s, there has been an explosion of malpractice actions against physicians who treat retinopathy of prematurity (ROP). In many cases, similar actions have been taken against hospitals and manufacturers of appliances, including devices that supply oxygen and control humidity in incubators.

Most of these cases were based on the findings of the National Cooperative Study of 1953–1954. Studies during that era demonstrated a generally increased risk of retrolental fibroplasia (RLF) among infants treated in a high-oxygen group, compared with infants given limited oxygen. This fact was given much play in the medical and lay press and other media, alerting a good percentage of the victims of this disease or their parents to the possibility of litigation. As will be shown below, most of the cases cited “improper administration of oxygen” to the claimant. That analysis of the data also repeatedly showed that some babies in the low-oxygen groups went on to develop RLF, whereas many in the high-oxygen group had no signs of the disease, which is almost never mentioned when these malpractice cases are reviewed. Nor has it been mentioned, as one study showed, that there is no single arterial oxygen tension level at which premature infants will uniformly show changes of ROP; this implies that there is no uniform level at which this disease will develop. Why certain premature infants are more susceptible to the disease than others remains one of many questions still unanswered.

Lucey and Dangman reviewed the subject in the latter part of 1983<sup>1</sup> in a comprehensive article that concluded that RLF should not be considered an avoidable iatrogenic disease in very low birth weight infants, and that its

cause in these infants is not known. They postulated that it is probably incorrect to make the assumption that "excessive" use of oxygen in treating prematurely born infants is the cause of this disease. They cited three prospective controlled studies and one large retrospective review as demonstration of their position. They pointed out that when the experiences of the four original studies were combined, 37% (51/137) of the high-oxygen group of infants did not develop RLF, while 22% (89/407) of the low-oxygen group of infants did develop the disease. Further, they located 95 infants of low birth weight who never received oxygen but nevertheless developed ROP. They pointed to one study which produced evidence suggesting that lack of oxygen, rather than excess oxygen, might be the cause.

Another study showed increased risk for the disease among infants who received exchange transfusions. One study analyzed several cases of unilateral RLF or marked discrepancies in the severity of the disease between the two eyes in human infants, which is inconsistent with a simple, generalized, toxic (hyperoxic) etiology.

Other questions such as the role of vitamin E have received much attention in the medical literature and much controversy still surrounds this aspect of the problem. As the results of studies and research proliferate, the work of plaintiff malpractice attorneys will become more difficult, if not impossible, until a true breakthrough occurs in prevention.

Because the number of premature infants saved at lower and lower birth weights continually increases, we can expect the problem to remain with us for a long time.

Attorneys need established facts, statutes, and precedents in order to successfully argue their cases before judges and juries. Perdue, an attorney writing in the textbook, *Retinopathy of Prematurity* by McPherson, Hittner, and Kretzer<sup>2</sup> states:

If qualified medical experts are willing to present the necessary scientific knowledge, a medical standard may be established to the law's satisfaction. In the area of retinopathy of prematurity, this could involve claims for damages arising from improper oxygen therapy; withholding vitamin E prophylaxis; for death or hepatic failure as a result of using vitamin E, not F.D.A approved; for late retinal screening, so that cryotherapy could not be properly applied; and for withholding cryotherapy.

In malpractice litigation involving cases of retinopathy of prematurity, this would be the plaintiff lawyer's dream, but as is obvious from the above, from a general review of the literature, and in other parts of this book, the necessary scientific knowledge is nowhere near being established, and such a medical standard cannot be established to the law's satisfaction.

Nevertheless, in the arena of malpractice litigation, high awards have been granted where even the defendant admitted negligence by "prolonged

exposure to relatively high concentrations of oxygen.” This is illustrated in *Penetrante v United States*<sup>3</sup> (Table 1–1, case 14), in which awards of \$2,292,123 to one twin and \$900,000 to the second twin were made by the United States District Court in a nonjury retrial. How relatively high the concentration of oxygen was and the details of the monitoring were not mentioned. Interestingly, one twin was extremely bright intellectually, while the other, who was totally blind and who received the larger award, was severely mentally retarded. No mention was made about whether the mental retardation was the result of lack of sufficient oxygen. Is there a trade-off between cerebral damage and eye damage, especially when we cannot prove the eye damage is simply caused by “excess oxygen”? In the legal analysis of these cases, the traditional medical concept of risk vs. benefit becomes the issue. A fascinating aspect of this case is that the defendant admitted negligence and presented no evidence in his defense, despite the many articles in the literature and the research studies that questioned the role of oxygen as a sole etiology of ROP. This gave the plaintiff attorneys an opportunity to produce expert medical testimony by an ophthalmologist, a neurologist, and a clinical psychologist. The ophthalmologist testified that the second infant, who was blind in the right eye, had vision of 20/50 in the left eye when his head was turned to a degree when he attempted to read the eye chart, and that he was more likely by 20% to have a retinal detachment in the left eye in his later years. If this did occur, the best result would be a failure of the retina to reattach, such that no vision in the left eye could exist. The ophthalmologist further testified that the second twin was directed to avoid all contact sports and other activities which could cause jarring of the head, that he would be unable to obtain a driver’s license or a license to drive for hire, and that his range of future employment possibilities would be limited accordingly. The neurologist testified that the second infant was not well-coordinated, and had difficulty doing chores his peers might perform. While his intelligence was judged normal, if not superior, serious psychological problems were anticipated according to the results of psychological tests. On appeal, the appellate court held that “the award for damages was not excessive nor shocking.”

In the case of *Burton v Brooklyn Doctor’s Hospital*<sup>4</sup> (Table 1–1, case 18), the allegation was that a baby who was five to six weeks premature developed RLF as a result of being exposed to a “high oxygen state” for 28 days in an incubator, causing irreversible blindness. Except for faint light perception in his left eye, the plaintiff was totally blind. His attorneys alleged that he suffered daily pain and irritation which had worsened in recent years. An opinion was rendered that because his eyes were shrinking, they would have to be enucleated and replaced with plastic eyes. At the trial, the jury found for the plaintiff, awarding him \$2,887,000 in damages. This amount was

**TABLE 1-1.**  
Cases Involving Administration of Oxygen to Premature Infants

| Case   | Dates   | Issues   | Outcome   |
|--|---|--|---|
| 1. <i>Toth v Community Hospital at Glen Cove</i><br>22 NY 2d 255<br>(NY App)   | July 6, 1965: NY Supreme Ct, Trial Term, Nassau Co.<br>July 10, 1967: App Div 2d Depart.<br>July 5, 1967: Court of Appeals. | RLF and blindness allegedly caused by improper oxygen administration by ophthalmologist, pediatrician, and hospital.   | 1. Complaints dismissed. Jury verdict in favor of pediatrician and ophthalmologist.<br>2. Divided court in appellate division.<br>3. New trial against hospital and pediatrician but not ophthalmologist ordered by court of appeals. |
| 2. <i>Swank v Hallivopoulos</i><br>108 NJ Super 120<br>(NJ Super Ct App Div)   | Argued November 24, 1969: NJ Super Ct.<br>Decided December 29, 1969, by App Div.  | Administration of excess oxygen to plaintiff, allegedly causing RLF (less than 40% administered and only for 5 days).  | Verdict for the defendant. Affirmed on appeal.  |
| 3. <i>Hule v Newcomb Hospital</i><br>112 NJ Super 429<br>(NJ Super Ct App Div) | Argued November 23, 1970.<br>Decided December 7, 1970 (Super Ct, Law Div).  | Order requiring defendant physician to produce and submit for examination by plaintiff's attorney an article previously prepared for publication by physician. Physician appealed. Original action against physician and hospital for injury and disability sustained by infant by reason of allegedly negligent administration of oxygen. | Superior court entered order requiring physician to produce article. Order affirmed by appellate division.  |
| 4. <i>Siirila v Barrios</i><br>66 WI 2d 394<br>(WI Supreme Ct)                 | February 4, 1975.   | Loss by parents of child's aid, comfort, society, and companionship as a result of injuries sustained allegedly by administration of excess oxygen causing RLF.  | Circuit court, Milwaukee County, ruled for defendant.<br>Reversed by Supreme Court.   |



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|--|--|--|--|
| 5. <i>Kanon v Brookdale Medical Center</i><br>87 Misc 2d 816<br>(Supreme Ct Special Term Kings County, Part I) | November 5, 1975.  | Amendment by plaintiffs of their complaint of medical malpractice in cases of RLF in premature infants born between 1953 and 1975 to include class action allegations and to add additional party defendants.  | Motion denied.   |
| 6. <i>Poulin v Zartman</i><br>Nos. 2120, 2127<br>(AK Supreme Ct)   | November 12, 1975.                                       | Titration technique of oxygen administration. Proper treatment of jaundice and brain damage. Respiratory distress syndrome. Lack of prenatal care. Background of father. Informed consent. Proof of insurance. Violation of duty by certain jurors. Supervision. | Superior court entered judgment on verdict against plaintiff. Supreme court affirmed in part and reversed in part, remanding new trial regarding issue of proper supervision. ("Issue of methodology and informed consent may not be retried."). |
| 7. <i>Siirila v Barrios</i><br>398 MI 576 No. 11<br>(MI Supreme Ct)  | December 21, 1976.                                       | Continued exposure to oxygen of premature infant in an isolette as cause for RLF and permanent blindness.  | Judgment for defendants, a general practitioner and a hospital, upheld by court of appeals, 58 MI App 725, 228 N.W. 2d 801, and affirmed by Supreme Court.   |
| 8. <i>Quick v Aetna Casualty &amp; Surety Co.</i><br>No 13251<br>(LA App 2d Cir)                               | May 23, 1977.<br>En Banc rehearing denied June 22, 1977. | Improper administration of oxygen to child while in incubator.   | Plaintiff denied by expiration of statute of limitations by first judicial Court. Affirmed by court of appeals.  |
| 9. <i>Greenberg v Bishop Clarkson Memorial Hospital</i><br>201 Neb. 215 No. 41477<br>(NE Supreme Ct)           | June 21, 1978.   | Proper use of oxygen in case of respiratory distress developing RLF. Inadequate number of nurses in special nursery.   | District court entered judgment for defendants. Supreme Court affirmed in part regarding nurses and instruction of jury summarizing allegations in one instruction but reversed and remanded on instruction that testimony of disa-              |

(continued)