The Role of Oxygen in Retrolental Fibroplasia

E. Mead Johnson Award Address

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In presenting an E. Mead Johnson award to Dr. Patz, Dr. Bakwin, President of the Academy, made the following remarks: "Dr. Arnall Patz, Recipient of the Second E. Mead Johnson Award, was born in Elberton, Georgia, in 1920. He attended Emory University at Atlanta and graduated from the Medical School at that University in 1945. Dr. Patz interned at Sinai Hospital in Baltimore; served in the Medical Corps of the Army for 2 years; following which he became resident in Ophthalmology at the District of Columbia General Hospital. In 1950 and 1951 Dr. Patz was Research Fellow in Ophthalmology at the Armed Forces Institute of Pathology.

"Dr. Patz is certified by the American Board of Ophthalmology and serves as an instructor in Ophthalmology at Georgetown University and Johns Hopkins University. During the past 9 years Dr. Patz has published 15 papers, 10 of them relating to his clinical studies, backed up by animal experimentation, which have clearly demonstrated the adverse effects of oxygen administration in relation to retrolental fibroplasia in small infants. No one in this country has been more influential in solving the problem of retrolental fibroplasia than Dr. Patz. His contributions are considered to be a beautiful exercise in experimental medicine, the more noteworthy because he made them while engaging in the private practice of ophthalmology.

"It is for these works that the Academy's Committee on Awards has selected Dr. Patz as the recipient of an E. Mead Johnson Award for 1956. This award consists of a handsome scroll and a check for $1000 which we take pleasure in now presenting to Dr. Patz.

"Dr. Patz will honor us by giving a résumé of his work which has contributed so much to pediatrics."

Dr. Patz: "I should like to express my thanks to the American Academy of Pediatrics for the honor you have accorded me. As an ophthalmologist it is particularly gratifying to know that the work done in conquering retrolental fibroplasia has received recognition from this distinguished group.

"Although I have been named as the recipient of this award, it is, in fact, a tribute to all the prominent scientists who have contributed to the ultimate victory against retrolental fibro-
plasia. The work of Owens and Owens in identifying the true clinical course and of Friedenwald and Reese in clarifying the histopathology of the disease deserve special recognition. Important contributions have been made by Boe Hällström and Lars Gyllensten of Sweden, Norman Ashton and Mary Crosse of England, Kate Campbell of Australia, Harry Gordon, Everett Kinsey, and Jonathan Lanman of this country, and several others.

"I have been fortunate in having a loyal group join me in these studies. Dr. Leroy Hoeck has collaborated in the nursery study. Dr. Edgar de la Cruz and Dr. Thomas Kleh assisted in the eye examinations. Mrs. Ann Eastham, Dr. Miriam Beiner and Dr. Don Higgenbotham contributed to the animal studies. In accepting this award I thank you in the name of my entire research team and I thank you for the privilege of addressing this assembly."

Observations on the role of oxygen administration in retrolental fibroplasia (RLF) have been conducted in the premature nursery of the District of Columbia Hospital with Dr. Leroy Hoeck, Department of Pediatrics, since 1948. Our attention was first focused on oxygen by one of our first cases of RLF occurring in an infant where special measures were utilized to deliver a high oxygen concentration for several days after birth. This incidental observation suggested, what then appeared an extremely remote possibility, that oxygen therapy might in some way be related to the disease.

The infants in the premature nursery were examined at intervals in the nursery and afterwards in a special clinic during a period between July, 1948, and December, 1950. However, during this period, there were no rigid controls on oxygen administration and indeed the only recording of oxygen that was available for some premature infants was that on the nursing notes where the number of days of oxygen therapy was recorded; occasionally the flow rate was also mentioned.

Even from this poorly supervised method of administering and recording oxygen administration, there was noted a strong association between the number of days of oxygen therapy and incidence of cicatricial RLF. Chart I summarizes these uncontrolled data collected between July, 1948, and December, 1950, and shows the correlation between number of days of oxygen therapy and incidence of retrolental fibroplasia (residual membrane cases only).

In 1949, Kinsey and Zacharias reported that three changes in pediatric care, namely, addition of iron medication, use of watermiscible vitamins and increased use of oxygen were associated with the increased incidence of RLF. I think it is fair to state that between 1948 and 1950 most pediatric and ophthalmologic authorities did not consider that overuse of oxygen was related etiologically to retrolental fibroplasia in spite of this epidemiologic report. Because of this lack of suspicion of oxygen by leading authorities on the subject, it was extremely difficult to convince ourselves of the justification of restricting oxygen for a certain number of infants, as would be necessary in a controlled randomized study.

Fortunately for us, Dr. Harry H. Gordon, then Professor of Pediatrics at the University of Colorado, spoke before the pediatric staff of the Johns Hopkins Hospital in November, 1950. He stated that at the Premature Center of the Colorado General Hospital, oxygen therapy routine was curtailed considerably for several months, and coincidental with this change in policy a sharp decrease in RLF cases occurred. Of more importance to us, he reported that during this period the smaller premature infants were apparently thriving with much less added oxygen, as they used to do before efficient methods of giving high concentrations of oxygen were available. This gave us the first reassurance that a rigid curtailment of oxygen might be a safe procedure. In January, 1951, our controlled study was started, placing alternate infants under 3.5 lb birth weight, into either a "high" or "low" oxygen routine. It was still with considerable anxiety on our part that the small infants who drew a "low" oxygen routine were entered into that regimen in the study. The nursing staff also shared this anxiety and it was not uncommon, early in
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the study, to find that the night nurse had turned the oxygen on or increased that already flowing to an infant in the "low" group, just to feel more secure.

The controlled study was carried out in the nursery from January, 1951, until May, 1953. At this latter date, we first observed in our laboratory ocular lesions that were indistinguishable from those of early human RLF following the administration of oxygen to young animals. Our controlled nursery data involving 120 infants under 3.5 lb birth weight implicated oxygen and, with the added incrimination of oxygen from the animal data, we felt that our own controlled study should be terminated. A brief résumé of the nursery study which has been previously reported is cited.

PREMATURE NURSERY STUDY

With five exceptions all infants included in the controlled investigation were delivered in the District of Columbia General Hospital Obstetrical Division. Premature infants with birth weights under 3.5 lb (1,590 gm), entered the study during the first year and under 3 lb 5 oz (1,500 gm) during the second year.

On an alternate admission basis, the infants were placed into either a high oxygen group or a curtailed oxygen group on admission to the nursery. Those infants in high oxygen received 60 to 70% oxygen concentrations for 28 days or longer; whereas, those in restricted oxygen received concentrations usually under 40% and only for specific clinical indications. The nursery routine was otherwise identical in the two groups.

Oxygen tensions were controlled by incubator samplings at 8-hour intervals with a paramagnetic analyzer (accurate within 2% concentration).

The infants in each group were examined ophthalmoscopically at regular intervals and followed after discharge from the nursery in a special clinic until they were 6 months of age.

The ocular findings were classified to conform to the standard classification recom
mended by Reese, Owens, and King. Chart II shows the number of cases in the controlled study developing advanced residual retrolental membranes (cicatricial stages C, D, and E) according to birth weight after dropping the 15 infants over 1,500 gm in the first year. From this chart one notes that 12 of 60 infants with birth weights under 1,500 gm in the high oxygen group developed advanced retrolental fibroplasia. In the curtailed oxygen group, 1 of 60 infants developed the advanced disease. This infant, however, received oxygen for 10 days.

There was no indication of any pediatric difficulties arising from the rigid curtailment of oxygen administration. No significant difference in mortality rate was noted between the infants in the high and in the low oxygen groups.

A statistical appraisal of the data obtained in the first 24 months of the controlled randomized study based on these 120 infants shown in Chart II shows a chi² of 1.44 with a p-value of 0.01.

During the controlled study 21 cases of active disease (active stages 1 and 2) which regressed to normal in the high oxygen group and 9 cases of active disease (active stages 1 and 2) which regressed to normal in the low oxygen group were noted.

This controlled nursery data is now supported by the controlled study of Lanman and co-workers and the larger co-operative study of Kinsey and associates. There are also several excellent nonrandomized studies further incriminating oxygen in the etiology of retrolental fibroplasia. The report of Gordon and co-workers, who received special mention in view of the long follow-up and large number of cases involved.

**EXPERIMENTAL OBSERVATIONS**

We were most fortunate in the experimental phase of this study in finding that at birth the retinas of mouse, rat, kitten and
dog were incompletely vascularized and differentiated so that we were dealing with retinas comparable to that of the small premature infant as depicted in Figure 1. Several experiments were then instituted in 1951 to evaluate primarily the ocular, but also the systemic effects of added oxygen on these species. The newborn opossum in the pouch stage was also studied. Due to many pitfalls and failures it was not until May, 1953, that the animal counterpart of human RLF was successfully produced.

The greatest obstacle during the early experiments was pulmonary oxygen poisoning in the nursing mother animals. It is well established that oxygen above 70% concentration after 48 hours causes irritation of the adult human or animal pulmonary alveolar epithelium. Pulmonary edema, hemorrhages and ultimate asphyxia result from the pulmonary engorgement. The alveolar epithelium of the newborn animal or premature infant is much more resistant to the pulmonary toxicity of oxygen, and these young subjects can withstand oxygen at 70% to 100% concentrations for much longer periods without alveolar damage resulting. Several months lapsed before a satisfactory solution for protecting the mother against pulmonary oxygen poisoning evolved. This was accomplished by maintaining a nursing mother animal with her young in room air for every litter in the oxygen chamber. At 24-hour intervals the mother animals in oxygen were exchanged with those in room air. This provided a 24-hour rest in air and eliminated pulmonary oxygen poisoning in the mothers. A healthy foster mother animal was then always available to nurse the young animals which were maintained continuously in oxygen. In some experiments the young were divided between the two mothers at the start so that each mother animal was assigned half her own litter and half of her control partner's litter. This provided litter mates as controls and insured practically identical nutritional factors from maternal lactation in oxygen treated and control young animals in air (Fig. 2). The opossum in the pouch stage was studied in view of the extreme prematurity of newborn pouch opossums. The newborn opossum is known to enter the maternal pouch in an extremely premature state and incubate there for several weeks. However, the mother animals showed a
very marked susceptibility to pulmonary oxygen poisoning and a system of exchanging foster mothers which worked with other species failed. Sixty-nine opossum young (eight litters) who had received from 3 to 5 days exposure to 70% oxygen showed no significant changes in the eyes or other organs when compared with controls.\textsuperscript{13} Longer exposures were impractical due to pulmonary changes in the mothers.

In the mouse, rat, kitten and puppy, the characteristic microscopic changes of early human retrolental fibroplasia were produced.\textsuperscript{1} These changes (Figs. 3 to 14) consisted of:

1. Endothelial nodules in the nerve-fiber layer of the retina.
2. Budding of capillaries from the retina into the vitreous with formation of capillary tufts.
3. Retinal edema.
4. Retinal and intraocular hemorrhages.
5. Vitreous degeneration.

It is important to point out that the experimental retinal lesions produced are indistinguishable histologically from those seen in the retina of early human RLF. Indeed, under high power magnification where other landmarks are not available to identify the species, one cannot distinguish the endothelial proliferating nodules of the human disease from those seen experimentally produced by oxygen in the animal retina. These experimental lesions are located in exactly the same layers of the retina, have identical histochemical response to periodic acid fuchsin stain and proceed in a similar manner of proliferating capillaries from the retina into the vitreous as is seen in human disease. Hemorrhages are readily observed, but not usually to the degree seen clinically. One minor inconsistency, however, in these animal experiments is that the terminal stage of retinal detachment of the human disease has not been produced except in two puppies in our laboratory.\textsuperscript{3} This extremely low incidence in several hundred animals exposed to oxygen raises the question of trauma or other undetermined factors being involved in these two cases.

It is pertinent, however, that Friedenwald, Owens and Owens\textsuperscript{14} described the proliferative endothelial retinal nodules and sprouting of capillaries into the vitreous as the essential characteristic pathology of human retrolental fibroplasia. They considered the stage of detachment of the retina as non-
Fig. 3 (Upper). Cross-section of retina of normal 21-day-old mouse. Note relatively acellular character of the nerve-fiber layer. (Hematoxylin-eosin; ×400.)

Fig. 4 (Lower). Section of retina of 21-day-old mouse raised in 70% oxygen since birth. Arrow points to abnormal proliferating endothelial nodules in the nerve-fiber layer. (Hematoxylin-eosin; ×400.)
specific resulting from organization of hemorrhage and vessels in the vitreous which detached the retina from its normal position. The close identity of oxygen-induced animal lesions to the primary pathognomonic lesion seen in human RLF is therefore highly significant and should give us confidence in applying data learned from animal experimentation to problems of human RLF.

It is indeed most remarkable that in species as far removed as the mouse and human that the identical histologic picture in both is produced by oxygen. Equally astounding is that the animal lesions like those in infants are limited exclusively to the eyes, are directly proportional to concentration and duration of exposure to oxygen, and depend in both cases on an incompletely vascularized retina for their production.

Representative photomicrographs of the human and animal lesions are presented in Figures 3 to 8. Retinal sections of normal premature infants and animals are shown for control purposes. Note the location of the characteristic endothelial nodules in the nerve fiber layer in infant and animal eyes. (Figs. 4 and 6) and the similar appearance of vessels erupting from retina into the vitreous (Figs. 7 and 8).

Independent animal data is now available from three other laboratories. Ashton and co-workers in England, Hellström and Gyllensten in Sweden and Gershman and co-workers in this country, have contributed important data to further support the conclusions drawn from the experiments cited here. The studies of Ashton on retinal vasocostriction and Hellström on retinal enzymes deserve special recognition.

**MECHANISM OF ACTION OF OXYGEN**

Fundamental to an understanding of the reaction of the retinal vessels to oxygen exposure is an appreciation of the mode of vascularization of the retina. The retina is unique in that it is well differentiated before having a definitive blood supply of its own. In the human, the retina is avascular until the fourth month of gestation, deriving its nutrition from the embryonic hyaloid vessels in the vitreous and by diffusion from the adjacent choroid. Starting at the fourth month, the vessels from the hyaloid vascular stalk in the optic nerve extend into the adjacent retina about the optic nerve and grow forward toward the anterior extremity of the retina (ora serrata). It is not, however, until the eighth month of gestation that the vessels reach the ora serrata (Fig. 1). Therefore, a premature infant born at 7 months gestation has the anterior portion of his retina still devoid of vessels. This avascular portion then becomes vascularized ex-utero. It is the incompletely vascularized retina of the premature infant that is susceptible to oxygen damage. Once vascularization is complete, added oxygen exerts no injurious effect on the retina. Indeed the common denominator in all our animal experiments—mouse, rat, kitten and puppy, has been the uniform susceptibility of the animal retina to oxygen while incompletely vascularized and the resistance to oxygen damage once vascularization is complete. The correlation between RLF incidence in our nursery and estimated growth of retinal vessels is seen in Figure 15. This susceptibility of immature retinal vessels is comparable to the greater susceptibility of growing bone to vitamin D. One might reason that just as rickets and scurvy are diseases of growing bones, so retrolental fibroplasia is a disease of growing retinal vessels.

The effects of oxygen on the immature retina can be divided into two phases: 1. A primary or initial vasoconstrictive effect; during this phase there is also a suppression of vascularization anteriorward. 2. A secondary or late proliferative phase.

The initial effect of oxygen is one of immediate vasoconstriction. In the normal adult retina or cerebrum, administration of oxygen at concentrations above 50% causes a slight (approximately 10 to 20%) decrease in caliber of the vessels. In contrast, the immaturesly vascularized retinal vessels in the animals studied undergo a rapid pronounced constriction when these con-
Fig. 5 (Upper). Cross section of retina of normal infant, aged 10 weeks. Note normal appearance of capillaries in the nerve-fiber layer. (Hematoxylin-eosin; ×400.)

Fig. 6 (Lower). Cross section of retina of 11-week-old infant in whom early active retrolental fibroplasia was diagnosed clinically. Arrow points to abnormal endothelial nodule characteristic of early human disease. (Hematoxylin-eosin; ×400.)
FIG. 7 (Upper). Twenty-four-day-old kitten raised in 70% oxygen from fourth day of life. Arrow points to capillaries proliferating from retina into the vitreous. Note similarity of this lesion to human case shown in Figure 8. (Hematoxylin-eosin; India-ink injected specimen; ×400.)

FIG. 8 (Lower). Section of retina of 14-week-old premature infant with early active retrolental fibroplasia diagnosed clinically. Arrow points to capillaries budding into the vitreous from the retina. (Hematoxylin-eosin; ×400.)
Fig. 9 (Upper). India ink-injected retina of normal 21-day-old kitten. Note normal pattern of vessels and vascularization of retina is complete to the ora serrata. The retina is cut radially to permit flat preparation (×8.)

Fig. 10 (Lower). Flat retina preparation from 33-day-old kitten exposed to 70% oxygen for first week of life, then removed to room air. Note abnormal pattern of retinal capillaries with numerous tuft formations. (Unstained preparation; ×20.)
Fig. 11 (Upper). Flat retina preparation of 18-day-old rat raised in 70% oxygen from birth. Arrow points to large retinal hemorrhage. (Unstained preparation; ×100.)

Fig. 12 (Lower). Flat retina preparation of 16-day-old rat maintained continuously in 70% oxygen from fourth day of life. Arrow points to abnormal capillary tufts resembling glomeruli. (Unstained preparation; ×100.)
Fig. 13 (Upper). Normal litter-mate control to animal in Figure 14; 21 days of age, raised in room atmosphere. Note clear homogeneous pattern of vitreous and absence of hemorrhage. The hyaloid vessels have regressed. (Hematoxylin-eosin; ×40.)

Fig. 14 (Lower). Twenty-one-day-old mouse eye exposed to 60% oxygen first 6 days of life and removed to room air for 15 days. Note abnormal persistence and dense proliferation of hyaloid vessels (H.V.). The vitreous is grossly disorganized and partially filled with hemorrhage (H). Hematoxylin-eosin; ×40.)
centrations of oxygen are administered. Why immature retinal vessels undergo total constriction and the mature retinal vessels only minor constriction on exposure of the subject to oxygen remains a mystery. Several experiments were done in our laboratory in an attempt to throw light on this enigma. The results of these studies are briefly enumerated:

1. Sympathectomy in puppies prior to oxygen exposure; results—no effect on retinal vasconstriction produced by oxygen.
2. Vasodilator drugs—no effect on retinal vasconstriction produced by oxygen.
3. Massive doses of vitamin E, an antioxidant—no effect on retinal vasconstriction.
4. Cobalt chloride, based on Dickens studies that cobalt protected brain slices from oxygen poisoning—no effect on retinal vasconstriction produced by oxygen.
5. Combining 5% carbon dioxide with 95% oxygen—no change in retinal vasconstriction. Yet in the same animal the carbon dioxide effect predominated over oxygen elsewhere and a visible vasodilatation resulted in the cerebral vessels as seen through a cerebral window. One might suspect that this exaggerated vasoconstrictor response to oxygen occurs in all immature vessels. Ashton and co-workers studied the effect of oxygen on the new vessels in granulation tissue of the rabbit and in new vessels in the rabbit cornea where vascularization was stimulated by foreign material injected into the anterior chamber. In neither case did a significant degree of vasconstriction follow administration of oxygen. We must conclude that the marked vasoconstrictive response of the immature retinal vessels is unique and not simply a property of immature vessels.

Our experiments with an oxygen electrode placed at the internal surface of the retina gives one clue to the vasoconstrictor question. Following severance of the retinal artery in the cat the retinal blood flow was totally eliminated. When the animal breathed oxygen, the range of oxygen diffusion from the choroid was extended to reach the internal layers as shown polarographically with the electrode. This kept the internal retinal layers oxygenated even though retinal blood flow had ceased. Choroidal diffusion of oxygen apparently furnishes the means of sustaining the vasoconstriction that occurs in the immature retinal vessel on oxygen exposure. If the
immature retina is detached from the choroid while the animal is in oxygen, the constricted vessels in the detached portion dilate immediately whereas in the intact retina, in its normal position against the choroid, the vessels remain in a state of vasoconstriction.

Still unanswered is why the immature retinal vessel totally constricts on inhalation of oxygen while the retina that has just become fully vascularized fails to show this marked vasoconstriction to oxygen. Animal experiments show that where the exposure to oxygen is of relatively short duration, the vasoconstrictive effect of oxygen is reversible. However, if vasoconstriction following exposure to oxygen lasts for approximately 2 days or longer, a true obliteration of some of the smaller vessels occurs. Ashton has suggested that the opposing endothelium of the vessel walls becomes adherent or an intravascular clotting occurs with obliteration of the lumen. It is apparent that during the phase of vasoconstriction and obliteration a decrease in retinal blood flow results. One can assume that all blood-borne constituents, e.g., glucose, normally supplied by the retinal vessels are thereby depleted. Also diminished retinal blood flow favors an accumulation of metabolic end-products, e.g., lactic acid, in the retina. The primary or initial effect of oxygen leads to the later proliferative or secondary stage which appears to be a compensatory overgrowth of the remaining retinal vessels to the depleted retina.

The secondary or later vasoproliferative phase may occur under two circumstances. First, proliferation can occur while the infant or animal is kept in oxygen continuously for a prolonged period. The secondary or late proliferative phase may also occur where vaso-obliteration has been initially produced by oxygen and the infant or animal removed to room air while some of the retinal vessels are still obliterated. An abnormal proliferation of the remaining capillaries results. The removal to air may theoretically add an oxygen deficit to the retina already depleted by vasoconstriction of its normal blood-borne constituents. A schematic representation of the primary vasoconstrictive phase and the secondary proliferative changes is presented in Figures 16 and 17.

Hellström has studied the in-vitro metabolism of the retina of oxygen exposed rats and found no change suggesting a metabolic injury of respiration of the retina in his oxygen treated animals. Likewise he found in histochemical studies that there was no evidence of a change in the

**Effect of Oxygen in RLF**

![Diagram showing primary and secondary stages of oxygen effect on retina.](image)

**Fig. 16.** Note in the primary stage that the retinal vessels are markedly constricted. In the secondary stage proliferating capillaries in the retina erupt through the retinal surface into the vitreous.
localization of succinic dehydrogenase activity following oxygen exposure. He has stated that his studies are not adequate to rule out conclusively a direct histotoxic effect of oxygen at the cellular level. Further studies are needed along these lines in view of the well established histotoxic effect of oxygen based on studies of Stadie, Dickens, Bean and Gersham.

It is important to translate these animal observations to clinical findings. The stages of retinal vasoconstriction and obliteration seen in experimental animals is also seen in the eyegrounds of premature infants. However, the standard classification of Reese, Owens and King which is now in widespread usage includes only the secondary proliferative retinopathy. This is readily explained by the origin of this classification which is based on the changes that are clinically observed from about the third week of life. However, in our nursery study where the eyegrounds were examined during the first few days of life, a large number of infants showed marked generalized retinal vasoconstriction while receiving oxygen. As retinal vasoconstriction is fundamental to the development of retrolental fibroplasia, the observation of advanced retinal vasoconstriction that persists while the infant is out of the incubator for examination should be considered as a preliminary stage of the classic disease. It is impractical to add another stage to the five now in use as they have already furnished an excellent standard for mass quantitative study. However, the observation of markedly constricted retinal vessels should certainly alert the examiner to the possible later development of proliferative retinopathy.

The larger vessels near the optic disc are usually not completely obliterated by oxygen during the initial exposure to oxygen and they undergo a marked dilatation and increased tortuosity during the proliferative phase. New vessels are seen in the peripheral sprouting from the retina into the vitreous. Apparently these new vessels and the existing older vessels are abnormally permeable, as hemorrhages and edema usually follow. Organization of the hemorrhages and vessels that have invaded the vitreous produce traction on the retina with detachment resulting. The leakage of serum or hemorrhage behind the retina augments detachment (Figs. 18 and 19).

**FACTORS INFLUENCING OXYGEN ACTION ON THE PREMATURE RETINA**

**Duration of Exposure:** Of all factors influencing the amount of oxygen damage to the premature retina, duration of exposure has been affirmed experimentally to be the principal one. Recent experiments on newborn mice in our laboratory show that even where concentrations of 35 to 40% oxygen (supposed safe levels of oxygen therapy) are given for periods of 10 days, a significant number of the animals showed ocular hemorrhages and other evidence of damage from the oxygen exposure (Table I). Yet for shorter exposure these concentrations produced no visible effect whatsoever.
on the immature retina. It is possible that the premature infant is even more sensitive to oxygen damage. Where high concentrations, for example 80% oxygen, are administered in carefully controlled studies, the difference in duration of exposure of only a few hours frequently represents the difference between severe damage to the premature animal retina and no effect whatsoever.

Concentration of Oxygen: Our data and those of Ashton and Hellström showed that the severity of oxygen lesions produced is directly proportional to the concentration of oxygen used. For short periods of exposure of the animal, under 2 to 3 days, concentrations under 40% pro-

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Fig. 18. Cross section of eye in terminal stage of retrolental fibroplasia. Arrow points to disorganized retina which is totally detached and against posterior surface of lens. This stage would appear clinically as in Figure 19.

Fig. 19. Terminal stage of retrolental fibroplasia with completely detached retinas presenting as white membranes filling the pupillary area. This child is totally blind.
duced no visible effect. Our studies on kittens show that exposure to oxygen at concentrations above 50% for 3 or 4 days produces lesions directly proportional in severity to concentration up to approximately 80%. There is very little difference observed on increasing the concentration from 80% to 100% oxygen.

Maturation of the Retina: In general, it has been demonstrated that the more immature the animal retina, the greater the susceptibility to oxygen effect. The common denominator to all the animal experiments has been a uniform susceptibility to oxygen where the animal retina is immature, that is, where the vessels have not fully vascularized the retina, and a resistance to oxygen damage once the retina is matured or fully vascularized.3

Rate of Withdrawal from Oxygen: Szewczyk3 and Bedrossian and co-workers34 have claimed that prolonged gradual withdrawal from oxygen reduces or prevents the damaging effect of the initial exposure of the premature infant to oxygen. Recent controlled studies on mice in our own laboratory32 and by Hellström35 in Sweden have shown that gradual withdrawal from oxygen does not prevent ocular lesions developing in the mouse eye. In our own studies it was demonstrated that, on the contrary, gradual withdrawal frequently in-

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**FIG. 20.** Showing effect of rapid and gradual withdrawal from 3-day stay of newborn mice in 80% oxygen. Note that immediate removal to air resulted in total ocular protection. Gradual reduction in oxygen over 6 days furnished sufficient additional oxygen to make total stay in oxygen damaging to 100% of animals.

**TABLE I**

The Effects of Long Exposures to Oxygen of Moderate Concentrations on the Eye of the Newborn Mouse

<table>
<thead>
<tr>
<th>Number of Animals</th>
<th>Number of Eyes</th>
<th>Days in Oxygen</th>
<th>Mean Oxygen Concentration</th>
<th>Number of Eyes with Hemorrhages</th>
<th>Ocular Lesions</th>
</tr>
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<tr>
<td>15</td>
<td>30</td>
<td>5</td>
<td>40%</td>
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<tr>
<td>9</td>
<td>18</td>
<td>7</td>
<td>42%</td>
<td>0</td>
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<td>40</td>
<td>10</td>
<td>88%</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>14</td>
<td>40%</td>
<td>5</td>
<td>90.8%</td>
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</table>
increased both the severity and frequency of ocular lesions. These mouse experiments showed that the additional oxygen that was administered in the period of gradual withdrawal from oxygen frequently represented the added amount of oxygen that was necessary to make an initial nontoxic exposure injurious to the animal eye (Fig. 20). These animal data suggest the possibility that this same situation may occur during prolonged gradual withdrawal of a premature infant from oxygen.

INTERMITTENT EXPOSURE TO OXYGEN: Although we have performed no positively controlled study on continuous versus intermittent oxygen, our studies on duration of exposure show that a given concentration of oxygen is much less injurious when given intermittently than when the same level of oxygen is given by continuous exposure.

FACTORS OTHER THAN OXYGEN

The development of an occasional case of RLF when infants received little or no supplementary oxygen caused considerable skepticism in accepting oxygen as a factor in the disease, early in these studies. In our own nursery study over a period of 8 years, not a single case in approximately 500 premature infants under 1500 gm birth weight occurred where a significant amount of oxygen was not administered. There are, however, well-documented cases of an exceptionally rare instance of RLF occurring without use of supplemental oxygen. I would prefer to explain these rare cases on factors other than oxygen. One may logically assume that many as yet unrecognized factors can alter normal growth of the immature retinal vasculature which in the premature infant matures ex-utero in contrast to its normal intrauterine environment.

However, for those who would prefer stretching the oxygen theory to attempt an explanation of these cases, it is pertinent to point out that while oxygen saturation of arterial blood is approximately 50% in utero, after birth arterial saturation rises while in room air without added oxygen to approximately 90% saturation. Retinal vasoconstriction might, theoretically, develop in a premature infant from this rapid increase in oxygen tension, and could explain an occasional case of RLF developing in a sensitive retina where this relative increase in oxygen tension caused vasoconstriction and ultimate vasoproliferation.

RETROLENTAL FIBROPLASIA IN FULL TERM INFANTS

The occurrence of an occasional case of typical retrolental fibroplasia in a full-term infant challenges the validity of our fundamental assumption that only the immaturely vascularized retina is susceptible to the disease. A significant variation in stage of retinal vessel growth for a given age animal of the same litter was noted in our laboratory on several occasions. It is reasonable to assume that an occasional full-term infant would have a small zone of the anterior retina still incompletely vascularized. This assumption is supported by the actual observation of an incompletely vascularized retina in cross sections of two full-term, apparently normal eyes in our laboratory. The greater predilection for retrolental fibroplasia to involve the temporal quadrants of the retina also supports the basic premise of oxygen susceptibility of only retinal immature vessels, as the anterior zone of the temporal retina is the last portion of the human retina to become completely vascularized.

RECOMMENDATIONS FOR NURSERIES

The following recommendations would seem to be prerequisite for adequate safeguards in the administration of oxygen in the premature nursery.

1. A program of orientation on the potential ocular dangers of oxygen for the premature infant should be frequently practiced in the nursery and all nursery and medical personnel working in the premature nursery should be acquainted with the ocular toxic effects of oxygen.

2. Every nursery should be equipped with an oxygen analyzer.

3. A special oxygen chart or some system of recording on the standard hospital chart should be provided.
4. Except for emergency use, oxygen therapy should require a doctor’s order in the nursery and oxygen should be ordered by concentration in stead of flow-rate.

5. The concentration of oxygen ordered should be, in general, the minimal concentration required to give a satisfactory clinical response. Attempts should be made to terminate or reduce the concentration of oxygen as soon as practical. It cannot be overly stressed that in a sensitive premature infant exposures for as long as 2 to 3 days at moderate concentrations may be injurious to the premature retina.

SUMMARY AND CONCLUSIONS

The results of a controlled nursery study, supported by observations of others in both uncontrolled and controlled studies, clearly established the overuse of oxygen in the premature nursery as an important and probably the principal factor in the development of retrolental fibroplasia.

The clinical data is supported by observations in the newborn or young mouse, rat, kitten, and puppy where retinal lesions, identical to those seen in early human retrolental fibroplasia are produced following exposure to an enriched oxygen environment.

Fundamental to all these experiments, and apparently to the pathogenesis of human retrolental fibroplasia, is the uniform ocular susceptibility to oxygen when the retinas are immutably vascularized, and a resistance to oxygen damage where vascularization is complete.

The animal lesions produced by oxygen are proportional to the concentration of oxygen administered and the duration of exposure, and inversely proportional to the degree of vascularization of the retina. Duration of exposure to oxygen proved to be the most important single factor in these experiments.

The ocular effects of oxygen on the immature retina can be divided into a primary phase of vasoconstriction and obliteration and a secondary phase of vascular proliferation.

These clinical and experimental data justify recommendations for a rigid supervision of oxygen administration to the premature infant to avoid any unnecessary overuse of this potentially toxic agent.

ACKNOWLEDGMENT

Figures 6, 7, 8, 9, 11, 15 were originally published by the author in the American Journal of Ophthalmology (see references 3 and 13). Permission has been granted for reproduction of these illustrations here.

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