ROBERT W. FLOWER

THE ROLE OF OXYGEN IN THE RETINOPATHY OF PREMATURITY

The problem of monitoring the administration of oxygen to premature infants led to a study of the ocular effects of hyperbaric gases and ultimately of the role of oxygen in the genesis of retinal pathology. The results of 15 years' research are discussed.

The study of the role of oxygen in retinopathy was one of the original group of projects, funded by the National Institutes of Health (NIH), which comprised the Johns Hopkins Medical Institutions (JHMI)/APL Interdisciplinary Research in Ophthalmology Program. This study actually predates its companion projects by about seven months and has continued as a collaborative effort for more than 14 years. During this period, support has been provided continuously by the National Eye Institute of the NIH, and funds have also been received from a variety of private sources. The collaboration was initiated by a request from Dr. Arnall Patz (now Director of the Wilmer Ophthalmological Institute) for technical assistance in investigating the toxic effects of oxygen on retinas of premature infants. Since that time, progress has always been toward the same goal of identifying and managing those factors that affect the pathogenesis of retinopathy of prematurity—retrolental fibroplasia (RLF).* Although progress has been slow, results of the work have changed our understanding of physiological events involved in the genesis of the disease, and they have opened new avenues of approach to understanding the developmental physiology of the human retina.

THE CLINICAL PICTURE OF RLF

Retrolental fibroplasia, a disease affecting the eyes of premature infants, has a history that is unique in contemporary medicine. RLF was first described as a clinical entity by Terry in 1942,[1] but within 10 years it became the single largest cause of childhood blindness in the United States —a greater cause even than all others combined. During the 1950's, oxygen was identified as a principal cause of the disease, and rigid curtailment of oxygen administration to premature infants in nurseries resulted in a dramatic decrease in the incidence of RLF. In the early 1960's, however, severe oxygen deprivation was linked to the high mortality rates among infants suffering from idiopathic respiratory distress syndrome and the shift back to increased oxygen therapy resulted in a slight, but definite, increase in occurrence of RLF.

The most recent estimate indicates that 650 infants are blinded by RLF in the United States each year.[2] This means that there will be an average of approximately 0.6 infant blinded by RLF in each neonatal critical care center in this country, making it a genuine, but not highly visible, public health problem. The disease is an insidious one, for it can leave an otherwise normal and healthy child with severe visual impairment or even totally blind. This alone justifies continued efforts to achieve an understanding of its pathogenesis. Moreover, it is becoming increasingly clear that this will ultimately lead to a better understanding of the pathogenesis of a much broader spectrum of retinopathies, particularly those involving neovascular growth.

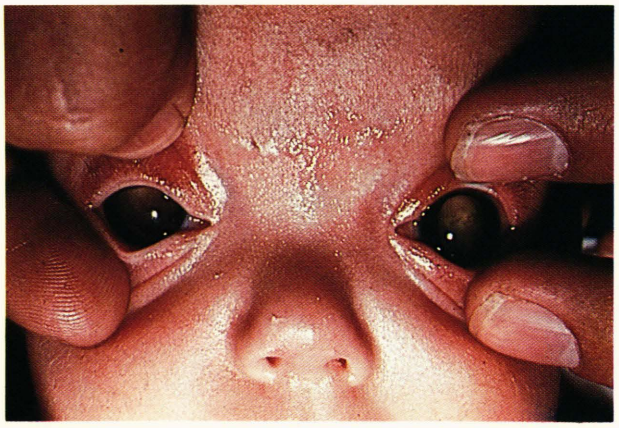
In Fig. 1 (top), an infant with end-stage RLF is shown. Note the whitish-gray reflection behind the dilated pupils of both eyes, which results from the sensory retina having been pulled away from its normal position flat against the choroid of the eye. Such an infant is either totally blind or has bare light perception at best. In Fig. 1 (bottom), the gross pathology of an eye with end-stage RLF is shown. In this bisected eye, the mass of scar tissue to which the sensory retina has been reduced is seen lying directly behind the lens of the eye. It is from this characteristic end-stage pathology that the disease took its original name, retrolental (behind the lens) fibroplasia—referring to the mass of scarred retinal tissue. Recently, however, the more proper name, retinopathy of prematurity, has begun to appear more frequently in the literature.

EMBRYOLOGY OF THE EYE

During the 40 years that RLF has been recognized and studied, two facts about its genesis have been well documented.

First, RLF is a disease of the immature eye. Up to the sixteenth week of gestation, although it is well differentiated, the sensory retina of the human fetus is avascular. Its nutritional requirements are met by blood flows through the adjacent choroidal vasculature and through the hyaloid arterial tree, which nourishes the primary vitreous of the eye and the

*See GLOSSARY, pages 151-152.



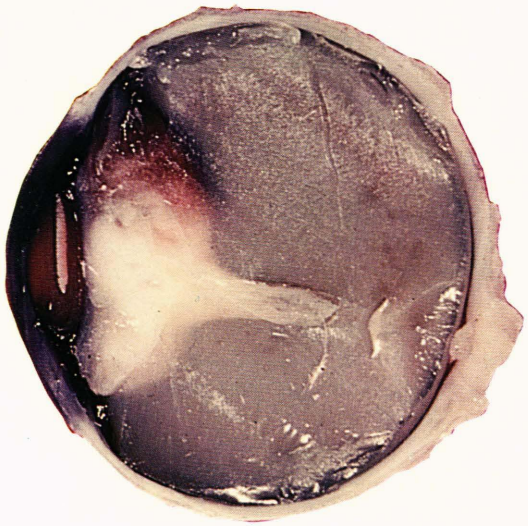


Fig. 1—At the top, an infant with end-stage RLF. The whitish-gray reflection from behind the dilated pupils of both eyes results from the sensory retina having been pulled away from its normal position — flat against the choroid of the eye. Such an infant is either totally blind or has bare light perception at best. At the bottom, the gross pathology of an eye with end-stage RLF. In this bisected eye the mass of scar tissue lying behind the lens is all that remains of the sensory retina.

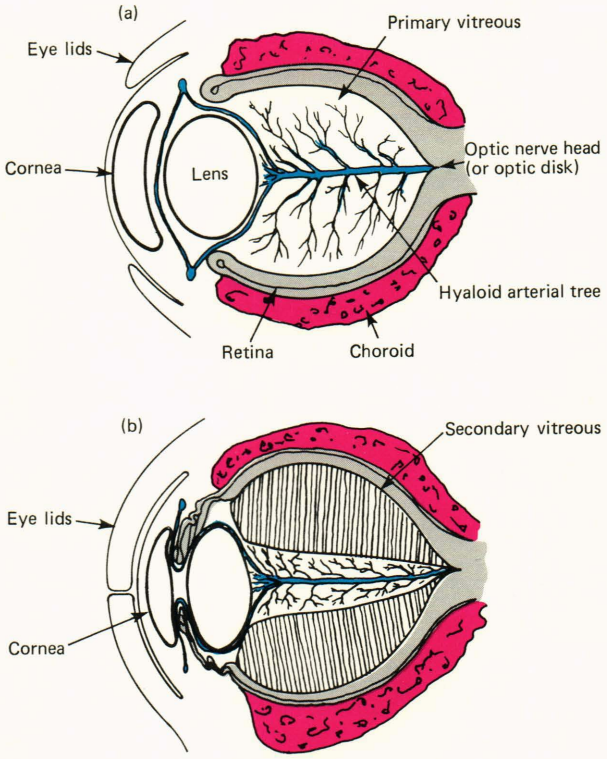


Fig. 2—(a) Schematic representation of the eye during an early stage of development, prior to 16 weeks gestation. At this stage, the sensory retina is avascular and receives its nutrients from blood flows through the adjacent choroid and through the hyaloid arterial tree that nourishes the primary vitreous and developing lens of the eye. (b) Schematic representation of the developing eye in cross section at a later period, indicating atrophy of the hyaloid arterial tree.

developing lens (see Fig. 2). Around the sixteenth week of gestation, the avascular retina is invaded by a vanguard of mesenchymal cells[3] from the stalk of the hyaloid artery at the optic nerve head. As this vanguard of cells moves radially across the face of the retina toward the periphery, it lays down in its wake a network of primitive, endothelial-cell-lined tubules, which gradually differentiate into the arteries, veins, and capillaries of the mature retina. By full-term gestation, this process is nearly completed, and the retinal vasculature extends all the way to the periphery of the retina. During that same gestation period, the hyaloid arterial tree undergoes atrophy, and the primary vitreous is replaced by adult, or secondary, vitreous.

Second, it has been well documented that sustained exposure to high oxygen concentration, resulting in arterial hyperoxia, triggers development of RLF. The effects of hyperoxia on the immature retinal vasculature can be divided into two stages (as shown in Fig. 3). The first of these consists of vasoconstriction and possibly vaso-obliteration of the retinal blood vessels. So long as high oxygen exposure continues and vasoconstriction persists, further forward growth of the retinal vessels toward the periphery of the retina is halted. The second stage occurs when breathing of room air resumes. Those retinal vessels not permanently obliterated can recannulate, and new vessel growth can commence again. However, the retinal vessels no longer necessarily develop along normal pathways; new vessels may grow out of the plane of the retina and into the vitreous (Fig. 3). These new vessels often lack normal structural integrity, so hemorrhage can occur. Fibrinous threads that develop out of hemorrhaged blood can result in traction on the sensory retina that pulls it away from its normal position against the choroid; severe scarring of the retina can also occur.

AN ANIMAL MODEL OF RLF

An animal model of RLF was introduced in the 1950's by Norman Ashton[4] who was aware that full-

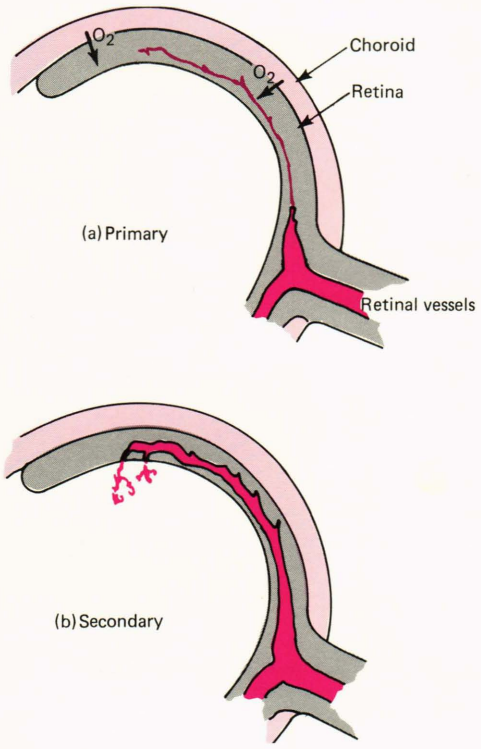


Fig. 3—Schematic representation of the oxygen effect in RLF. (a) The primary stage occurs upon breathing high oxygen concentrations. With sustained, excessively high arterial oxygen levels, the retinal vessels can be seen to constrict and possibly become obliterated. This condition can persist as long as breathing of high oxygen concentrations is continued. (b) The secondary stage occurs upon return to breathing room air. Those retinal vessels not permanently obliterated can reopen, and growth of retinal vessels toward the periphery can recommence. These new vessels need not necessarily grow along normal pathways; they may even grow out of the plane of the retina and into the vitreous. Such new vessels often lack normal structural integrity, and hemorrhage can occur.

term, newborn kittens and puppies have retinas whose vascularization approximates that of the seven-month-gestation human eye (Fig. 4). Ashton observed that the retinal vessels of kittens exposed to high oxygen concentrations underwent the same vasoconstriction and vaso-obliteration observed clinically. He and his co-workers exposed newborn kittens to various oxygen concentrations for various lengths of time, after which the kittens were returned to room air until they matured. At maturity, the animals were euthanized, their blood vessels filled with india ink, and their retinas removed and placed flat on glass slides for examination.

Retinas from four kitten littermates prepared according to this protocol are shown in Fig. 5. Kitten W served as a control and was reared breathing only room air. Its retinal vasculature is therefore completely normal, consisting of three major artery and vein pairs with a network of normal capillaries extending to the periphery of the retina. By comparison, littermates X, Y, and Z were reared in increasingly high oxygen concentrations, and their retinas show increasingly severe retinopathies. Increased deterioration of the normal vascular pattern is evident in these three animals, and the pattern is completely missing in Z. The extent of vascularization away from the central retina also was gradually reduced until it extended only halfway to the periphery of the retina in littermate Z. A major criticism of this animal model, however, is that it has failed to produce the cicatricial, or end-stage, forms of RLF.

Ashton and his co-workers also investigated morphological changes in the retinal microcirculation of kittens that developed RLF. They observed selective capillary endothelial cell destruction in the RLF vascular degenerative process; all other cells in the vicinity of affected capillaries remained normal, suggesting that blood vessel degeneration is a result of direct cytotoxic effects of oxygen on endothelial cells and is not secondary to vasoconstriction and diminished blood flow. However, their data did not permit them to establish the cause of vascular damage, nor were they able to identify conclusively the mechanism of oxygen vaso-obliteration. These questions have remained without definitive answers.

THE ROLE OF THE PROSTAGLANDIN CASCADE IN VASOMOTION

Recent reports link manipulation of the prostaglandin system to oxygen-dependent changes in the ductus arteriosus. Prostaglandins are potent vasoactive agents synthesized from 20-carbon polyun-

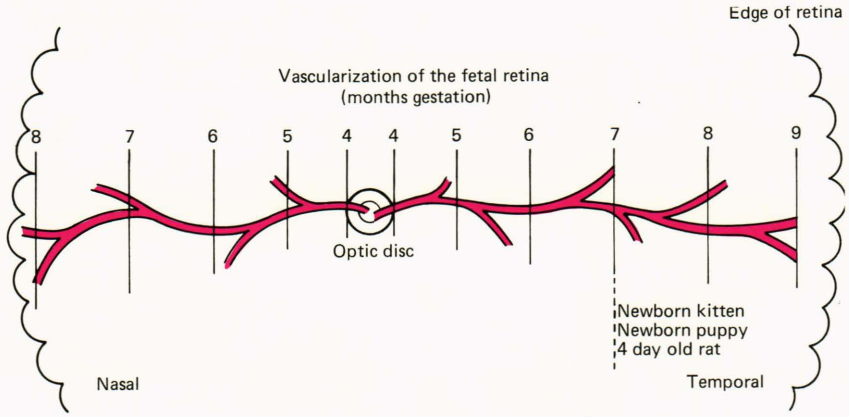


Fig. 4—Schematic representation of the vascularization of the human fetal retina as a function of gestational age. Note that the nasal side of the retina becomes vascularized nearly a month before the temporal side. This possibly accounts for usually finding the most severe RLF in the temporal periphery of the retina rather than elsewhere.

Fig. 5—India-ink-injected, flat-mounted retinas from four kitten littermates euthanized at the same age. W served as a normal control and breathed only room air. X, Y, and Z were raised in increasingly higher oxygen concentration environments, and their retinas show increasingly severe pathology. Note that the extent of vascularization away from the centrally located optic disc also decreases from retina to retina.

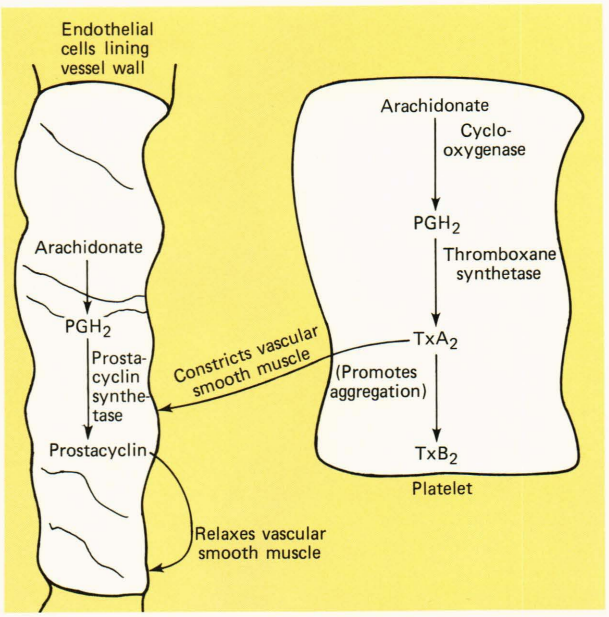


Fig. 6—Schematized representation of the synthesis of arachidonic acid by platelets circulating in blood to produce thromboxane A_2 (a potent vasoconstrictor and platelet aggregator) and the synthesis of arachidonic acid by endothelial cells to produce prostacyclin (a potent vasodilator and inhibitor of platelet aggregation).

saturated fatty acids. The main precursor of prostaglandins in man is arachidonic acid, which is found in virtually every tissue cell in the body. The ductus arteriosus is a vessel present in the fetal state that connects the aorta and the pulmonary artery, effectively forming a left-to-right heart shunt. Normally, at birth, this heavily muscular vessel constricts in response to the sudden rise in arterial oxygen content that occurs when breathing starts. However, it has been demonstrated in animals and man that the status of the ductus can be changed by pharmacologically altering the systemic level of prostaglandins.[5] These findings related to the ductus arteriosus led us to look for a similar link to oxygen-induced changes in the immature retinal vasculature.

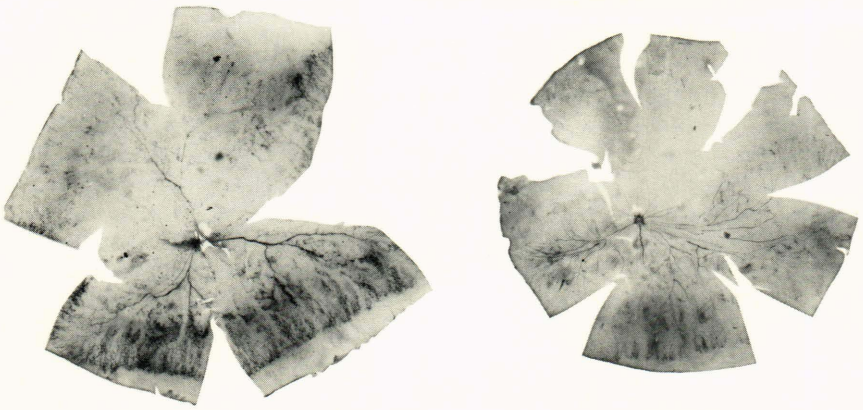
Although the biochemistry of prostaglandins is extremely complicated, our working hypothesis involved a fairly simplistic view of the processes involved. In Fig. 6, the synthesis of arachidonic acid by platelets circulating in blood and by endothelial cells that form the lining of blood vessels in the eye is schematized. In platelets, arachidonic acid is converted to thromboxane A_2 (TxA_2), a potent vasoconstrictor and platelet aggregator. Starting with the same arachidonic acid, the endothelial cells produce prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. We reasoned that if these two prostaglandins do mediate retinal vascular status, then normally they must be produced at such rates that an equilibrium is established between their opposing vascular effects.

It is known that aspirin inhibits prostaglandin synthesis in both platelets and endothelial cells; therefore, aspirin administration was used in an attempt to manipulate prostaglandin activity in the eye. In order to detect any resulting effect of aspirin on retinal vascular status, aspirin was randomly administered to some puppies of a litter and a placebo was given to the remaining littermates who served as controls in the experiment. (The aspirin doses administered produced plasma salicylate levels within the human therapeutic range.) All the puppy littermates were then placed in a high-oxygen-concentration environment known from past experiments to produce vasoconstriction. After about one hour, the puppies were euthanized and india ink was injected. Flat retinal mounts were prepared for examination.

Results of this experiment are summarized by the two retinas shown in Fig. 7. The retina from littermate A, which received aspirin, has significantly more major retinal vessels that are dilated than that from littermate B, which did not receive aspirin. Moreover, the higher density of ink particles in the peripheral capillaries of littermate A compared to that in littermate B indicates that the aspirin had inhibited vasoconstriction and, hence, blood flow was unaffected.

INHIBITION OF VASOCONSTRICTION DURING HYPEROXIA

Having demonstrated a vasoconstriction inhibitory effect of aspirin, experiments were conducted to



Littermate A Littermate B

Fig. 7—India-ink-injected retinal flat mounts from two puppy littermates that breathed the same high concentration of oxygen; littermate A received aspirin prior to breathing oxygen but littermate B did not. The higher density of india ink particles in the peripheral capillaries of littermate A compared to that in littermate B indicates that aspirin had inhibited vasoconstriction in littermate A, leaving it with a greater retinal bloodflow than B.

determine the effect of vasoconstriction on immature retinal vessels during sustained hyperoxia. Puppies from several litters were randomly allocated to receive either the aspirin dose or a placebo. One at a time, each litter of puppies and its mother were placed in an airtight chamber ventilated with humidified 100% oxygen. They were kept in the chamber continuously for 72 hours and given aspirin or placebo every 24 hours. Fourteen days after completion of oxygen exposure, the puppies were euthanized, india ink injected, and flat retinal mounts of their eyes were prepared. Evaluation of the retinas by several independent observers led to the conclusion that the aspirin-treated, oxygen-exposed puppies developed retinopathy of significantly greater severity than their unmedicated, oxygen-exposed littermates, although the degree of severity did differ somewhat among litters.

In several of the most severely affected puppies, grade III cicatricial retinopathy (falciform retinal fold) was found. Figure 8 shows composite fundus photographs of both eyes of one of these puppies and a retinal flat mount of one eye. Significant venous distention as well as evidence of hemorrhage was common in the eyes of these puppies. Moreover, examination of the retinal flat mount preparations revealed many examples of the vascular anomalies that characterize the human disease. Production of cicatricial RLF for the first time in an animal model answers a major criticism of the RLF animal model and thereby strengthens the confidence with which results from experimental animal studies might be extrapolated to the clinical situation in the future.

In still other puppy experiments, radioimmunoassay and bioassay techniques were used in order to assess the effect of *in vivo* aspirin treatment on prostaglandin biosynthesis. We found that marked inhibition of both vascular prostacyclin and platelet thromboxane occurred in aspirin-treated puppies. This may imply that the *in vivo* aspirin effect, if mediated solely by altering prostaglandin biosynthesis, was toward vasodilator predominance.

We postulated from these results that the more severe retinopathy developed by the aspirin-treated puppies resulted from prostaglandin-mediated inhibition of retinal vasoconstriction and that vasoconstriction may be a normal physiological mechanism to protect the immature retina from excessive oxygen content. That is, retinal vasoconstriction may in fact be a protective rather than a pathological process in response to hyperoxia.[6]

A WORKING HYPOTHESIS: RETINAL VASOCONSTRICTION AS A NORMAL PHYSIOLOGICAL EVENT

The vasoconstriction observed in oxygenated premature infants may be only an extreme of a normal physiological response by which retinal blood flow is modulated during the period of *in utero* development. During that period, retinal vascular development is such that retinal tissue gradually ceases to be totally dependent for maintenance upon the adjacent choroidal and hyaloid blood flows. This same mechanism may also be active throughout the perinatal period.

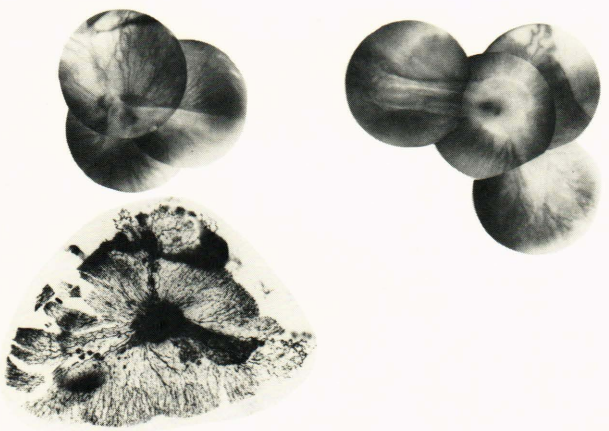


Fig. 8—Composite fundus photographs of both eyes from a puppy that developed grade III cicatricial retinopathy (falciform retinal fold) from hyperoxia and aspirin. The india-ink-injected retinal flat mount from the right eye of the puppy is also shown in proper orientation beneath its companion fundus photograph.

The possibility then arises that susceptibility of an eye to oxygen-associated retinopathy may depend upon the extent to which a protective vasoconstriction response is functional at birth as well as upon the degree of retinal maturity attained. From this point of view, it may be argued that cases of "spontaneous" RLF reported in premature infants never administered oxygen[7] or in full-term infants who were,[8] are simply examples of inadequate retinal vasotonia at birth for protection of structurally immature vessels. We also speculated that the apparently strong vasoconstriction response normally present in both the puppy and kitten may account for the fact that cicatricial RLF was never produced in these animals until vasoconstriction was presumed to be inhibited by aspirin administration.

An implicit assumption of the foregoing is that vasoconstriction is in fact a physiological property of the perinatal retinal vasculature. Justification for making such an assumption is found in the recent fetal and neonatal lamb retinal blood flow studies of Peeters *et al.*[9] Their results indicate that autoregulation of blood flow takes place in the perinatal eye. They reported that in the lamb eye, when arterial blood pressure increases at birth, choroidal blood flow increases but retinal blood flow does not. The simplest explanation for this observation is that some degree of retinal vasoconstriction occurs at birth concomitantly with the rise in blood pressure, and thereby the retinal vasotonia recognized as clinically normal is established.

Compared to its blood supply after birth, the immature retina receives venous-like blood *in utero*. Approximate values for those parameters that characterize arterial blood *in utero* are: PO_2 = 25 torr, PCO_2 = 45 torr, and blood pressure, 25 to 30 torr. But at birth, blood oxygen content rises (PO_2 = 70 torr) as does blood pressure (35 to 40 torr), and PCO_2 drops to about 35 torr. It therefore seems naive to ignore that breathing room air causes blood gas levels to assume values that are quite abnormal for a premature infant. The effects of arterial hyperoxia (especially during oxygen breathing) on immature retinal vessels have long been the subject of a great deal of interest, but the possible consequences of changes in arterial PCO_2 and blood pressure that occur at birth should also be considered.

On the assumption that retinal vasotonia is a predisposing factor in development of RLF, two mechanisms associated with perinatal changes in those factors that characterize the arterial circulation can be invoked to explain immature-retina vascular damage. The first concerns elevated arterial PO_2 and attributes vascular damage to increased contact between developing peripheral capillary walls and blood-borne oxygen known to be capable of damaging cell membranes. This could explain the more severe retinopathy in the oxygenated puppies whose vasoconstriction was aspirin-inhibited. On this basis, the animal model data might support the suggestion of Ashton and Peddler that retinal vessel damage may result from direct cytotoxic effects of oxygen on endothelial cells, although extensive electron-microscope evaluation of our animal retinas has not been completed. Compared to those of littermates in which normal vasoconstriction occurred during oxygen breathing, the dilated retinal blood vessels of the aspirin-treated puppies would have allowed a greater blood flow through the immature vessels, those farthest from the optic nerve. Walls of the immature capillaries in the vasoconstriction-inhibited animals would therefore have been in contact with greater concentrations of oxygen; endothelial cells of the vessel wall can be damaged by oxygen-induced peroxidation of lipids contained in them.

The second mechanism takes into account occurrence of a presumed normal degree of vasoconstriction at birth concomitant with rise in arterial blood pressure, as shown in Fig. 9a. However, vasoconstriction would not be uniform throughout the vasculature as shown. (This schematic simplification was used only in order to make a point about the peripheral capillary transmural pressure.) Vasoconstriction, nevertheless, could add resistance to blood flow throughout the retinal vasculature in such a way that the most peripheral, and hence the most structurally immature, capillaries would experience the smallest increase in transmural pressure. However, failure of such vasoconstriction to occur at birth (Fig. 9b) could result in excessively high transmural pressures, possibly producing retinal capillary hemorrhage. This second mechanism might conceivably work independently of or concomitantly with the first.

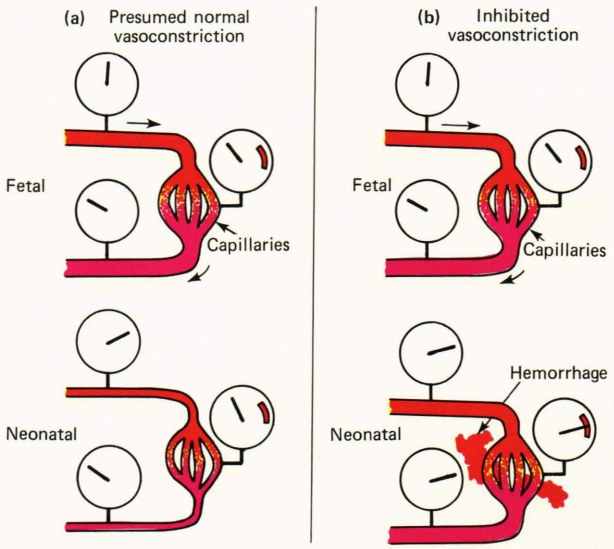


Fig. 9—Schematic representation of the changes in transmural pressure that might occur in the retinal vasculatures of fetal and neonatal eyes. (a) Pressure relationships resulting from a presumed normal degree of vasoconstriction. (b) Pressure relationships resulting from inhibited vasoconstriction. Under such circumstances, it is possible for hemorrhage to occur.

TESTING THE WORKING HYPOTHESIS

Again we returned to the experimental RLF animal model in order to examine the effects of changes in those parameters that characterize arterial blood during the perinatal period.

Figure 10 summarizes results of experiments performed to show how the immature retinal vasculature responds to manipulation of arterial PCO_2 levels while holding blood pressure constant. The middle fundus photograph shows the condition of the retinal vessels of an anesthetized puppy while it breathed room air. After the oxygen content breathed was increased, causing an elevation in arterial PO_2 without changing either PCO_2 or blood pressure, the retinal vessels constricted and some became obliterated. Then the breathing gas mixture was manipulated so that arterial PCO_2 was also elevated while arterial PO_2 remained high and blood pressure remained unchanged. The top fundus photograph in the figure shows that, with elevated arterial PCO_2, those vessels that constricted or became obliterated reopened to calibers exceeding those observed during room-air breathing. The vasodilation persisted in the presence of elevated arterial PO_2 even when arterial PCO_2 dropped as low as 70 torr. Results of the experiments led to the impression that the tendency for immature retinal vessels to dilate in response to elevated arterial PCO_2 is greater than their tendency to constrict in response to elevated arterial PO_2.

Thus, in keeping with the aforementioned hypothesis that vasoconstriction plays an important role in the developing retinal vasculature, the response of the RLF animal model to changes in arterial PCO_2 can be considered analogous to changes in retinal vascular status throughout the perinatal period. The top fundus photograph of Fig. 10 can be thought of as representing the retinal vasculature *in utero*. The middle fundus photograph then represents retinal vasculature status at birth (i.e., clinically normal retinal vasotonia), and the bottom fundus photograph is consistent with the known retinal vasculature response in the newborn breathing a high concentration of oxygen.

These observations led to the performance of experiments aimed at producing retinopathy via the latter of the two hypothetical mechanisms proposed above. Specifically, as an alternative to aspirin administration, hypercapnia produced by chronic inspiration of 10% CO_2 was used as a method of inducing vasodilation. Litters of newborn puppies were randomly divided into two groups. The first group was reared for a period of three days in an environment of humidified 10% CO_2 and 90% O_2, and the other littermates were reared in an environment of humidified 10% N_2/90% O_2. The mother nursed each group alternately during the three day period, and then both groups were returned to her and allowed to mature to 20 days of age. At that time the puppies were euthanized and their retinas prepared for study as previously described.

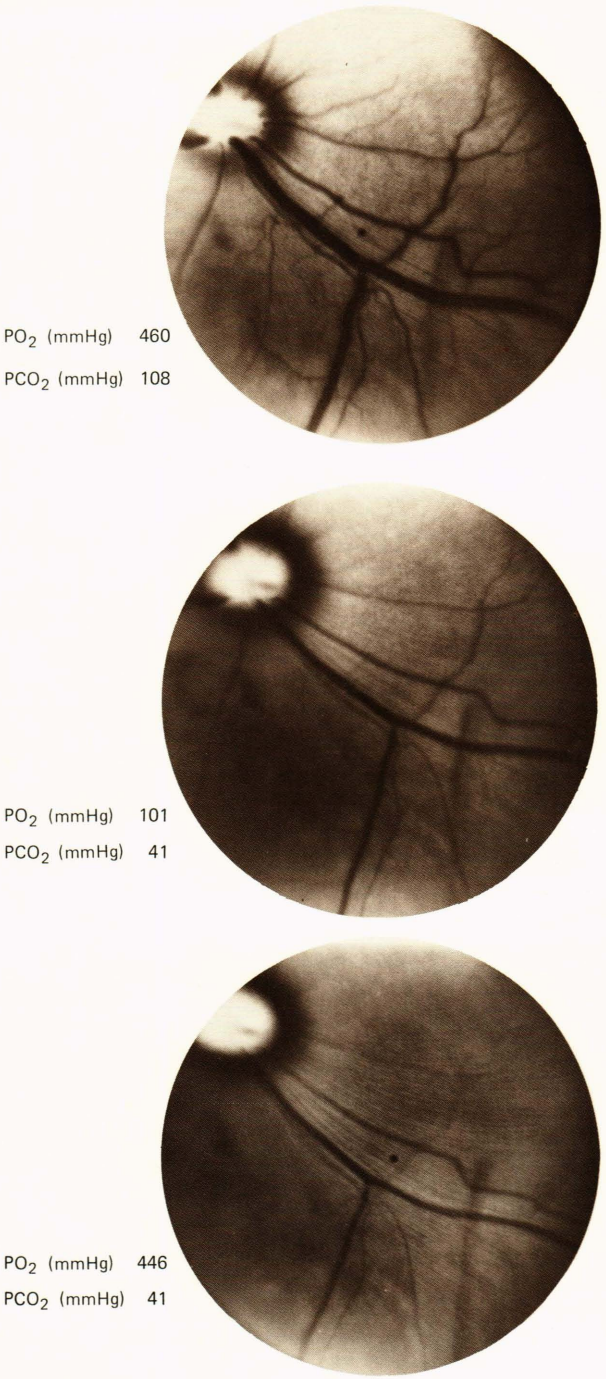


Fig. 10—Response of the immature retinal vasculature to manipulation of arterial PCO_2 level while holding systemic blood pressure constant. The middle fundus photograph shows the condition of the retinal vessels of an anesthetized puppy that was breathing room air. The bottom fundus photograph shows the constricted state of the same retinal vessels after the puppy breathed oxygen, which raised the arterial PO_2 but did not affect arterial PCO_2. The top fundus photograph shows retinal vessels, both arteries and veins, more dilated than during either air-breathing or oxygen-breathing states as a result of simultaneously breathing a high oxygen and high CO_2 concentration gas mixture.

Only a subjective evaluation could be made of the resulting preliminary data, but it suggested that a

vascular response pattern may exist. The impression gained was that the vascular patterns in both groups of littermates were abnormal, but the CO_2/O_2-reared groups had vascular anomalies distinctly different from those in the N_2/O_2-reared groups. The major retinal vessels of the CO_2/O_2 puppies were significantly dilated in comparison to those of the N_2/O_2 littermates, even though the animals had been removed from the high CO_2 environment for more than two weeks before euthanasia. Moreover, whereas the capillary densities in the N_2/O_2 puppies tended to be uniform throughout the retina, capillary densities in the CO_2/O_2 littermates were significantly higher in the peripheral retina than elsewhere. At the microscopic level, the retinas of the N_2/O_2 puppies showed characteristic oxygen-induced vascular changes. Note the randomness of the capillary net pattern and the presence of an abnormal shunt-like vessel (arrow) permitting virtually direct communication between artery and vein in Fig. 11.

Also in Fig. 11, the peripheral retina of a CO_2/O_2 littermate is shown. In this case the peripheral capillaries have such large diameters that they resembled the sinusoid-like capillaries of the choroid more than they did the retinal capillaries. Their appearance is consistent with the pressure within them having risen to the point where they dilated beyond the elastic limits of their walls, resulting in the ballooned-out appearance.

Although this interpretation of the data supports the working hypothesis, it represents a concept sufficiently contrary to traditional thinking about RLF that still further investigation of the transmural pressure damage hypothesis was warranted. In order to achieve a separation of the presumed oxygen toxic effect from that presumably associated with excessive transmural capillary pressure, randomly selected puppy littermates were reared for three days in an environment of humidified 10% CO_2/90% O_2. Following previously described protocols, at approximately three weeks of age, retinas of these puppies were compared to those of their control littermates reared in room air. In general, the same differences—but of much smaller magnitude—were found to exist between CO_2/air-reared puppies and their air-reared littermates as those found previously between the CO_2/O_2- and N_2/O_2-reared puppies. In two of the CO_2/air-reared littermates whose ocular media were sufficiently clear to permit ophthalmic examination prior to euthanasia, lesions resembling those found in clinical RLF were observed and photographed. These lesions were also found to leak intravenously injected sodium fluorescein dye as in clinically observed RLF.

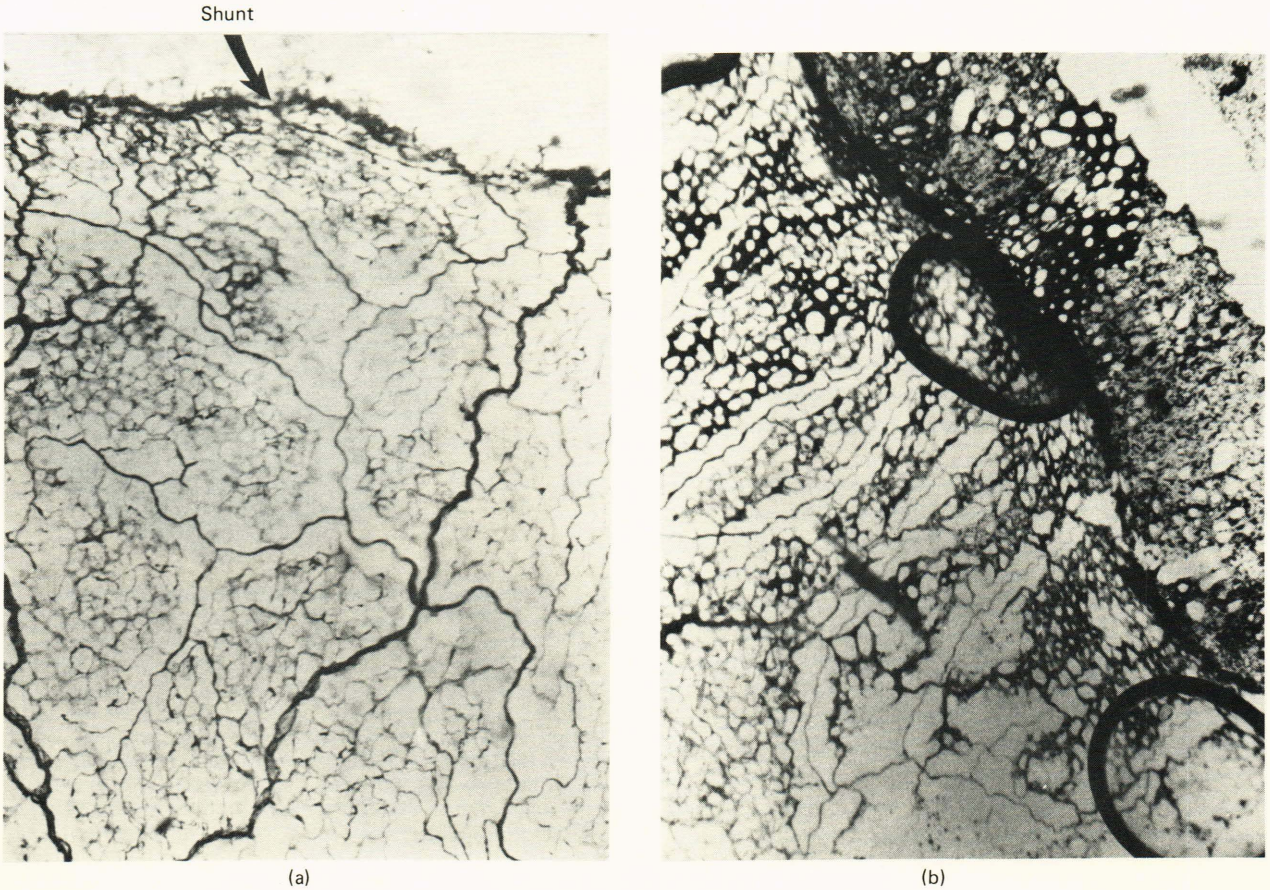


Fig. 11—Micrographs comparing the peripheral retinal capillaries of two puppy littermates: (a) maintained for three days in a 10% N_2/90% O_2 environment and (b) maintained for three days in a 10% CO_2/90% O_2 environment.

CLINICAL IMPLICATION OF THE STUDIES

Until completion of more rigorous experiments to confirm the subjective evaluation of data currently at hand, these conclusions must be viewed as preliminary. Nevertheless, the results, as such, were recently presented at a University of Miami seminar jointly attended by ophthalmologists and neonatologists. As a result, the neonatologists re-evaluated their data on a group of 74 surviving infants whose birthweights were under 1000 grams; of these, 37 were diagnosed to have RLF. Of 28 independent variables evaluated by discriminant analysis to determine their roles in occurrence of RLF in this patient population, nine variables were found to correlate.[10]

The total function, consisting of the nine variables, correctly predicted infants with RLF 84% of the time. It is interesting that the most significant variable was the highest arterial PCO_2 measured in each infant. This was followed by the total number of arterial PCO_2 measurements greater than 50 torr that occurred simultaneously with an elevated arterial PO_2 (greater than 100 torr). The third most significant variable was the total number of arterial PO_2's greater than 100 torr, and the seventh most significant variable was the highest recorded arterial PO_2 in an infant.

On the strength of these rather surprising findings, the same neonatologists are planning to conduct a prospective study that will include a close look not only at the effect of oxygen on RLF but also at the effects of elevated arterial PCO_2 and blood pressure.

A conservative view of these clinical data now would be that they are anecdotal, but the possibility that factors other than oxygen alone may contribute to genesis of RLF is compelling; so is the possibility that clinically observed RLF may be only a narrow range of a broad spectrum of retinopathies that could be produced in the immature retina if appropriate physiological parameters were varied outside the current clinically acceptable range. In this context, the significance of all these preliminary investigations—both the animal model and the clinical—is that the clinician is alerted to look for correlations between incidence of RLF and factors other than oxygen alone.

Finally, the finding that vasoconstriction may be a normal physiological rather than pathological event underscores the paucity of our knowledge about normal developmental physiology of the eye. A better approach to elucidating the pathogenesis of RLF than has been used to date might be to develop first a thorough understanding of normal developmental ocular physiology before attempting to understand the abnormal developmental processes.

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GLOSSARY

Atrophy — A defect or failure of nutrition manifested as a wasting away or diminution in the size of cell, tissue, organ, or part.

Avascular — Not supplied with blood vessels.

Choroid — The middle coat of the posterior eye lying beneath the sensory retina, consisting of large veins and somewhat smaller arteries, with an innermost layer of smaller capillaries, the choriocapillaries. This vascular network is responsible for providing nutrients to approximately the outer two-thirds of the thickness of the sensory retina.

Cicatricial RLF — An advanced form of RLF involving the formation of cicatrices, or scar tissues.

Cytotoxic — Pertaining to a toxin or antibody that has a specific toxic action upon cells of a specific organ.

Endothelial — Pertaining to or made up of epithelial cells which line the cavities of the heart and of the blood and lymph vessels and the serous cavities of the body.

Falciform — Shaped like a sickle. In advanced RLF, vitreous traction on the retinal vessels can form a fold of retina extending from the

optic disc toward a mass of opaque tissue usually lying in the retinal periphery.

Fundus — The bottom or base of anything; used in anatomical nomenclature as a general term to designate the bottom or base of an organ, or the part of a hollow organ farthest from its mouth.

Hyaloid — Resembling glass.

Hypercapnia — Excess carbon dioxide in the blood.

Hyperoxia — An excess of oxygen in the system.

Idiopathic respiratory distress syndrome — Newborn respiratory distress of unknown causation.

Mesenchymal — Pertaining to the meshwork of embryonic connective tissue in the mesoderm from which are formed the connective tissues of the body and also the blood vessels and lymphatic vessels. In the embryo, there are three primary layers of living substance, or germ, capable of developing into an organ, part, or organism as a whole. (The mesoderm, or middle layer, lies between the ectoderm and the endoderm.)

Neonatal — Pertaining to the first four weeks after birth.

Neovascular — Pertaining to new vessel growth.

PCO_2 and PO_2 — The pressures of carbon dioxide and oxygen.

Perinatal — Pertaining to or occurring in the period shortly before and after birth; generally considered to begin upon completion of 28 weeks of gestation and variously defined as ending one to four weeks after birth.

Prostaglandin — A naturally occurring substance, first found in the semen of man and sheep, that causes strong contraction of smooth muscle and dilation of certain vascular beds; subsequently found in menstrual fluid.

Retinopathy — Any noninflammatory disease of the retina.

Retrolental fibroplasia — The retinopathy of prematurity, which takes its name from the characteristic end-stage pathology of the disease: retrolental (behind the lens) fibroplasia – referring to the mass of scarred retinal tissue.

Transmural — Pressure difference measured across a blood vessel wall.

Vascularization — The process of becoming vascular, or the development of vessels in a part or tissue.

Vasoconstriction — The diminution of the caliber of vessels, especially constriction of arterioles leading to decreased blood flow to a part.

Vaso-obliteration — Complete disappearance of vessels from an area.

Vasotonia — Pertaining to tone or tension of the vessels.

Vitreous — Glasslike or hyaline; often used alone to designate the vitreous body of the eye.