In this issue dedicated to Dr. V. Everett Kinsey, it is appropriate to recognize his scientific contributions in so many areas of ophthalmic research. However, none of his endeavors reflect more on the quality of this innovator in research medicine than his studies on retrolental fibroplasia (RLF). Although Dr. Kinsey's prime assignment on joining the staff of the Massachusetts Eye and Ear Infirmary in Boston in 1940 was to study the dynamics of the aqueous humor, his interest in RLF dates to its discovery by Terry in 1942. Everett made himself available for consultation to Dr. Terry on many occasions and obtained laboratory space in the pathology building of Harvard to conduct animal experiments. When Owens and Owens of Hopkins reported their studies on vitamin E, Everett was ready to augment their work by providing the Doctors Owens with serum tocopherol analyses on infants from Hopkins, and he initiated a similar study on vitamin E at the Boston Children's Hospital. When a controlled nursery study was reported in 1952 suggesting that over-use of oxygen was a factor in RLF, Dr. Kinsey again provided the leadership to organize a national cooperative clinical trial to test this hypothesis. It was imperative that the most meticulous documentation of the oxygen etiology be provided since oxygen is a life-saving drug for the premature infant. Had the proponents of the oxygen etiology been wrong, then large numbers of premature infants might have been placed at unnecessary risk by curtailing oxygen therapy. Indeed, the pediatric community had just seen two studies on other causes of RLF by distinguished investigators "backfire" on further testing. Recognizing this climate of feeling in July 1953 when the cooperative study chaired by Dr. Kinsey began, the importance of his soundly conducted clinical trial can be appreciated in proper perspective.

Everett's continued interest in the RLF problem led to his cochairing a five-hospital Cooperative Study in the late 1960's to investigate the precise arterial oxygen values associated with RLF in an effort to define safe levels of oxygen for the premature infant. In 1975, the American Academy of Pediatrics, cognizant of the need to provide a historical document on the oxygen story in RLF, has sought Everett's counsel in a specially formed committee to prepare this document.

Since RLF continues to present a significant challenge to the pediatrician, ophthalmologist, and research investigator interested in retinal vascular diseases, it is appropriate in this special issue dedicated to Dr. Kinsey to briefly summarize the current status of oxygen in retrolental fibroplasia.

The incrimination of oxygen of oxygen came about through a combination of clinical nursery studies and the experimental production of RLF in animals by oxygen administration. The most important of the nursery investigations was the cooperative multi-hospital study chaired by Kinsey. The animal studies reported by Ashton and co-workers provided a clarification of the precise mechanism of oxygen on the im-
mature retina. Although the epidemic of RLF was abated by curtailment of oxygen, cases of RLF continued to occur, even up to the present time, in spite of the most careful restriction of oxygen. Indeed, occasional recent cases of RLF have been described where no oxygen, or oxygen for only a few hours, was administered.

A swing of the pendulum from rigid restriction of oxygen, to prevent RLF, to a more liberal use occurred during the 1960's as pediatric investigators demonstrated the severe oxygen deprivation in the premature infant with the idiopathic respiratory distress syndrome (RDS). Infants with RDS required high incubator concentrations of oxygen to raise the arterial oxygen tension \( (P_{A02}) \) to levels compatible with survival and prevention of brain damage. The spectre of increased mortality and brain damage resulting from restriction of oxygen to prevent blindness was raised by several investigators.

At the present time there appears to be an irreducible minimum of RLF cases in spite of the most meticulous arterial \( P_{A02} \) monitoring. There have been documented changes indistinguishable from retrolental fibroplasia in stillborn infants and in those living only a few hours after birth. The presence of these abnormal new vessels indicates that causes other than prolonged and excess use of oxygen in the nursery may occasionally produce vascular lesions virtually identical to the changes of RLF.

The present state of our knowledge of the pathogenesis of RLF will be briefly summarized. The retina is unique in that prior to the fourth month of gestation it contains no blood vessels. Starting at four months' gestation, the retina becomes vascularized starting from the optic nerve. The nasal retina becomes fully vascularized by approximately eight months' gestation, but the temporal retinal periphery, which is further away from the optic nerve, is not completely vascularized until approximately one month after birth of the full-term infant. This pattern is significant as the more immature portions of the retina have been shown in experimental studies to be more sensitive to oxygen. Experimental animals lose their sensitivity to retinal vessel damage when the retina is fully vascularized. Accordingly, the temporal periphery, which is less completely vascularized at any particular stage of gestation, is more vulnerable in humans and animals.

The effects of oxygen on the infant or experimental animal, with an incompletely vascularized retina, can be conveniently divided into the initial response to oxygen and a secondary one after removal to room air. In the initial or primary response there is a severe vasoconstriction. During the exposure to oxygen, direct injury to the vessel endothelium occurs and ultimate obliteration of the more immature vessel complexes results. After removal to air, new vessel formation occurs at the area of retinal capillary damage and obliteration. These new vessels erupt through the surface of the retina to grow into the vitreous in the classical manner of proliferative retinopathy very similar to that seen in diabetes and sickle cell disease. The changes after the intravitreal proliferation of new vessels are relatively nonspecific. These vessels invariably leak proteinaceous material and in more advanced cases hemorrhages occur from these intro-vitreal new vessel formations. Traction produced by vitreoretinal adhesions detaches the retina. Active RLF may regress at any stage of the proliferative disease. Vitreo-retinal traction in the temporal periphery frequently produces a dragging of the retinal vessels across the disc and a displacement temporally (heterotopia) of the macula may occur. Many infants who have had active proliferative disease but go on to regress without further scar tissue will be left with a high degree of myopia. The mechanism for this refractive change is unknown.

There is a major need for the development of better arterial blood-gas monitoring capability. Ideally, a noninvasive technique would be useful and, second, it should provide for continuous monitoring, or the ability to monitor at much more
frequent intervals than can now be done. Further biochemical studies in the premature nursery are recommended to determine if other factors may play a cofactor role with oxygen in the etiology of RLF.

There is a need for further research in the basic mechanisms for the unique oxygen-induced retinal vasoconstriction in the immature retina.

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REFERENCES