The Lesson of Retrolental Fibroplasia

This type of blindness was epidemic among premature infants in the 1950's. How the problem was solved by trial and error is a parable of the issues that arise in medical experimentation on human beings

by William A. Silverman

The form of blindness known as retrolental fibroplasia arose abruptly in the early 1940's among infants, most of whom had been born prematurely, and quickly became an epidemic. It is an irony of medicine that the disease stemmed from the efforts of physicians to increase the premature baby's chances of survival in good health. After some 12 years of intensive and widespread investigation the cause was found and the disease was virtually eradicated. The entire episode bears recall now because it presents so sharply the painful questions that surround experimentation with human beings, particularly newborn infants.

The story of retrolental fibroplasia can be told within the framework of the French physiologist Claude Bernard's description of the stages of development of experimental knowledge: "In all experimental knowledge there are three phases, an observation made, a comparison established and a judgment rendered." Here the first phase began on February 14, 1941, when Stewart H. Clifford, a Boston pediatrician, made a routine home visit to examine a baby girl who had been born prematurely three months earlier. "Although the baby's general development was excellent," Clifford recalled recently, "I was shocked to note roving nystagmus [jerking movements of the eyeballs] and opacities in the eyes. I had to tell the family I was afraid the baby could not see. I immediately referred the baby to one of our leading ophthalmologists, Paul A. Chandler."

Chandler examined the infant's eyes and told Clifford he had never seen anything like them before. He had the baby admitted to a hospital, where her eyes could be examined while she was under anesthesia, and consulted with Frederick H. Verhoeff, a leading figure in American ophthalmic pathology. The examination revealed a heavily vascularized grayish membrane, which appeared to be on the rear surface of each lens. The problem was diagnosed as a fibrovascular sheath of the lens. An operation was considered but dismissed, since Verhoeff thought the prognosis was poor.

Within a week Clifford saw his second case of the disorder when he was called to examine a baby boy who was the survivor of twins born prematurely in July, 1940. (The baby's twin sister had died within a few hours of birth.) Clifford called in Theodore L. Terry, a Boston ophthalmologist, who declared that the condition was congenital cataracts. He arranged for the baby to be admitted to a hospital for an operation, but shortly before the operation was scheduled to begin Clifford, Chandler and Verhoeff, who were present as consultants, convinced him that the condition was inoperable.

The nursery records of these first two children were recently reviewed. They showed that each infant had been given the standard treatment of the time for premature babies, which included incubation in an environment enriched in oxygen. It was evident from the records that the disorder seen by Clifford in their eyes was what later came to be known as retrolental fibroplasia, from the Latin for formation of fibrous tissue behind the lens. (The term was coined by Harry Messenger, a Boston ophthalmologist who, as Chandler put it, was "quite a Latin and Greek scholar and who was often called on to provide a suitable name for various things.")

It soon became apparent that the disease was widespread. In 1942 Terry published in *The American Journal of Ophthalmology* a note on five cases he knew of. The note included two prophetic sentences: "In view of these findings [that all five children had been born prematurely] perhaps this complication should be expected in a certain percentage of premature infants. If so, some new factor has arisen in extreme prematurity to produce such a condition."

Between 1942 and 1945 Terry collected data on 117 cases of the disorder. Only eight of the cases were in infants said to have been born following a pregnancy of normal length. Terry became convinced that the condition developed after birth, because in three premature infants whose eyes were normal at birth he subsequently found well-established retrolental fibroplasia. Notwithstanding his view, the notion persisted until 1948 that the condition resulted from an inherent or acquired abnormality of the eye due to factors operating before birth or, at the latest, immediately after birth.

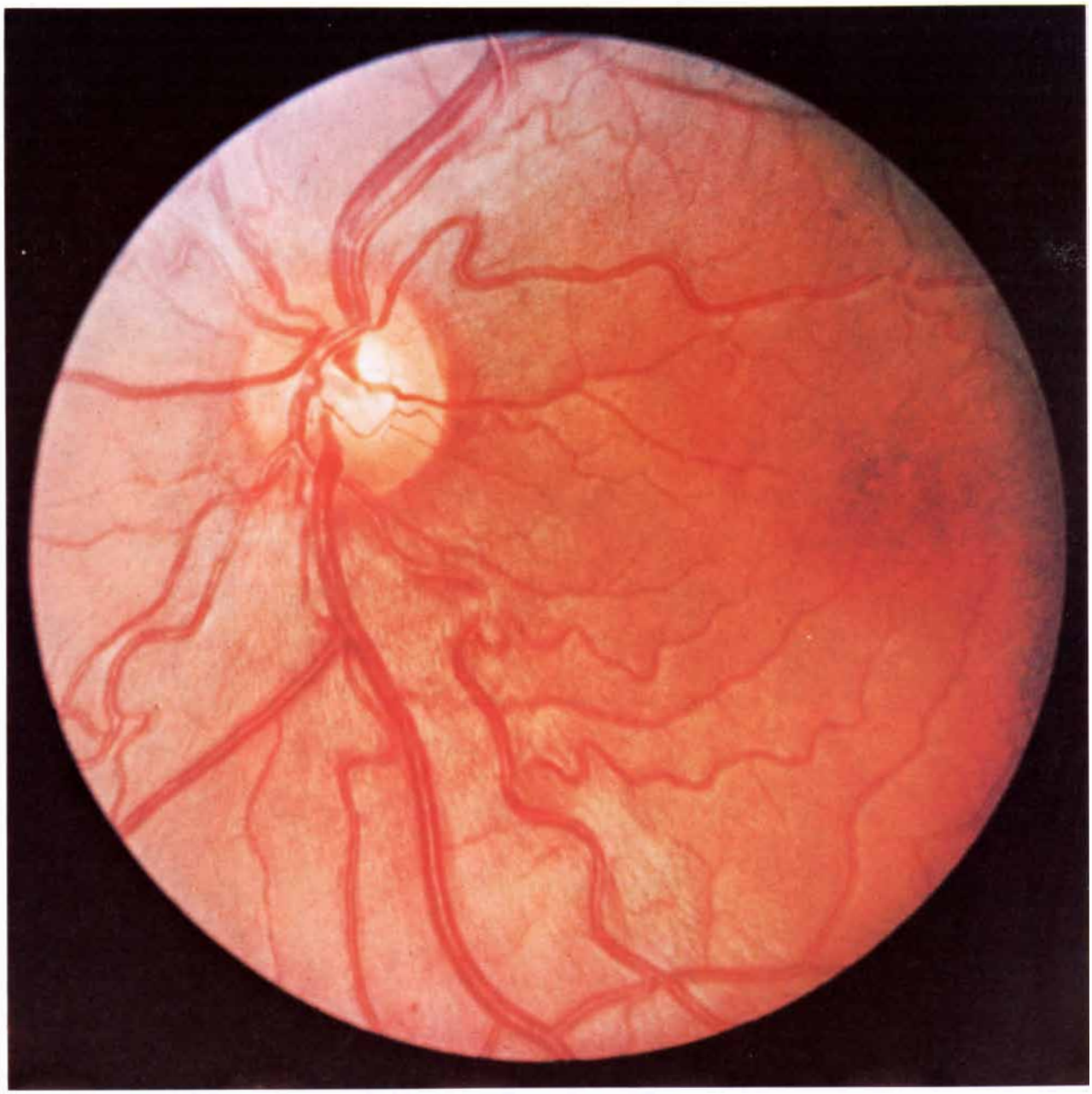
In 1948 two ophthalmologists at the Johns Hopkins Hospital (William C. Owens and Ella U. Owens) examined more than 200 premature infants at birth. None of them had retrolental fibroplasia. Half of the babies were reexamined monthly until they were six months old; by then 4 percent had developed the disease. The survey showed that the first detectable abnormalities began from two and a half to three and a half months after birth and involved a progression of changes in the blood vessels of the retina. The findings were quickly confirmed, and it soon became routine in large research centers studying the disorder to make ophthalmoscopic examinations of the eyes of all premature infants at weekly intervals in the hope of diagnosing retrolental fibroplasia early.

During those years I was in the department of pediatrics at the Columbia University College of Physicians and Surgeons and also on the staff of Babies Hospital of the Columbia-Presbyterian Medical Center. A case of retrolental fibroplasia in a prematurely born infant we cared for in 1950 is illustrative of the anecdotal and uncontrolled approach

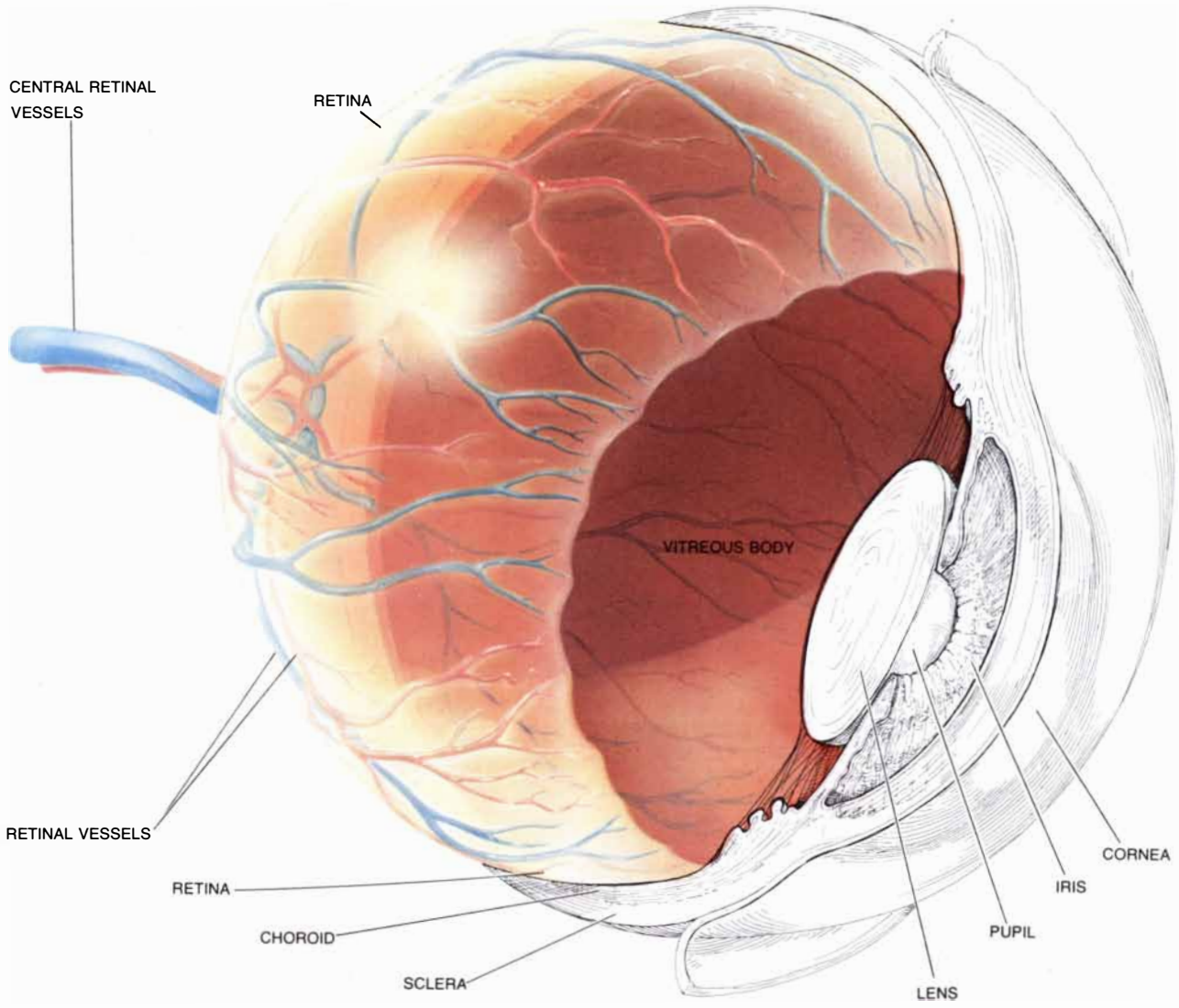
that has characterized much clinical research. On the day after the detection of the early signs of the illness I wrote on the baby's chart: "It is clear that any measures undertaken to influence the course of the disease must begin now. It must also be mentioned that at least one instance has been recorded (Owens and Owens) where these changes of... the retina [abnormal twisting of veins and unusual conspicuousness of blood vessels] have apparently failed to go on to the fibroplastic retrolental membrane stage and reverted to normal. This admittedly is a very remote possibility, but the fact that it has been observed will make interpretation of the beneficial effect of any therapeutic measure just that uncertain.... It has been decided to try ACTH [adrenocorticotrophic hormone] on the rationale that (1) it is a connective-tissue disease, (2) prematures may be ACTH-deficient and (3) no other agent or therapeutic regime has given any indication of beneficial effect."

The previously untried treatment was begun. The vascular changes in the eyes improved, and so the dose was lowered. The changes became worse, whereupon the dose was increased. The eyes returned almost to normal, and ACTH was withdrawn. The infant gained weight and was sent home.

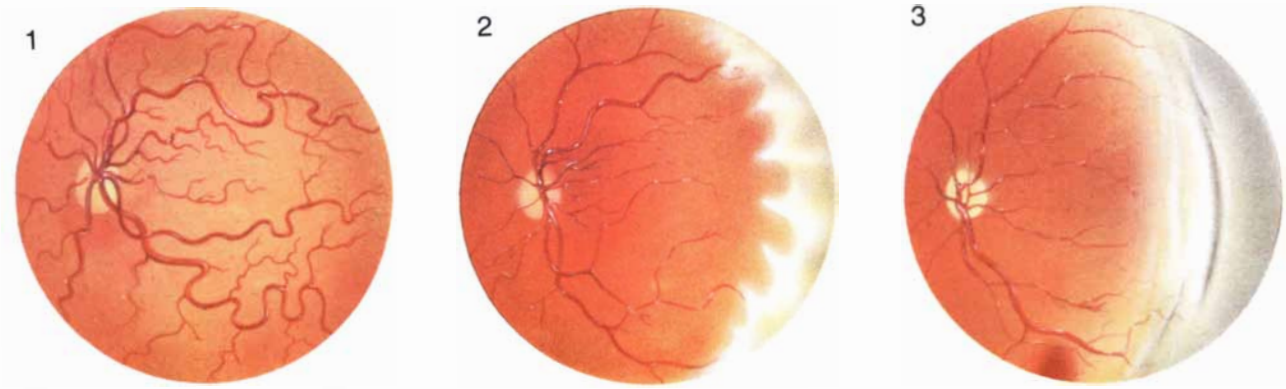
Soon after this dramatic experience 31 infants with the early changes of retrolental fibroplasia were treated with ACTH at Babies Hospital. Permission for this innovative approach was ob-



VIEW OF RETINA through a direct ophthalmoscope shows blood-vessel abnormalities characteristic of retrolental fibroplasia, notably the hairpin bends in many of the arteries. In the normal retina the arteries are nearly straight. This photograph shows the retina of a teenage child who was born prematurely and became afflicted with retrolental fibroplasia as a result of the oxygen-rich environment that was then standard treatment for premature infants. The affliction did not lead to impairment of vision, but the arterial changes persist.



NORMAL HUMAN EYE is depicted in a view that shows structure of the blood vessels of the retina. Arteries are portrayed in red, veins in blue. The retina extends around the eyeball inside the choroid and the sclera. Much of the center of the eyeball is filled with the clear structure known as the vitreous body. In the normal eye the retinal blood vessels do not leave the retina, but in the wild and twisting growth associated with retrolental fibroplasia the capillaries may frequently break through the retina and penetrate the vitreous body.



DEVELOPMENT OF RETROLENTAL FIBROPLASIA is traced in a series of drawings based on what was seen through a direct ophthalmoscope. The drawings show part of the background of the left eye of a prematurely born infant at the age of five weeks (*1*), nine weeks (*2*) and 11 weeks (*3*). In the first drawing the retinal blood vessels are severely dilated and twisted. At nine weeks a crescent-shaped swelling of the retina has begun to form at the right outer edge of the field and the retina has started to detach. In the final drawing the detachment of the retina has progressed to the stage where a fold, which is shown by curving line near right edge, has developed in the retina.

tained from the parents in the same informal way that it had been a few years earlier when another "miracle" drug, penicillin, was employed to treat life-threatening infections of various kinds. Of the 31 infants, 25 left the hospital with normal eyes, two became blind, two lost all vision in one eye and two had useful vision with only minor retinal scars.

These results were particularly impressive compared with those of seven infants with early retrolental fibroplasia at Lincoln Hospital in New York who did not receive ACTH because its efficacy had not been proved. Six of them became blind. ACTH seemed to be the cure for the disease.

We were puzzled, however, by two infants (one from Lincoln Hospital and one from another New York hospital) whose early changes subsided without treatment and who were left with normal eyes. It seemed clear that only a randomized and concurrently controlled trial (in which one group of patients continues to receive the standard treatment and one receives the proposed new treatment, with a patient being allocated to one group or the other strictly at random) would settle the question of the effectiveness of ACTH.

The trial was made. About a third of the infants who received ACTH became blind, whereas only a fifth of the control infants did. Moreover, there were more deaths in the ACTH group. Two years later William Owens published the observation that approximately three-fourths of the infants showing the early changes of retrolental fibroplasia returned spontaneously to normal. This was exactly our experience in New York during the treatment with ACTH.

More than 50 separate causes of retrolental fibroplasia were proposed. About half of them were examined formally; only four were tested by prospective experimental clinical trials. Gradually, as the clinical evidence accumulated, attention was focused on the oxygen-rich environment routinely provided for premature babies as a factor in the causation of retrolental fibroplasia. Significantly, as one looks back, a question that was hotly debated in the early 1950's was whether the causative factor was an excess of oxygen or a lack of oxygen in the baby's retinas. Two physicians, Kate Campbell in Australia and Mary Crosse in England, who have been credited with discovering the cause of the disease, published anecdotal evidence incriminating an excess of oxygen in observations made in a population of 142 infants. In Paris the opinion (based on observations of 479 infants) was the reverse. Charity Hospital in New Orleans, which had the largest premature-baby unit in the U.S., was free of retrolental fibroplasia notwithstanding the routine continuous administration of oxygen.

Norman Ashton of the Institute of Ophthalmology of the University of London advanced a hypothesis that the disease entailed an abnormal overgrowth of the developing blood vessels of the retina. There was indirect evidence suggesting that the normal stimulus attracting blood vessels into the fetal retina is an oxygen demand arising in the inner layers of that part of the eye in the fourth month of gestation. This view came from the work of the Israeli ophthalmologist I. C. Michaelson on the development of the retina in several species, including man.

Michaelson had injected India ink into the arterial system of the eye of human fetuses at autopsy and then teased the retina out to make flat preparations. One of his principal findings was that the capillaries bud from the veins, away from the oxygen-laden arteries, leaving a zone free of capillaries. Later work showed that when animals were reared at a simulated high altitude, in an atmosphere with a reduced oxygen content, the capillary-free zone became narrower. Although the relevance of these observations to retrolental fibroplasia went virtually unnoticed for several years, the findings supported Ashton's later hypothesis that the disease was caused primarily by a severe lack of oxygen in the deep retinal layers of the developing eye.

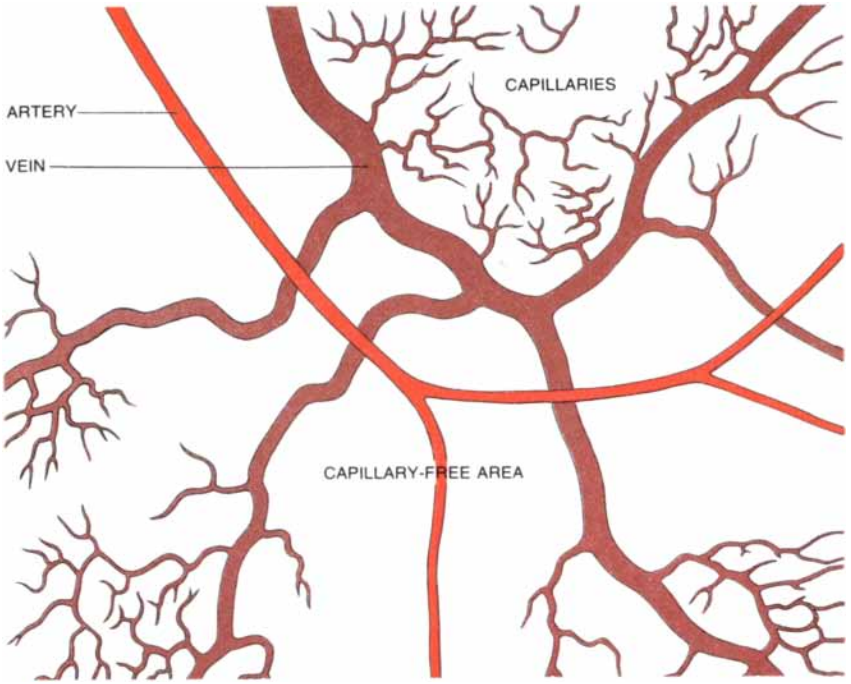
Ashton came to the problem armed with the knowledge that the newborn kitten had an incompletely vascularized retina, roughly comparable to the retina of the human infant at about the seventh month of gestation. Ashton and his coworkers put a cat and three kittens in an atmosphere enriched in oxygen. The first experiment showed that after four days of continuous exposure to an atmosphere that contained from 75 to 80 percent oxygen the outgrowing blood vessels of the retina were completely attenuated. The initial effect of the oxygen was shown to be a marked narrowing of the immature retinal vessels, followed by their obliteration. Paradoxically it was exposure to the high level of oxygen, with the resulting eradication of germinating blood vessels, that appeared to cause the ultimate deficit of oxygen in the deep retinal tissues of the eye. After the kittens had been returned to a normal atmosphere the blood vessels grew in a disorganized fashion, with a budding of new capillaries out of the normal retinal area into the vitreous body.

At Gallinger Municipal Hospital in Washington, D.C., Arnall Patz, a resident in ophthalmology, designed a test in which some premature babies in incubators would be given less supplemental oxygen than was the standard at the time. The study turned out to be a difficult trial for the investigators. As Patz recalls it: "The nurses were convinced that we were going to kill the babies in the low-oxygen group; at night some of the older nurses would turn the oxygen on for a baby who was not receiving oxygen and then would turn it off when they went off duty in the morning." Although the test, involving 76 infants, appeared to incriminate high levels of oxygen in the causation of retrolental fibroplasia, the debate over oxygen continued.

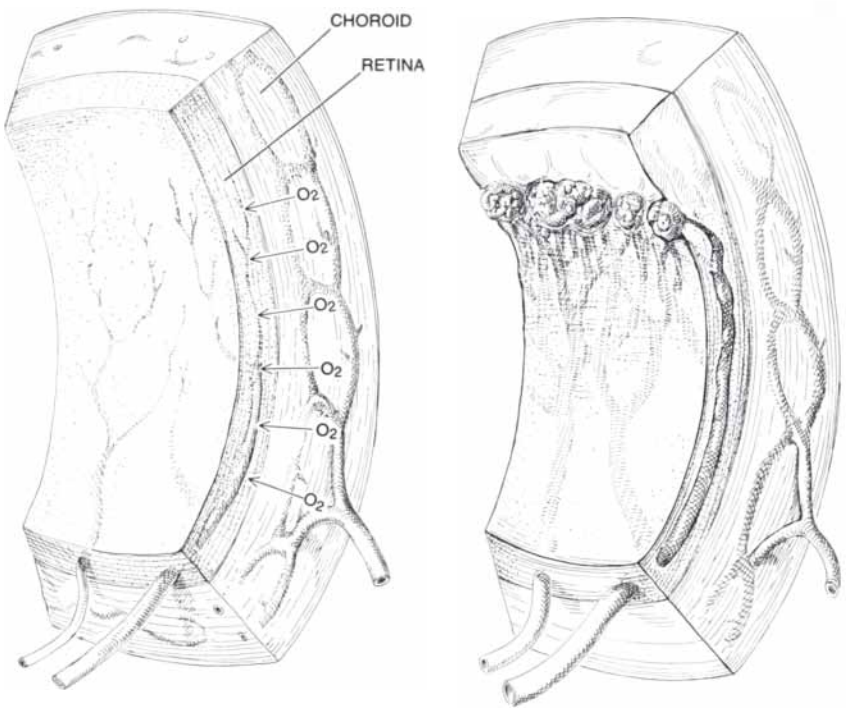
Early in 1953 the oxygen issue was discussed at a meeting called for the purpose at the National Institutes of Health. Two strong views emerged. A majority thought that a formal, controlled trial should be carried out simultaneously in several medical centers. A minority, arguing that there was already enough observational evidence to indict oxygen, opposed the trial as immoral. The dispute reflected a basic problem in medicine, which Bernard had described 100 years earlier: "Many physicians attack experimentation on human beings, believing that medicine should be a science of observation, but physicians make therapeutic experiments daily on their patients, so this inconsistency cannot stand careful thought. Medicine by its nature is an experimental science but must apply the experimental method systematically." Briefly, the majority thought the participants who opposed the need for formal and controlled experiments were in effect asking for the substitution of informal and uncontrolled experiments.

The study began in July, 1953. Over a period of a year nearly 800 infants in 18 hospitals were studied. They had in common the fact that they were born prematurely and that each one weighed 1.5 kilograms or less at birth. During the first three months enrollment was in random sets of three. Two infants in each set were allotted to a group that received supplemental oxygen only when clinical indications called for it, and then in a concentration of no more than 50 percent; the third infant received what was at that time the routine treatment of being given oxygen continuously at a concentration of more than 50 percent for 28 days. For the remaining nine months of the trial all the infants were given curtailed oxygen only.

The results were dramatic. Retrolental fibroplasia occurred in 23 percent of the infants in the routine-oxygen group and in 7 percent of the group that received oxygen in curtailed amounts. (This last finding is a seldom remembered detail of the trial and deserves emphasis. Not every infant receiving "curtailed" oxygen by the standards of the



BLOOD-VESSEL DEVELOPMENT in the retina was examined by the Israeli ophthalmologist I. C. Michaelson, who found that in normal conditions the capillaries bud out from the veins and tend to stay clear of areas around arteries. When experimental animals were reared in an environment low in oxygen, the capillary-free zone became narrower. The findings supported a hypothesis that oxygen demand in the retina caused blood vessels to proliferate and that therefore a lack of oxygen was cause of retrolental fibroplasia. Later it was shown that retinal oxygen deficit was in fact caused by prolonged breathing of oxygen at high concentration.



EFFECT OF OXYGEN on the infant retina is at first (*left*) to cause the developing blood vessels to constrict and then to wither and become obliterated. The arrows indicate increased diffusion of oxygen from blood vessels of the neighboring choroidal layer; these channels are not appreciably affected. Later the withered blood vessels of the retina regrow in a disorganized fashion (*right*), erupting through the retinal surface into the vitreous body. These effects appear only in incompletely developed retinas, which is why retrolental fibroplasia afflicted mostly prematurely born infants who had been exposed to high levels of oxygen in incubators for days.

time escaped the disease.) The study also showed that the risk of the disease increased with each day in an oxygen concentration of more than 50 percent for up to two weeks of exposure; thereafter it leveled off.

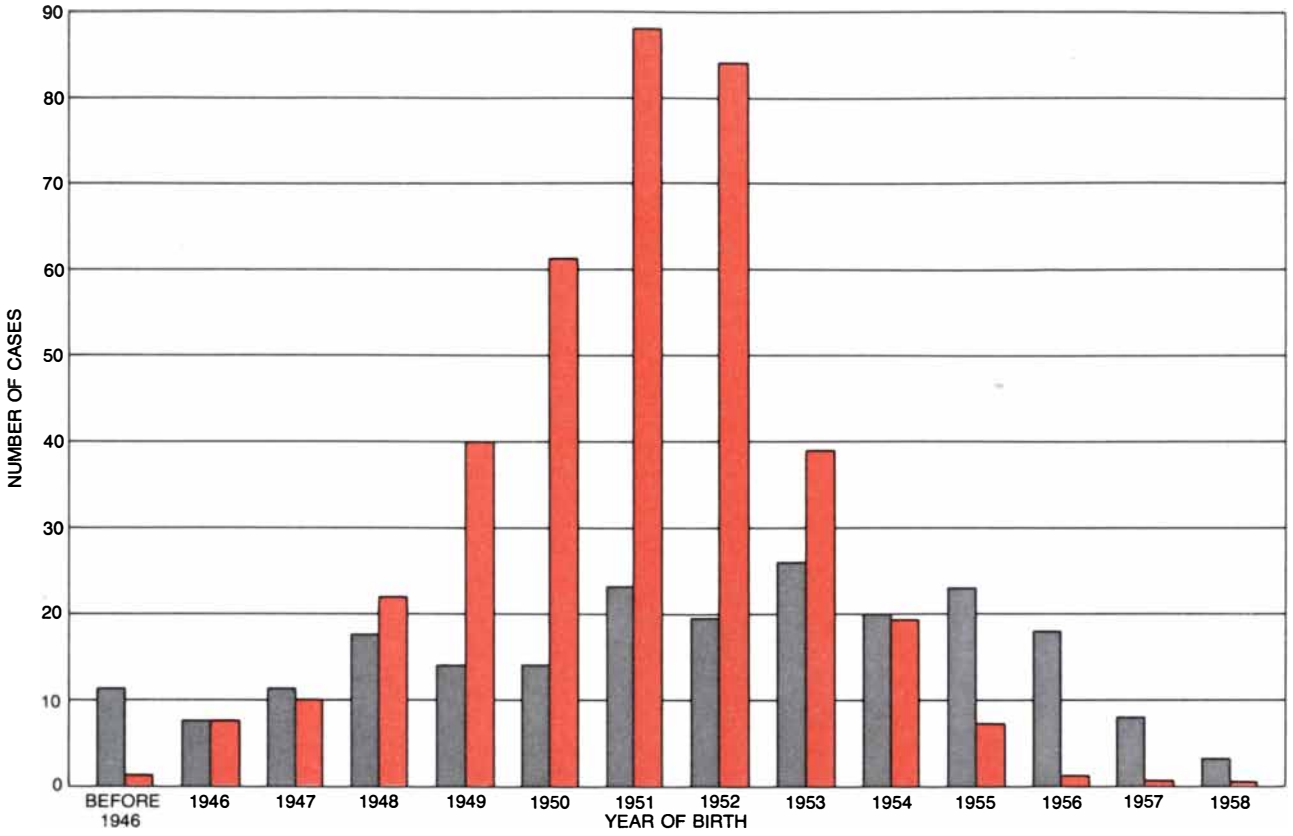
The study and its results represented the second and third stages mentioned by Bernard, "a comparison established and a judgment rendered." The results were announced at the annual meeting of the American Academy of Ophthalmology and Otolaryngology in 1954. The announcement was immediately and widely publicized. Within a year the practice of giving premature infants a high concentration of oxygen was widely modified. The disease subsided as quickly as it had arisen.

By now it was apparent that the reason for the sudden appearance of the disease was related to the general acceptance of a hypothesis (put forward in the early 1940's) that the high toll of brain damage in premature infants was caused by a lack of oxygen that up to then had not been recognized. This view provided the rationale for the continuous administration of a high concentration of oxygen, even to babies who showed no abnormal symptoms. At the end of World War II incubators were designed and built to meet the new specifications of physicians for providing high concentrations of oxygen.

Oxygen at high concentrations can be toxic, as it proved to be to the developing blood vessels of the retina of the premature infant. The result in retrolental fibroplasia was that the developing retinal vessels withered. Subsequently there was a wild regrowth of the vessels. Although this proliferative process usually subsided, leaving a normal retina, in a small number of cases extensive hemorrhages developed and fibrous scar tissue formed, causing the retina to become detached from its normal position and to billow out against the back of the lens.

Medically the story appeared to be complete, and interest in the disorder quickly waned as it became one of the rarer complications of premature birth. Actually many of the challenges of the experience with retrolental fibroplasia had not yet been confronted. Now, more than 20 years later, several crucial questions remain.

The first sign of trouble began five years after the cooperative study. Mary Ellen Avery and Ella H. Oppenheimer of the Johns Hopkins School of Medicine reported that the frequency of death from hyaline membrane disease was higher in infants at the university hospital than it had been during a five-year period before 1954, when oxygen was administered liberally to premature babies. In 1963 Alison D. McDonald of



RISE AND DECLINE of retrolental fibroplasia is reflected in this chart of blindness among children in southern California. The chart shows the number of cases of blindness attributable to retrolental fibroplasia (*color*) and to other causes (*gray*). Eventually the abrupt appearance of retrolental fibroplasia was traced to the adoption of a policy of liberal administration of oxygen to prevent brain damage in premature infants. The brain damage is caused by a lack of oxygen that is difficult to recognize. At the end of World War II incubators were designed to make it technically feasible to administer a high concentration of oxygen continuously to a premature infant.

Guy's Hospital in London reported the experience of 19 centers for the newborn in England and Wales before and after the restricted use of oxygen. She found that with increased treatment with oxygen the frequency of retrolental fibroplasia rose but the incidence of spastic diplegia (palsied lower extremities) fell.

Kenneth W. Cross of the London Hospital Medical College recently examined the trend in the death rate of newborn infants in England and Wales over the past 40 years. He found a smooth exponential decrease in the rate of death during days one to six after birth, but the curve for the rate of death on the day of birth (day zero) showed a skewed break in the downward trend, particularly in infants whose weight was low at birth. The same anomaly appeared in data from the U.S. The break corresponded closely with the beginning of restrictions on oxygen therapy for infants.

Cross estimated the number of excess deaths per year following the adoption of the restrictive policy by subtracting the number of deaths that were expected (a figure obtained by extrapolating the smooth curve preceding the reduction in oxygen therapy) from the number of deaths that had occurred. The excess amounted to about 700 per year. Dividing this figure by a number representing the decline in blindness from retrolental fibroplasia, Cross calculated that 16 deaths occurred to produce each sighted infant during the years of oxygen restriction. (The study did not take into account the fact that the break in the curve also coincided with the introduction of certain medicines to prevent and treat infection; these substances were later shown to be dangerous to premature infants.)

One may ask why the cooperative study in the U.S. failed to discover the risk that curtailed oxygen therapy might increase the death rate in certain infants. This disturbing oversight is related to a deliberate quirk in the original design of the study. Infants were not enrolled in the trial until they had survived for 48 hours. The reason was that most of the deaths among premature infants are in the first two days of life; it was argued that the inclusion of these early deaths would not help to answer the question of oxygen damage to the retinal blood vessels. The strategy also had the advantage of placating the nurses, most of whom were extremely resistant to the policy of restricting oxygen. It was some time before a balance was struck (which is not yet an ideal one) whereby premature infants who need extra oxygen to survive without brain damage receive it, but in concentrations that do not seem to be giving rise to blindness.

The success of the effort to solve the puzzle of retrolental fibroplasia had a good deal to do with the large expansion by Congress of appropriations for medical research beginning in the late 1950's. Much of the research was directed at problems affecting the fetus and the newborn infant, with fruitful results for both biology and medicine. Notwithstanding the advances in every branch of medicine, which have taken the profession out of the age of magic for the first time, one sees a widespread erosion of public confidence in the medical profession.

Perinatal medicine, which is directed at disorders of the infant during the period shortly before and shortly after birth, provides an example. The nature of the problem, as it has been stated by Howard Brody of Michigan State University,

is that "scientists or clinicians are prone to error when they confuse scientific problems with value problems and try to solve the latter with tools of the former." As knowledge of perinatal disorders has deepened, physicians have too often come out of the laboratory advising treatments that have been neither fully tested nor presented to the community for consideration and approval. However noble the objectives of these physicians may appear to be, both the practice and the science of perinatal medicine have been handicapped.

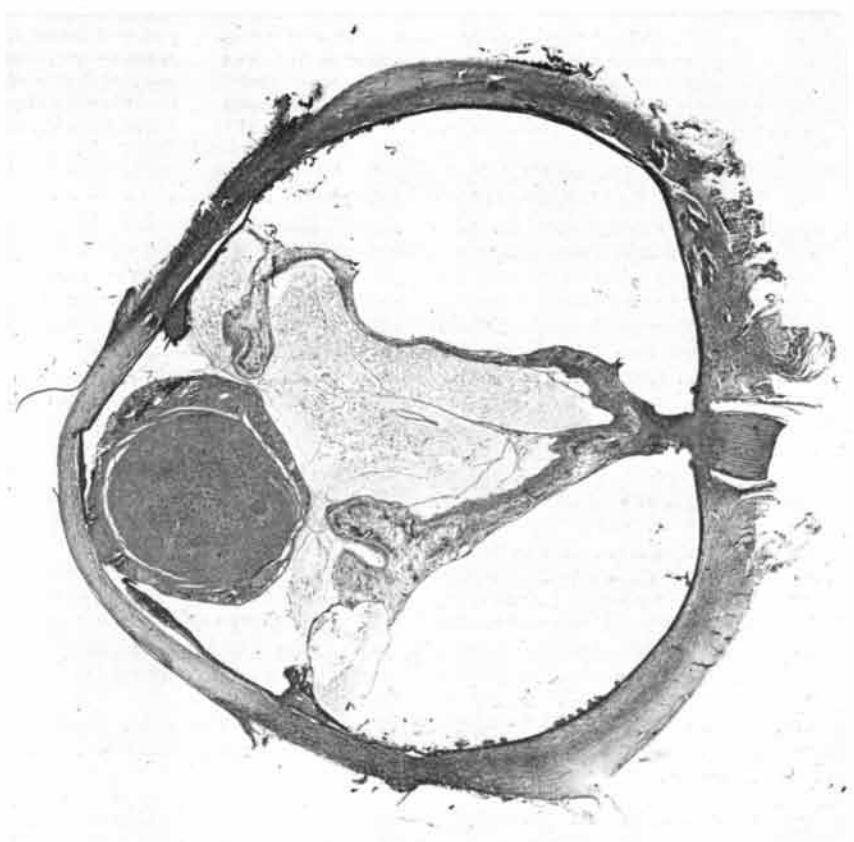
The philosopher Kurt von Fritz notes that "there are no absolute criteria by which a value system of a society can be judged objectively." I go further: There are no absolute criteria by which the values of an individual can be judged with complete objectivity. As a result the evaluation of risk versus benefit in all medical interventions (whether they are proved or experimental) is a difficult and individualized process, particularly in the pluralistic society of the U.S.

The late Henry K. Beecher of the Harvard Medical School classified all experiments on human beings into groups that have been summarized in two mutually exclusive categories: therapeutic and nontherapeutic. His basis for classification was the intent of the experimenter, not the risk. This classification has been accepted uncritically by almost everyone.

The scientific view of the world, however, is probabilistic: risk and benefit are relative, not absolute. They should be evaluated in what could be called a systems view, in which categories of risk and benefit would be weighted. The heaviest weight usually would be assigned to the risk and benefit affecting the individual (or the mother-baby unit while the infant is still a suckling), with progressively less weight being given to the family, the community, the subculture and so on.

Indeed, the current debate about informed consent for experimentation on the fetus and the newborn infant is pointless. Interpretations of risk versus benefit and the social status of these individuals are value judgments that will be decided differently by different subcultures in the society. To impose one solution on everyone is immoral.

The situation now is that the Federal Government has imposed restrictions on "nontherapeutic" research affecting the human fetus and suckling infants. In my view this is a sorry state of



ADVANCED STAGE of retrolental fibroplasia appears in this photograph of a horizontal cross section of an eye. The lens is the oval structure at the left, and the gray mass next to it is the retina, which has become completely detached. Retrolental fibroplasia was originally thought to be a lens disease because of the gray fibrous tissue found behind lens in severe cases.

affairs. The profusion of new drugs, the advances in medical practice and the concern over the effects of environmental factors on health have made this a time when more rather than less experimentation involving human beings, including children, is needed. The experiments should be scrupulously designed and carefully surrounded with safeguards. Unfortunately those conditions are not always observed in modern experiments, which are frequently not even acknowledged to be experiments. Regrettably the medical profession had a role in creating the situation.

In 1967 a state senator in New York attracted wide public attention with the assertion that barbarous experiments on children were being conducted in the municipal hospitals of New York City. He drafted legislation to outlaw all experimentation on children. The medical profession responded with a proposal for legislation that would allow carefully safeguarded clinical investigation involving children. The senator abandoned his attack, apparently because it was no longer exciting public interest, and the medical profession thereupon dropped the subject too. Subsequent events, which culminated in the current restrictions, indicate how wrong it was not to pursue the matter in a more responsible way at the time.

The threat in 1967 had the effect of encouraging bootleg studies, that is, experiments that are neither formal nor informal and so avoid the issues of informed consent and strict review. By the simple device of labeling innovative treatments as "not experimental" but merely "modification or evolution of existing practice" and "based on sound physiologic principles," investigators have proceeded to apply new therapy. The rules of evidence for scientific investigation are ignored in these anecdotal trials.

Thus the trial-and-error approach that led to the retrolental fibroplasia episode is being repeated on a wide scale. This Russian-roulette strategy of empirical studies is condoned and even widely praised, whereas efforts to test new treatments with randomized, controlled clinical trials that limit risk are characterized as "daring." A recent comment by an academic physician described the controlled-trial method as "always comforting" but "probably not a very effective way to assess therapy that may be dependent on a number of variables." In the present situation of ill-conceived restrictions and bootleg experiments it is as if more than 10,000 children had not been blinded by retrolental fibroplasia, Bernard's words had never been spoken, R. A. Fisher had never developed the randomization approach to the problem of multiple variables and A. Bradford Hill had never perfected the format for controlled clinical trials.