Appendix A
The story of retrolental fibroplasia

A 'NEW' DISEASE

Retrolental fibroplasia (literally, fibrous tissue behind the lens of the eye) was 'discovered' in February 1941 by two Boston physicians—pediatrician Stewart H. Clifford and ophthalmologist Paul A. Chandler. They examined a three-month-old girl and found what appeared to be dense white membranes filling the pupils of her eyes; the abnormalities were unlike anything they had ever seen before. This blind baby and four additional RLF-affected children were reported the following year in a preliminary note by Boston ophthalmologist, Theodore L. Terry. He found that all five of the patients had been born prematurely. 'In view of these findings,' he wrote prophetically, 'perhaps this complication should be expected in a certain percentage of premature infants. If so, some new factors have arisen in extreme prematurity to produce such a condition.'

Rising frequency

The prediction was fulfilled; following the initial report, Terry examined well over a hundred children with the strange type of infant blindness by the time of his death in 1946. Search of past records revealed that the unusual condition had been noted sporadically (under a variety of obscure labels) for more than 30 years, but there was little question that it was now occurring as a fairly common complication of extreme prematurity (the condition was less frequent in relatively mature babies and rare in full-term infants). Surveys conducted in cities throughout the world confirmed a suspicion that the complication seemed to occur most frequently in infants reared in premature centers with the most highly organized and advanced programs for care.

Descriptive studies

During the first years of study, affected babies were examined when they were several months old. It was assumed that the disorder had developed before or, at the latest, immediately after birth. Retrospective studies focused on associations with complications of pregnancy and delivery, and with treatments given to mothers or to their offspring immediately after premature birth.

Prospective observations

Understanding was improved after the results of a prospective investigation were reported. William and Ella Owens, a husband and wife team of ophthalmologists at Johns Hopkins University, examined more than 200 prematurely born infants in a hospital nursery; all had normal eyes. Half of these babies were examined at regular intervals; 4 per cent developed RLF. They described a progressive development of proliferative blood vessel changes (manifested by dilation and tortuosity of retinal arteries and veins seen in the interior of the eye with an ophthalmoscope) beginning at age 2½–3½ months in the afflicted babies. Soon there were retinal hemorrhages, the retinal layer of the eye became elevated and grayish masses of detaching retinal tissue billowed forward in the chamber of the eye and formed an opaque scar-like cast behind the lens. At this stage of the abnormal process (at 4–6 months of age), the pupil of the eye appeared white even to an untrained observer. Both eyes were usually involved and, not infrequently, the severity of the scarring changes was unequal. It was now clear that the disorder usually began well after delivery, and focus of interest shifted to postnatal events and treatments.

The frequency of occurrence of RLF, first in the United States and later in other developed countries, rose sharply at the end of the 1940s. It quickly became the leading form of blindness in infants, but peculiar geographic and temporal differences in incidence were reported.

Circumstantial associations

An attempt to seek an explanation for the alarming new epidemic was undertaken in 1949. The co-occurrences of RLF and 47 factors relating to mothers and children (298 normal and 53 RLF-afflicted children) delivered in Boston during the years 1938–48 were examined. A number of associations were discovered. The most interesting were those related to treatments: the rise in incidence paralleled the use of medicinal iron, water-miscible vitamins, and supplemental oxygen. The investigators found, however, that the correlation 'was less striking for oxygen than for ... vitamin preparations and for iron' (p 17). Numerous other associations were described in a flood of anecdotal reports published in the late 1940s and early 1950s.

EARLY COMPARATIVE TRIALS

Vitamin E

The results of the Boston survey led to a suggestion that the eye condition might be related to vitamin E deficiency (marginal body stores of this substance at birth aggravated by the use of water-miscible vitamins that increased the requirement for vitamin E, and by a destructive effect of iron salts on the E substance—alpha tocopherol). The hypothesis was tested in a quasi-experimental trial for a period of 10 months (alternate infants admitted to a premature nursery in Baltimore during 1949 received either synthetic vitamin E or no treatment). The early trend of difference in the two groups (no RLF among 11 treated infants, 5 developed the condition in the control group of 15 babies) was sufficient to impress advisers who were keeping an eye on the study; they persuaded the researchers to abandon the controlled trial. Subsequently all infants received vitamin E treatment, and, as word of the Baltimore experience spread, the preventive treatment was started in many hospitals throughout the world. These experiences showed no impressive protective effect of tocopherol treatment; after a few years, all interest in this approach faded away.

ACTH

Following the vitamin E disappointment, numerous other treatments were tried. One of the most promising of these was the use of a powerful agent ACTH (adrenocorticotropic hormone), to inhibit the wild proliferation of retinal blood vessels seen on examination of the eye in the early stages of RLF. At a New York Hospital, 31 infants with vascular changes were treated with ACTH; 25 experienced a regression of the abnormalities and they were left with completely normal eyes. By contrast, 7 babies at a nearby hospital had not been treated when they showed early signs of the affliction; 6 of the 7 went on to become totally blind.

ACTH seemed to be the cure for the disease. But further studies quickly dashed this hope. A formal randomized clinical trial of the new treatment—ACTH compared with untreated controls *in the same hospital*—indicated that the outlook was better for babies who were untreated. The potent therapy had been without appreciable effect on what is ordinarily a benign course (later studies demonstrated that early changes of RLF usually subside spontaneously), and the investigators were disturbed to find that ACTH-treated infants appeared to have a higher risk of fatal infections.

SUPPLEMENTAL OXYGEN

First associations

In 1951—a full decade after the 'discovery' of the affliction—oxygen enriched incubators were implicated by association. Expensive, gas-tight American incubators had been introduced in Britain when the newly inaugurated National Health Service provided the funds to pay for them. RLF began to appear shortly thereafter. Mary Crosse, a Birmingham pediatrician, wondered aloud whether or not the disease might be linked to the new equipment. An Australian doctor, Kate Campbell, set out to confirm Crosse's idea by tallying the outcomes in infants who had been treated with different oxygen regimens in three Melbourne hospitals. Her observations connected the eye disease to liberal use of supplemental oxygen (p 18).

Conflicting observations

When other investigators tried to confirm Campbell's circumstantial evidence, the results were confusing. A survey in Oxford partially supported the oxygen hypothesis, however, a hospital in New Orleans found no RLF among oxygen-exposed babies. A Paris group observed that infants treated with continuous high concentrations of oxygen were no more likely to develop blindness than others who received the medicinal gas only sparingly. And the findings of Thaddeus Szewczyk, an ophthalmologist in East St Louis, seemed to contradict the 'oxygen is dangerous' theory completely. Szewczyk believed that RLF developed when babies were removed from high concentrations of oxygen too quickly. When the early signs of

blood vessel abnormality were observed in 19 infants, they were returned to high oxygen environments; all improved and their eyes became normal after four days.

A quasi-experimental trial

Two young physicians, ophthalmology house officer Arnall Patz and pediatrician Leroy Hoeck, attempted to conduct a controlled clinical trial of oxygen treatment in a Washington D.C. hospital. Seventy-six small premature infants were assigned in alternate order to liberal oxygen or to restricted oxygen regimens. The results of this trial, published in 1952, seemed to indict continuous oxygen treatment. But the investigators and their critics had a number of unresolved doubts about the trial: compliance with the prescribed treatments was questionable (p 107), the potential bias introduced by non-random assignments could not be evaluated, 11 infants were withdrawn or dropped out, and fears about the matter of safety of oxygen restriction (risk of death and of brain damage) could not be allayed by the small experience.

Animal evidence

Research with experimental animals was also frustrating. In the early 1950s, British ophthalmologist Norman Ashton found that exposure to oxygen in high concentrations caused changes in the eyes of newborn kittens that exactly mimicked the early stages of the human disease; the blood vessels in the retina first constricted, the immature vascular network then withered, and this was followed by wild proliferation of vascular tissue when the kittens were removed from oxygen. These experiments strongly supported a role of supplemental oxygen in the genesis of RLF, except for one crucial limitation. The animals, unlike human infants with the disease, never became blind. Thus, doubts persisted concerning the prime cause of blinding complications in babies.

A national trial

By early 1953, it became obvious that the confused picture concerning the associations between care-taking practices and outcomes (RLF, death, and brain damage) would only be clarified by means of a large scale critical experiment using a newly devised investigative plan—the randomized clinical trial. It was hoped that this would lead to the prevention of a disease that had, by this time, blinded about 10 000 infants throughout the world (approximately 7000 of the victims were born in the United States).

A meeting was convened in early 1953 by the US Public Health Service; most of the American pediatricians and ophthalmologists who had been studying the epidemic were invited. Although the majority felt that a controlled trial must be undertaken immediately, a minority felt that excess oxygen had already been demonstrated to be the cause of RLF and that it was immoral to expose infants to the high oxygen treatment regimen that had been used for years in the routine management of small babies. A still smaller group believed that treatment with high oxygen concentrations was absolutely necessary to ensure intact survival; they argued that the proposed new approach of oxygen curtailment was unethical. The great divergence of opinion showed, as much as anything, that a definitive, well controlled trial was essential to settle the controversial issues. It was finally agreed that 18 hospitals

throughout the US would join in a cooperative effort to compare the effects of two contrasting regimens of oxygen administration.

A fixed time period of one year was chosen by the planners (it was estimated that 750 infants would be available for study during this interval). A complex design for random allocation to treatments was chosen: for three months two thirds of the enrolled infants were to be managed according to the new curtailed-oxygen policy, while one third were to receive routine treatment of continuous high concentrations of the gas. Mortality rates were to be closely monitored during this initial phase of the trial; if no dangers of oxygen restriction were detected, all enrolled babies would be managed under the curtailed-oxygen regimen for the remaining nine months of the trial. In view of the many disappointments and false hopes of the past, all participants in the trial agreed that no results should be released until the carefully planned exercise was completed and all the accumulated data were analyzed. The complicated clinical trial began on 1 July 1953.

'Under 40 per cent is safe'

In May 1954 a publication appeared reporting the results of a single-hospital randomized clinical trial comparing the effects of high versus low oxygen therapy (under 40 per cent concentration) among 85 premature infants. Mortality in the low-oxygen group was greater than among those who were assigned to liberal oxygen, but the difference was attributed to chance (p 122). No instances of scarring RLF were observed among 28 survivors in low oxygen; 8 examples were found among 36 surviving babies treated with high oxygen. The authors concluded that a policy of oxygen restriction was not harmful and that RLF was entirely preventable if oxygen (kept below 40 per cent) was administered only when necessary. Many observers, noting the small number of infants in the study, chose to await the results of the national trial before altering the methods of care that might increase mortality or brain damage. But the suspense and concerns grew as the final months of the large study dragged on.

Epidemic conquered

In September 1954 (after the eyes of the last enrollees in June were followed for three months) the results of the collaborative effort were announced. No appreciable increase in mortality had been observed under restricted oxygen, but there appeared to be a striking reduction in scarring RLF: 23 per cent of 53 babies who had received standard high concentrations of oxygen (above 50 per cent for 28 days) were affected; 7 per cent of 533 infants in the curtailed group (only as indicated and under 50 per cent oxygen concentration) developed the permanent lesions of the eye disorder. Physicians were warned that supplemental oxygen should no longer be administered on a routine basis. It was advised that the gas should be administered only when absolutely necessary and that both the duration of treatment and concentration of oxygen should be kept to a minimum.

The battle to eliminate the twelve-year scourge of premature infants seemed to be won at last—the incidence of RLF dropped precipitously around the world as restricted-oxygen policy was widely adopted. In the flush of success it was forgotten that the original plans called for monitoring the long-term neurologic status of the

large number of infants enrolled in the unique US study. Follow-up studies of these children were never carried out.

A PYRRHIC VICTORY

As it turned out, the victory over RLF was not as glorious as first thought, but it took years to piece together what may have happened. Epidemiologic evidence began to suggest that RLF had virtually disappeared because the infants at highest risk were dying in the first hours of life. (This fact lay buried in summaries of mortality rates which were not analyzed by age at death and by birthweight.) The frequency of the most common fatal lung disorder in the smallest premature infants (hyaline membrane disease) and overall first-day mortality in the most immature babies both increased as RLF fell. Equally disturbing was an apparent increase in the number of premature infants who developed a form of cerebral palsy (spastic diplegia) during the years after 1954 when the policy of oxygen restriction was in effect. A British follow-up study of children who had been born prematurely, reported in 1962 by Alison D. McDonald, then of Guy's Hospital Medical School, found a correlation between spastic diplegia and postnatal breathing disorders, and an inverse relationship between the rate of brain damage and duration of oxygen treatment.

Over-interpretation of evidence

The findings came as a shock since the national cooperative study and single-hospital trials had seemed to provide clear answers about the relationship between oxygen treatment and RLF. In retrospect, it was realized that many of the interpretations had been unwarranted. The single-hospital trials were too small to test the mortality question vigorously and the cooperative trial enrolled infants too late—they were enlisted at age two days. Since the first 48 hours of life is the period of highest mortality risk (a full 45 per cent of premature infants admitted to the 18 collaborating hospitals died before they were old enough to be enrolled), the 'curtailment of oxygen is safe' question had not been put to a critical test in the national study. The suspicion slowly grew that oxygen was being restricted too stringently, particularly in the crucial first two days of life. But the agonizing question was never put to a formal test.

The confusing situation in the 1960s was further complicated by the widely broadcast claim that RLF would not occur if oxygen concentration was kept under 40 per cent (based on extrapolation of results in the small single-hospital trial reported in May 1954). Again, the possibilities of a critical threshold of oxygen concentration, a critical duration of exposure, or some combination measure of oxygen dosage were never tested by means of formal experiment. Moreover, questions about the exact role of supplemental oxygen began to surface when it was found that RLF in premature infants who were *never* exposed to the gas was not rare; some examples were discovered in stillborn infants (who had never been exposed to 21 per cent oxygen in ordinary room air).

DETERMINATIVE ERA OF OXYGEN TREATMENT

In the late 1960s, physicians cautiously began to administer oxygen more liberally than in the post-1954 years of strict curtailment. A new technical development—measurement of oxygen tension in minute samples of arterial blood—made it possible to monitor the oxygen status of treated babies. It was hoped that this new determinative approach would now make it possible to administer oxygen so precisely that the twin dangers of too little and too much of the gaseous substance could be avoided. This was a very reasonable expectation; unfortunately, the exact definition of safe limits of arterial oxygen were unknown and it was considered unethical to carry out an experimental trial to determine this vital information. (Studies in experimental animals were not applicable because other species did not exhibit scarring lesions and blindness when exposed to oxygen.)

The relatively weak investigative approaches of analytic surveys and, in one instance, a collaborative observational study, failed to provide clear-cut answers to the perplexing questions that plagued treating physicians. (For example, the observational study found no association between arterial oxygen and RLF risk; circumstantial evidence that linked duration of oxygen treatment and risk was uninterpretable because oxygen was administered to infants according to physician prescription, that is, on an as-needed basis.)

Resurgence of RLF

During the 1970s, life-support techniques were perfected to the point that the survival rate of very small premature infants increased sharply. With this rise it slowly became evident that RLF increased apace. Despite improved techniques of monitoring the oxygen status of these very small infants—by continuous measurement using sensors applied to the skin—the estimated number of RLF-afflicted babies seen each year began to approach pre-1954 levels.

As the 1980s began, the oxygen hypothesis was badly shaken. There was reason to think that oxygen exposure played a role in the development of retinal blood vessel changes, but it was obvious that understanding about the complex mechanisms responsible for producing the irreversible complication of blindness after premature birth was far from complete.