Two million eight hundred and eighty thousand dollars was awarded this year in New York to a 27 year old man who had been blinded as an infant. His case is of more importance to our profession than the outrageous size of the award because, as a baby, he was part of a proper, controlled study. The plaintiff had a birthweight of 1300 grams, was born in a small hospital on July 3, 1953 and was at once transferred to New York Hospital, one of the 18 hospitals participating in the Cooperative Study of Retrolental Fibroplasia. Following the system of randomization properly used by that study, the baby was assigned to the non-experimental, or "Routine Oxygen," group. His incubator was filled with 50% oxygen for 28 days, as was customary in that era in New York and most other parts of the United States. The Cooperative Study was somewhat of a pioneering one in the application of statistical techniques to a medical problem; such techniques are now widely used to achieve early answers to questions about which doctors hold divergent views. Though a pioneering one, the Study was planned to quickly obtain an answer concerning the effect of lowering the concentration of oxygen on survival and on retrolental fibroplasia. Partial support was received from the National Institute of Neurological Diseases and Blindness of the U.S. Public Health Service. The coordinating committee was formed of members of the American Academy of Ophthalmology and Otolaryngology, the American Academy of Pediatrics, the Society for Pediatric Research, the American Pediatric Society and the National Society for the Prevention of Blindness. Perhaps because it dealt with such serious events as death on the one hand or
blindness on the other, the Study has been criticized, especially by highly ethical people who do not understand what the word "experiment" means in clinical research. Such individuals desire progress but they do not realize that progress requires something new which is better than something which is old. To establish the virtue of some new treatment, a comparison must be made. A controlled, randomized study is not only the fastest and safest way to make that comparison, but it has the added virtue that unexpected side effects of either the new or the old treatment may be unmasked.

The Cooperative Study, in addition to having been criticized for having been held at all, has also been thought by some to have been begun too late or continued too long or terminated too soon. Hindsight may show some of these criticisms to be correct. The fact remains, however, that it was that study which terminated a terrible epidemic and contradicted the widespread beliefs of the time that the disease could actually be treated by exposure of the infant to oxygen and that 40% oxygen was totally safe and effective.

In contrast to the barrage of criticism of the Cooperative Study, one hears, as Dr. William Silverman[1] has said, very little complaint about the twelve years of floundering which preceded it. Over 50 erroneous hypotheses as to the cause of retrolental fibroplasia had appeared in print, a medical mess which was summarized thoroughly by Leona Zacharias in October, 1952.[2] Inept as that history shows our profession to have been, it must additionally be said that the entry of the legal profession into the practice of medicine through unjust malpractice suits is doing harm to people who are sick now or will become ill in the future. New laws will not solve the problem, because the U.S. Constitution gives every citizen the right to trial before a jury if his grievance is great enough and juries rarely understand intricate medical situations and are quite naturally easily swayed by the appearance of a blind or crippled individual in the courtroom.

It seems to me to be very sad that now, just as our profession itself is coming to understand the value and place of controlled, randomized trials, legal precedents such as the case I have described, occur. Such cases make it difficult, for example, to follow the advice of Chalmers.[3] He asks, "Why not randomize the first case?" "Why not?" As someone has said, a doctor can give a new drug to all his patients, but if he so treats half of them, in a randomized way, he must get permission from a hierarchy of authorities. And now, it would seem, even that protection is insufficient against unusual legal practices.

To get back to medical history, perhaps a description of the reasons oxygen was used wrongly may, as Dr. Silverman[1] has said, serve as a useful parable for those currently doing research. The theory was reasonable. Most deaths of premature infants seemed to be respiratory in nature. The nervous system defects found in former preterm infants resemble those that are reasonably attributed to asphyxia at birth in term infants. The capillaries of small infants are not completely developed, so it is not too far fetched to imagine that an elevation of oxygen pressure might help tissue metabolism. Immature infants often breathe irregularly and, when placed in an oxygen enriched atmosphere, they tend to breathe like adults. The toxicity of oxygen has been looked into with care, both in animals and men; furthermore, young animals were resistant to concentrations as high as 100%. This last feature was also noted by both Ashton
and Patz; the young could live happily in 100% oxygen but the mothers who nursed them had to be removed to room air frequently. The kitten eyes, of course, developed vascular stages of retrolental fibroplasia but did not become visually impaired. Finally, when ophthalmologists began to examine eyes of premature infants, it was often noted that babies who had received oxygen therapy for a day or less would, it seemed at least, develop no vascular overgrowth of retinal vessels for many days or weeks. How strange that the insult seemingly preceded evidence of damage by such a long interval! Only later did investigators with improved ways of viewing the retina realize that vasoconstriction took place within seconds of the administration of oxygen, and subsequent to that, if the case were to be severe, obliteration of vessels could be seen, as in animal models. To add to theory, doctors pointed to practice to support an enriched atmosphere. Oxygen was fed into incubators from the very beginning of incubator care.

Early incubators were always connected to an oxygen tank. There were no convenient oxygen analyzers in those far-off days. The rate of flow of oxygen was the criterion and, usually, the nurse was in charge of that. Nurses, in fact, often ran the whole show and, in the rare event that a doctor actually entered a nursery to undress and examine a preterm weakling, he did so despite the occasional unfriendly stares of nurses. One of the marvels is that they could and did adjust oxygen flow rates according to apparent need and yet, with hindsight, we know that since no retrolental fibroplasia was seen, the oxygen levels must have been slightly above those of room air.

The epidemic of retrolental fibroplasia, with which this report is supposed to deal, began in 1941, when an astute Boston pediatrician, Stewart Clifford, saw two blind babies in a single week presenting with an identical ophthalmoscopic picture. Both had been born prematurely. From then until roughly 1956, it has been estimated that some 10,000 babies were blinded. Suddenly, many opinions appeared in print with ideas expressed, sometimes forcefully, which later turned out to be wrong. The epidemic spread across the country, as though caused by a virus, and a viral etiology was suggested. The cases were associated with the Chapple incubator. It became commercially available at about that time, though its cost prevented its widespread use at first. An analyzer became available and doctors were able to prescribe the concentration of oxygen in the incubator. While the epidemic raged in some cities, it was absent in others. The Charity Hospital in New Orleans was a conspicuous example of freedom from the trouble, not only because it had the largest nursery in the country but also because oxygen was available without cost. Every infant's incubator was connected to an oxygen tank for weeks. It took some time for pediatricians to realize why Charity Hospital was so lucky. All the incubators were of the Armstrong type, with louvres which were kept open. To dress the baby or feed him, the lid had to be opened. Oxygen analyses were not often done.

The Cooperative Study left many questions unanswered and these continue to plague us. Doctor Dale Phelps and others are aware that the disease, though rare, still occurs. Phelps has told me she estimates about 500 babies per year graduate from intensive care nurseries with impaired sight. Retrolental fibroplasia is a lively subject for research. It remains a mystery, because some babies who are treated with oxygen for long periods never show signs of active disease and, occasionally, one encounters an infant who never needed or received any oxygen therapy who, nevertheless, suffers from impaired vision. There must be some factor or factors which result in these wide differences in outcome.
The logarithmic increase in mechanical and endocrine as well as medicational therapies is a great credit to the resourcefulness of the present generation of investigators. I wonder, though, if the lesson of previous mistakes has been taken to heart. It is obvious that mortality has gone down but why the scarcity of randomized trials? Few of the new ideas have been subjected at their inception to this rapid and safe way to get an answer. The first case has not been randomized. Why not? Is it the oppressive weight of peer groups and misguided ethicists which has led present day investigators to try new devices and new medications on an individual basis thus avoiding law suits and administrative encumbrance? The education of ourselves and of the public on the reason for proper studies has lagged. How else can one explain the astonishing legal attack upon the manufacturer of one brand of incubators for not telling doctors what concentration of oxygen to use? This suit on the West Coast still smoulders in the incredibly bad system of justice in this country.

Something must be done. The medical profession, through its leaders, should meet with the American Bar Association and hammer out a code. Lawyers and doctors who do not follow that code should be suitably chastized. The public should be educated in all of this. New laws cannot solve the problem; a new spirit is needed.

REFERENCES


