Blindness of Prematurity Unexplained

Physicians once thought they knew why premature babies may become blind, but there appears to be a new epidemic of blindness and the old explanations simply do not suffice

In the mid-1950's, pediatricians and ophthalmologists thought they had finally solved the problem of retinopathy of prematurity—a disorder that was leading to an epidemic of blindness among premature infants. A clinical trial had demonstrated conclusively that the culprit was oxygen. Clinicians were convinced that if they just cut back on the oxygen they give these babies, the eye damage should virtually disappear.

Yet retinopathy of prematurity, or ROP, is back with a vengeance. Neonatologists say that there seems to be an even higher incidence of the disorder now than before the clinical trial nearly 30 years ago. And no one knows quite what to do about it. At a meeting on 22 and 23 November, held at the National Institutes of Health and sponsored by the National Children's Eye Care Foundation, medical researchers discussed various hypotheses of the causes and possible treatments for ROP. But what was perhaps most surprising was the extent to which research on the disorder has been hobbled by physicians' fears of litigation.

Meeting participants stressed that although there is no generally recognized standard of care for premature infants that will minimize their chances of developing ROP, distraught parents of blind children are bringing lawsuits against neonatologists, hospitals, and departments of neonatology. And they are winning. As many as half of all ROP lawsuits are won by the plaintiffs, according to John Flynn of the University of Miami School of Medicine, who did an informal survey. The judgment usually is that the babies were given too much oxygen. "That's a very high success rate in medical malpractice," says Marshall Simonds, an attorney with the Boston firm of Goodwin, Proctor, and Hoar. "It is probably due to the uncertainty in the profession [on how to prevent ROP] coupled with the dramatic impact of a blind baby. The public expectation is for compensation."

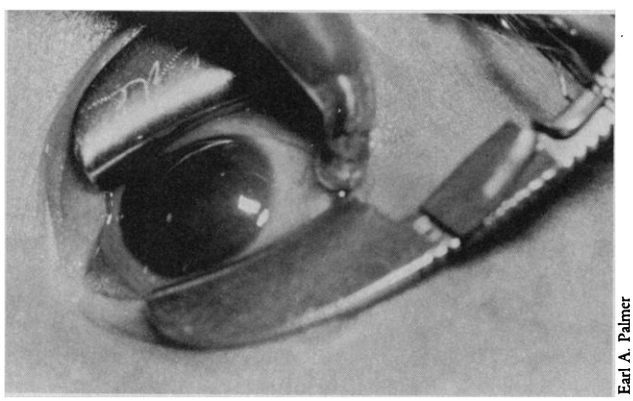
It is a "particularly unfair" situation, says Burton Kushner of the University of Wisconsin in Madison because the medical consensus today is that the current cases of ROP are not caused by too much oxygen. Instead, ROP is a disease of immaturity. "There are well-documented cases of ROP in babies who were never given oxygen," says Gordon Avery of Children's Hospital National Medical Center in Washington, DC. "If you are supposed to be a fetus, even breathing room air may be too much."

As a consequence of the threat of litigation, some physicians say they are reluctant to even publish data on the incidences of ROP at their hospitals. "It's a funny business," says Jerold Lucey of the University of Vermont. "Everyone's a little ashamed of having incidence figures at all." Meeting participants said privately that they fear if they publish incidence figures, lawyers will be at their doors bringing suits based on the numbers of blind babies that leave their hospitals. As a result, Lucey notes, "I don't believe there are any [population-wide] figures that allow us to establish the epidemic we all think we are seeing."

Moreover, when investigators do publish results, even if they are preliminary or controversial, attorneys frequently seek to use them as a standard of care in their ROP lawsuits. For example, last August, Penny Glass and her associates at Children's Hospital National Medical Center in Washington, DC, published a paper in the *New England Journal of Medicine* describing a sequentially controlled study that seems to indicate the incidence of ROP might be reduced if babies are shielded from bright lights. The study, since it was not randomized, "opened the door" to the possibility that light is a factor in ROP, says William Silverman, who participated in the original oxygen study and who is now in Greenbrae, California. But neither Silverman nor others at the meeting are convinced yet. Nonetheless, the lawyers descended. "Within 3 weeks of that study, I had three patients and a lawyer in my office asking if light was the cause of ROP," says Kushner.

The retinas of premature babies are "embryonic organs," notes Avery. Blood vessels in the retinas are still developing and as they spread from the center of the retina to the periphery, their growth may become disorganized. There can be an increase in the number of blood vessels and the vessels may bleed and invade the interior of the eye. This proliferation and bleeding appears to be more prevalent in babies who are given oxygen, and it can be the start of ROP.

The first thing that can be seen as ROP develops is a "demarcation line" in the developing retina which represents the point of arrest of the advancing blood vessels. If the disease progresses, a ridge of tissue appears, looking like a thin white line and representing proliferating tissue, including endothelial cells. As cells and blood vessels grow, scar tissue forms and the retina starts to buckle. Finally, in the most advanced cases of ROP,



Earl A. Palmer

A baby is given cryotherapy

In a last ditch attempt to prevent retinal detachment and likely blindness, the edges of the infant's retina are destroyed by cryotherapy. If it works, the progressing ROP will cease.

the retina detaches and rolls up like a scroll.

The prevailing hypothesis on how to prevent ROP dates back to the oxygen study of three decades ago. It was the first randomized controlled clinical trial in the United States and it showed that the standard medical practice in the 1940's and 1950's of giving 50 percent oxygen for 28 days to all premature babies, whether they needed it or not, was leading to ROP.

Since that study, however, there have been virtually no randomized controlled clinical trials of methods to prevent or treat ROP. And there have been many false trails. "This disorder is filled with one trap after another," says Silverman. "It's *unbelievable*. Unless the clinical science is good, you've got to scream. So many mistakes have been made."

And even though the original study implicated oxygen in the development of ROP, it is not at all clear what that study means today. "The baby getting ROP now has a totally different oxygen history than the baby getting ROP in the 1930's and 1940's," says Flynn. "The duration of oxygen administration, the concentrations of oxygen, and the reasons for giving oxygen all have changed." Now, says Lucey, ROP seems clearly to be primarily a disease of very sick babies—not necessarily a disease of too much oxygen. "If the sick eye is a reflection of a sick baby, as every study seems to show, I don't think we can do much about it in the next few years," he remarks. The best hope is prevention of low-birth-weight babies in the first place.

In the meantime, however, medical researchers are pursuing a number of strategies that they hope might lower the incidence of ROP and, once a baby develops the disorder, limit the damage it does. One highly controversial hypothesis is that perhaps vitamin E can prevent the damage that oxygen might inflict. But the studies so far have not provided good evidence that high doses of vitamin E are truly beneficial. And vitamin E is not innocuous, Avery points out. If it is given in high doses, it can lead to sepsis and necrotizing enterocolitis, a disorder in which the lining of the gut breaks down. The babies then are vulnerable to systemic infections from bacteria that normally live in their intestines and to gangrene of the bowel.

For these reasons Flynn warned that, "it is incumbent on the vitamin E-ologists—and you know who you are—to get yourselves together and do a clinical trial. You have to be sure you are not endangering the lives and future health of these babies. You also need to verify the oxygen hypothesis—and it is an hypothesis."

Once ROP begins, physicians would like

Methane Doubling Upheld

A reanalysis of 35-year-old spectra of the sun has shown that atmospheric methane has been increasing by about 1 percent per year. The same analysis supports recent measurements showing carbon monoxide increases during the past several years. It is now clear that, as predicted, the complex web of chemical reactions involving trace gases has taken a jolting blow. Aside from a reduced capacity of the atmosphere to absorb greater abuse, one result will be an increased global warming due to methane's greenhouse effect.

In three papers in the 21 November issue of *Nature*, Curtis Rinsland, Joel Levine, Thomas Miles, and Geoffrey Tennille of NASA's Langley Research Center in Hampton, Virginia, present their reanalysis and interpretation of solar spectra recorded in 1950 and 1951 at the Jungfraujoch International Scientific Station, 3600 meters up in the Swiss Alps. Astronomers were then using the spectra to study the solar atmosphere, but they could also determine the concentration of both methane and carbon monoxide in the troposphere (the lowest 10 kilometers of the atmosphere) by measuring the gases' absorption of sunlight in the spectra. The originally determined values for methane have been cited recently in support of the constancy of methane concentrations until the late 1970's, when direct sampling began to suggest a 1 to 2 percent per year increase. Analyses of air trapped in glacial ice, on the other hand, seemed to support strongly an increasingly rapid increase beginning several hundred years ago.

Rather than accept the cited values, Rinsland, who was trained as an astronomer, and his colleagues gathered the original spectra and started from scratch. The resulting concentrations were distinctly lower than present values as well as values previously reported for that time. They found 1.14 parts per million by volume (ppmv) of methane in 1951–52 compared with about 1.68 ppmv at present. B. Stauffer and his colleagues at the University of Bern recently reported a concentration of 1.16 ppmv from ice formed in 1949–50. Thus, the upward trend in methane of the past few years is only the most recent part of a long-term increase of about 1.1 percent per year that has indeed been faithfully recorded in ice cores. The previously reported stability of methane concentrations resulted from the use of less imprecise values for the absorption per molecule of methane.

The determination of carbon monoxide in the historical solar spectra presented greater difficulties than in the case of methane. The concentration of carbon monoxide varies by a factor of about 2 through the year and from hemisphere to hemisphere, so that the spectra from 9 days over the course of 1 year clearly fall short of a thorough sample. The best the Langley group can do is cite an average rate of increase over Europe since 1950 of about 2 percent per year with an uncertainty range of 0.5 to 4.1 percent per year. But that, they say, is consistent with more recent measurements of increasing carbon monoxide around the world.

Computer models depicting the possible effects of increasing methane and carbon monoxide point to a significant weakening of the system of chemical reactions that would normally keep trace gases, both natural ones and some pollutants, in balance. The pivotal element in this balance is the highly reactive hydroxyl radical. Without hydroxyl radicals, few trace gases would react with each other and any additions, whether natural or pollutant, would lead to increases in abundance.

During the past 35 years, according to a computer model that was run by the Langley group, the methane and carbon monoxide accumulating from anthropogenic sources have overwhelmed the hydroxyl radical and reduced its abundance by perhaps 25 percent. Such estimates are vital because, despite its central role, atmospheric chemists have yet to reliably measure hydroxyl radicals.

Old astronomical spectra should provide valuable insight to the behavior of some trace gases at times before chemists reliably measured them directly. The Langley group is now working on the measurement from the 1950–51 spectra of two other greenhouse gases, carbon dioxide and Freon-12, and earlier records may also prove usable. ■ **RICHARD A. KERR**

to intervene, if possible, and prevent the disease's progression. Enter the next controversial procedure—cryotherapy. The idea is that since the developing blood vessels are growing wildly toward the edge of the retina, perhaps their growth might cease if the edge of the retina were destroyed by cold. It is an idea born of desperation. "We would only try it in those with active disease that is getting worse and for whom we forsee disaster. Except for cryotherapy, the only thing to do is to hunker down and wait until the retina detaches," says Avery. Yet cryotherapy also has its risks. It can result in hemorrhage, optic atrophy, or the inadvertent freezing of the optic nerve or the macula, which is essential for clear vision.

But this time, an answer to whether cryotherapy works is forthcoming. The National Eye Institute is beginning a multicenter randomized controlled clinical trial of the treatment. It will involve about 300 babies at 24 centers. As a side benefit, it should result in some incidence data for ROP.

Once a baby's retina has detached, the only treatment left is to try and attach it again. But this is a difficult and controversial surgery—"*the* most difficult retinal attachment in ophthalmology," says Gary Abrams of the Medical College of Wisconsin in Milwaukee.

Surgeons disagree on when to do the surgery and, even in the best of hands, the success rate is none too high. If the surgery is done early, the ROP might progress anyway and undo the surgeon's work. If it is done later, when the proliferative process in the child's retina has ceased, it may be too late for success. "We have not settled the question of timing," says Steve Charles of the University of Tennessee. "ROP is an active proliferative process. With early surgery, you're damned if you do and damned if you don't." Even if a surgeon does manage to attach a child's retina, there is no guarantee the child will see. In many cases, there is other damage to the eye. "What we need is a very careful evaluation of pre- and postoperative functioning of the eye," says Flynn. "The most pressing question is, Are these babies benefiting from the surgery? Nobody has the answer."

Yet perhaps the recent meeting was a start. Everyone acknowledged the gaps in the data and the need to be more systematic and scientific in gathering evidence in the future. The national cryotherapy study is a step in the right direction. Solutions to the problem of preventing and treating ROP most likely will not be immediately forthcoming, but at least there should be some information on the incidence of the disease and on whether current experimental treatments are worth continuing at all. ■

GINA KOLATA

Ballistic Electron Transport Seen in GaAs

Ballistic electrons are not slowed by collisions; but an ultrahigh-speed transistor using them is conjectural

THE first published evidence for the proposition that electrons can travel through a semiconductor without being slowed by collisions—that is, ballistically—is now in. Last November, two groups of researchers, one a joint AT&T Bell Laboratories/Bell Communications Research collaboration and the other from IBM's Yorktown Heights Laboratory, reported experimental data showing a ballistic peak in the electron energy spectra of gallium arsenide test devices.

With competitive groups shooting for the same goal, it is not surprising that each would strongly press its claim. Moreover, a year ago, Japanese researchers from Fujitsu Limited in Atsugi, Japan, had also reported energy spectra showing a peak for fast-moving electrons in gallium arsenide, but at the time they could not attribute it to ballistic transport. The Bell Labs/Bellcore collaboration has the distinction of presenting the first spectroscopic evidence for ballistic transport, beginning with a presentation of its findings at a physics meeting last March. However, for reasons related to the somewhat different device structures adopted by the American groups, physicists contacted by *Science* tended to credit IBM's with being the more conclusive experiment.

In theory, the faster the electrons zip through a transistor, the faster the device can switch on and off. Accordingly, overblown accounts of ballistic electrons traveling at nearly the speed of light and providing the makings for transistors that can switch trillions of times per second have appeared in the popular press. Actually, however, no one has shown how to take advantage of ballistic transport in a practical transistor.

As they stand, the test devices are just that. IBM's, for example, exhibits ballistic behavior only when cooled to 140 K or below, and a key transistor parameter, the gain, is still small. Moreover, the results of static spectroscopic measurements do not translate directly into such dynamic properties as switching time, so how fast a ballistic transistor might be is a matter of conjecture. "We were trying to prove ballistic transport is possible, not make a transistor. There is no final device concept yet," says Mordehai Heiblum, speaking for the IBM group, which also includes Marshall Nathan, David Thomas, and Christina Knoedler.

Nonetheless, the estimated electron velocity achieved, about 10^8 centimeters per second (cm/sec), is about five times faster than the maximum in gallium arsenide under ordinary conditions and ten times faster than in silicon, which provides considerable incentive to search for transistor designs that can exploit such speeds. Moreover, the increased understanding of the physics of ballistic electron transport that the test devices provide could yield clues as to how to proceed. "With this knowledge, we would know how to make a real ballistic device," says John Hayes of Bellcore who collaborated with Anthony Levi, Philip Platzman, and William Wiegmann of Bell Labs.

Finally, ballistic transport is of substantial interest apart from any electronic device applications to solid state physicists, who want to understand the behavior of nonequilibrium or hot electrons. Even the existence of ballistic behavior has been questioned. "Until the [IBM and Bell] reports, the only conclusion reachable was that there is no ballistic transport," comments David Ferry of Arizona State University, who has specialized in the properties of electrons under highly nonequilibrium conditions.

If electron transport were ballistic, electrons would accelerate without interruption to the velocity compatible with a kinetic energy gain of eV, when a voltage V is applied. Ordinarily, collisions prevent ballistic behavior. Elastic collisions scatter the electrons in all directions in a characteristic