Current topic

Epoché in retinopathy of prematurity

W A SILVERMAN

California, United States of America

The Pyrrhonic Sceptics in ancient Greece employed a useful catchword, *epoché* ('suspension of judgment'), in philosophic argument.¹ The expression serves admirably to summarise the current state of knowledge concerning the unique retinopathy that affects prematurely born infants. There are renewed, intense debates about pathophysiological mechanisms that may lead to retinopathy of prematurity, and there is now general agreement that we have been unable to devise a reliable plan to prevent occurrence of the potentially blinding disorder.

Active stages newly classified

Improved techniques for examining the ocular fundus—for example, binocular indirect ophthalmoscopy, fluorescein angiography, and retinal photography^{2 3}—have, in recent years, provided a new perspective on the retinal changes that occur in retinopathy of prematurity. It became clear that the 1953 classification scheme,⁴ based on the relatively restricted view of premature infants' fundi through the direct ophthalmoscope, was inadequate, and, by 1981, a pressing need to obtain general agreement on a modern classification was recognised.⁵ In 1982 a group of ophthalmologists from 11 countries met in Calgary, Canada, to begin work on a revised system. The final schema was published in mid-1984⁶ after each of those who had attended the conference had had an opportunity to use the proposal to classify retinal changes in newly affected patients seen in their institutions over a period of one year.

The international classification (tagged, predictably, with a euphonious acronym—ICROP) introduces two new axes of categorisation: the location of disease in the retina and the extent of the developing retinal vessels involved in the pathological process. For the purpose of localisation, the retinal field of each eye is divided into three concentric zones oriented around the optic disc. The extent of involvement in each eye is specified by hours of the clock. Severity of active retinopathy, in designated

zones and of indicated extent, is ranked in four stages, beginning with recognition of a definite demarcation line that separates avascular from vascularised retina (stage 1) through progressive changes that may end with unequivocal retinal detachment (stage 4). The fundal changes are recorded on a form that consists of a 'map' drawing of the retina of each eye that indicates three zones and clock hours. The disease stage assigned to each eye is based on the most severe manifestation at the time of the current examination.

Publication of the ICROP proposal focuses attention on the problem of uniformity of diagnoses; the accomplishment of the international group of ophthalmologists raises expectations that there will be improvement in the quality of observations in future comparative studies of prevention and treatment of retinopathy of prematurity. There is now hope that investigators will include analyses of reproducibility and of observer variation of eye examinations in reports of clinical trials. And there is the possibility that the ICROP 'yardstick' will be used in comparing experiences between localities and in the same institutions over time.

Cooperative efforts are now under way to re-examine classification of the stages in retrolental fibroplasia (this old term is appropriate as a description of the late changes in severely affected infants). The new scheme of coding retinal damage will attempt to reconcile two considerations: the visual potential of the eye and the potential for surgical treatment. The final proposal will complete the difficult task and welcome goal of formulating an up to date diagnostic standard of retinopathy of prematurity for international use; it should be available before too long.

Gaps in knowledge about the risk of moderate hyperoxaemia

Is the risk of cicatricial retinopathy appreciably greater in premature infants who received supplemental oxygen, resulting in moderate hyperox-

aemia, than the hazard in infants who never receive supplemental oxygen? (The definition of moderate hyperoxaemia here is an arterial partial pressure of oxygen under the threshold found necessary to reduce retinal blood flow in the anaesthetised kitten (190 mmHg),⁷ particularly when this state is intermittent rather than continuous.)⁸ There is now little doubt that the eye risk for the group breathing air only is not zero, and there is much speculation that the relative hyperoxaemia at birth (from arterial partial pressure of oxygen 20–25 mmHg in utero to 45–110 mmHg with the onset of air breathing) threatens the incompletely vascularised retina. But innumerable declarations and educated guesses to the contrary notwithstanding, there is no convincing evidence that risk increases materially with moderate hyperoxaemia.

It has been said that nothing is so dangerous as an idea—when it's the only one you have. The liability is exemplified in the experience with a 30 year old idea that holds that treatment with supplemental oxygen is the sole necessary and sufficient cause of all instances of cicatricial retinopathy of prematurity. After these many years of uncritical acceptance of circumstantial evidence, suggesting a positive correlation between duration of exposure to moderate hyperoxaemia and the risk of eye damage, it is time to admit that the untested association is uninterpretable because it is confounded beyond the help of statistical manoeuvres.⁹ We are forced to confess that the shape of the oxygen:retinopathy risk curve is simply unknown.

Need for faithful animal models

There is little hope that human trials will (or can, given the current level of understanding) be devised to narrow the broad area of uncertainty about the details of the oxygen risk issue. As a result, it is encouraging to see an upsurge in interest to find faithful animal models of the retinopathy as the surrogates could be used to sharpen questions and, thus, lead to testable clinical proposals.

Gole advises use of the term 'oxygen induced retinopathy' to describe the changes produced when animals are exposed to the gas because of important differences in effects found in the eyes of various animal species as compared with the human disease.¹⁰ The words 'retinopathy of prematurity' are misleading when applied to changes in animals, he emphasises, as the non-human studies have not been conducted in prematurely born animals. The caution is appropriate. For example, Flynn speculates that to produce a reliable analogue it may be necessary to deliver experimental animals before term and induce some or all of the cardiopulmonary,

central nervous system (CNS), and septic states that accompany the retinopathy in many extremely premature neonatal patients.¹¹

Dependable animal models are urgently needed to explore, at some depth, the numerous interventions that have been proposed over the years to prevent or to treat the human eye disease. Very few of the agents brought to notice in the past were tested rigorously. Looking back, we can see now that most of the planned clinical studies conducted in the 1940s and 50s—for example, correction of vitamin E deficiency, reduced exposure to light, or withholding transfusions of adult blood—were much too small to rule out important effects. I will return to the issue of the numbers of observations below.

The vitamin E debate

The hope that vitamin E prophylaxis would eliminate retinopathy of prematurity has waxed and waned since the late 1940s. In recent years the proposition has been subjected to a number of randomised clinical trials, but a convincing answer has yet to be vouchsafed.¹² Many of the studies suffer from crippling methodological defects: sampling (no multicentre trials to assure representativeness), diagnosis (no standard classification of retinopathy of prematurity), and sizing (low power as the result of failure to provide a pretrial estimate of sample size needed to detect a postulated difference in outcome). There is no agreement about the details of administration of tocopherol: time to initiate prophylaxis (before or at the time of birth), route (intravenous, intramuscular, or by mouth), and proper dosage. Unfortunately, there is insufficient pharmacological information about the vitamin (absorption, tissue uptake, storage, and disposition) when it is administered by various routes and in various doses to premature infants. Finally, there are unresolved questions concerning important side effects (fatalities associated with intravenous tocopheryl acetate in polysorbate,¹³ increased frequency of sepsis, necrotising enterocolitis,¹⁴ and CNS haemorrhage¹⁵ in some groups of infants receiving vitamin E prophylaxis; and decreased CNS haemorrhage in infants enrolled in other trials).^{16 17}

The vitamin E:retinopathy of prematurity relation has been given new prominence because of Kretzer's intriguing observations of the ultrastructure of the developing retina in infants supplemented with vitamin E and others not supplemented with vitamin E who died in the neonatal period.¹⁷ On the basis of these observations, he has erected a testable thesis that specifies initial spindle cell injury from alterations in oxygen tension (intrauterine hypoxia, or postnatal hyper- or hypoxia), increase in

gap junctions between adjacent injured spindle cells, increase in cytoplasmic volume of rough endoplasmic reticulum within spindle cells and subsequent decrease of volume with the down modulation of gap junctions, a period of synthesis and secretion of angiogenic factors (only found in extracts of the vanguard retina of infants who did not receive vitamin E supplements), and, finally, invasion of myofibroblasts into the vitreous. The hypothesis also provides an explanation for the purported lack of efficacy of vitamin E in infants ≤ 27 weeks' gestational age (due to the complex relation between an interstitial retinol binding protein, which transports fat soluble substances across the polar subretinal space, and the developmental position in the retina of outwardly migrating spindle cells). If this fascinating concept of pathogenesis survives attempts to replicate the observations and rigorous experiments to test the postulated mechanisms it will go a long way in unravelling the mysteries of retinopathy of prematurity.

An ablative cryotherapy trial

The most encouraging development about surgical intervention to halt progression of proliferating retinal changes is a general acknowledgment that the most promising approach, ablative cryotherapy, needs to be formally tested to determine the procedure's limits of usefulness. A multicentre randomised clinical trial has been designed to take advantage of the known tendency of retinopathy of prematurity to progress symmetrically.¹⁸ In most enrolled infants, therefore, one eye will be treated with experimental cryotherapy while the fellow eye is to be observed as a control. When there is asymmetric involvement—that is, only one eye progresses to meet the eligibility criteria, expected in about 20% of cases—patients themselves are to be assigned in random order to treatment or control groups. The design assures that no patient will receive the unevaluated treatment to both eyes afflicted with the notoriously capricious disorder. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP is the almost pronounceable acronym here) is now under way. (With 30% of infants affected by retinopathy of prematurity expected to suffer a visually unfavourable outcome and a postulated 35% reduction in this risk rate, roughly 300 infants will be required to ensure that an outcome difference of this magnitude will be detected with 80% power and a Type 1 error set at 5%.) There is every reason to hope that interpretable results will be available in the next few years.

Multinational cooperation?

One of the great difficulties that has plagued those interested in putting an end to the threat of retinopathy of prematurity is that of accumulating sufficient numbers of extremely premature at risk infants for formal studies of the disorder. Chalmers and Sinclair have pointed out that the problem of small sample sizes is common to all perinatal studies.¹⁹ They warn of two potential consequences when comparative studies are too small. Firstly, real and clinically important differences between treatments may be incorrectly dismissed because they fail to achieve significance. Secondly, if significant differences are observed these will tend to result in an overestimate of true differences.

As renewed interest in retinopathy of prematurity grows and the inevitable increase in number of treatment proposals—for example, use of antioxidants, indomethacin, or antenatal betamethasone; reduced exposure to light; vitrectomy . . .—compete for the attention of perplexed caretakers it would be well to keep in mind that the duration of confusion can be reduced by cooperative action. For example, success of the international effort to reclassify retinopathy of prematurity might lead the way to collective experiences of the kind recently reported by neurosurgeons in 71 centres on three continents.²⁰ The latter specialists have shown that the multinational trial is an acceptable, believable, and scientifically necessary method to obtain large enough numbers of patients to answer important therapeutic questions in a reasonable period of time.

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Correspondence to Dr W A Silverman, 90 La Cuesta Drive, Greenbrae, California 94904, United States of America.