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Editorials

Evidently, evidence based

Trying to grapple with the term evidence based medicine[1] brings to mind events which have occurred over the past four decades in retinopathy of prematurity (ROP) management. When it was discovered in the early 1950s that oxygen was a major factor in its pathogenesis, the demise of this condition was openly anticipated. All too soon it became apparent that this optimism was misplaced and that ROP induced blindness still occurred. The first attempt at surgical treatment came from Japan in the late 1960s, and this sparked off a decade and a half of studies using xenon arc photocoagulation, argon laser photocoagulation, or cryotherapy, none of which provided convincing proof of efficacy. In retrospect this is not surprising, with small patient numbers, different treatment criteria, and above all the absence of an agreed clinical description of the disease. The turning point came in 1984 with the introduction of a user friendly internationally agreed classification.[2] This stimulated a tremendous burst of clinical and research activity and provided a firm basis for collaborative research; most notably the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (Cryo-ROP Study). The results of this study[3] demonstrated conclusively that cryotherapy improves the outcome of severe ROP and now for the first time, the ophthalmologist has a role in ROP management – both screening and treatment. This chain of events, which is pure evidence based medicine, has modified ophthalmic practice worldwide and generated the publication of clinical guidelines.

Treatment significantly improves the outcome of severe ROP, but in the Cryo-ROP Study 46·6% of treated and 57·5% of controls had acuities below 6/60 (unfavourable outcome) at $3\frac{1}{2}$ years of age.[4] As favourable outcome in this study was defined as acuity better than 6/60, it follows that many children included within this favourable category had significant vision impairment. Even more disturbing, at $5\frac{1}{2}$ years about equal numbers of treated and untreated children achieved normal acuity (6/12 or better).[5] Treatment is clearly no panacea, so one of the challenges of the post Cryo-ROP era is to find additional ways to improve severe ROP outcome. Clinicians need a foolproof method for predicting which eyes with mild or moderate ROP will progress to 'threshold' ROP and require treatment, and which eyes will spontaneously regress even though they reach threshold severity. Schaffer *et al*[6] found that poor prognosis was associated with several factors such as posterior disease (zone 1), plus disease severity by stage and extent. Unfortunately, however, none of these is robustly predictive on an individual eye basis, which is what the ophthalmologist needs in the acute situation. Among acknowledged experts there can be considerable interobserver variability in the recognition of plus disease.[7] As plus disease is considered a powerful predictor of severity, it is important that its characteristics are better defined. Treatment has recently advanced through the use of indirect ophthalmoscopic laser, especially diode.[8] Noonan and Clark, in this issue of the *BJO* (p 278), have analysed 64 eyes they treated and found that for ROP in anterior mid zone 2, cryotherapy and laser were equally effective, while for more posterior disease, laser appears to be superior to cryotherapy. This is important because threshold ROP that occurs in or close to zone 1 carries a very poor prognosis and is technically difficult to treat with cryotherapy.

The current indication for intervention is threshold disease (stage 3 ROP extending over 5 or more continuous clock hours, or 8 cumulative clock hours, in the presence of plus disease), when the risk of blindness, if untreated, is about 50%.[3] Confining treatment to this stage was appropriate in the 1980s, but does this still hold true when treatment has been proved to be beneficial? Does it make sense to withhold treatment until the risk of blindness is so high? 'Threshold' has different prognostic implications according to the zone of involvement, but as the outlook for zone 1 threshold is so poor, lowering the intervention threshold to 'any' stage 3 in this location is already practised. Lowering the treatment criterion from threshold to include all stage 3 disease, regardless of zone would have resulted, in the Cryo-ROP Study, in the treatment of at least an additional 520 eyes.[9] Some of these (especially with more anterior involvement) had as little as 0·7% chance of ending up with an unfavourable structural outcome if left untreated.

We need to consider critically the indications for treatment. Should our judgment be tempered by stage 3 location in addition to threshold (which is based on total clock hours of involvement)? For instance, stage 3 ROP adjacent to the macula might well have a greater risk of affecting vision compared with retinopathy nasal to the optic disc. Generating evidence to establish future treatment criteria will be difficult as severe ROP is sufficiently infrequent to preclude any single clinician acquiring a series of the required magnitude. To overcome this problem, clinical information needs to be recorded meticulously as this will facilitate and increase the value of large scale audit and research, such as that funded by the UK Department of Health.

In the recent past, treatment related issues have received a large share of attention with clinicians tending to regard severe ROP as an inevitable, albeit unpredictable, consequence of extreme prematurity. Recent research has focused interest once more on pathogenesis, and yet again on oxygen. Continuous,[10 11] or frequent,[12] transcutaneous Po_2 monitoring has demonstrated that oxygen administration in the first few weeks of life is a risk factor for ROP incidence and severity. It emerges from these human[11 12] and animal[13] studies that fluctuations, even within the normal range, can increase the risk of severe ROP, and Pao_2 monitoring – being intermittent – may mask important variations. Laboratory studies[14] have shown that hyperoxia induces down regulation of vascular endothelial growth factor (VEGF) expression which in turn induces endothelial apoptosis and excessive capillary regression. Retinal ischaemia, whether the result of excessive capillary regression or periodic hypoxic episodes in the baby's clinical course, upregulates VEGF, thus inducing angiogenesis and vasoproliferation. These findings have major implications for neonatal care, and support the tenet long held by clinicians, that the scene for ROP is set very soon after birth. They go no way to explain, however, why retinopathy onset is governed predominantly by postmenstrual age rather than neonatal events.

The management of ROP is a fascinating example of evidence based medicine. Although the Cryo-ROP Study has greatly improved the outlook for babies with severe ROP, complacency would be misplaced as our knowledge still falls short of the ideal. Studies like that of Noonan and Clark are important as they contribute to the new evidence base for future refinements of treatment.

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