

Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: Beetham WP, Aiello LM, Balodimos MC, Koncz L (1969) Ruby-laser photocoagulation of early diabetic neovascular retinopathy: preliminary report of a long-term controlled study. *Trans Am Ophthalmol Soc* 67: 39–67

In 1969, Beetham et al reported a brave, new approach that broke with contemporary practice. Its aim: to prevent the progression of diabetic retinopathy by the mild, partial destruction of the retina of eyes that still had normal acuity.

The authors of the paper described preliminary findings from a longer-term study of ruby-laser photocoagulation for angiopathic and neovascular retinopathy based at Harvard Medical School's Joslin Diabetes Center, USA.

Participants had grade II or III retinopathy at baseline and were part of the larger study that included grades I–VIII. By the definition used, these were those with “Neovascularization of the retina at retinal level except the disk” (Group II), and “Very early neovascularization of the disk with or without other neovascularization” (Group III). In the participants described, 39 out of 72 had normal (“20/20”) acuity at baseline, most of them ($n=33$) in the less severe Grade II group. The ages of the participants ranged from 21 to 72 years with mean age of 34.4 years and 39.4 years for men and women respectively. The mean duration of diabetes in both men and women was 19 years.

Each patient was treated in one eye only, the other eye serving as a control. The treatment involved several sessions during each of which 200–300 chorio-retinal lesions 0.75 mm in diameter were produced to all areas of the posterior pole, sparing the disc, macula and maculopapular bundle. The average number of lesions per patient was 647 for Group II and 625 for Group III. As the lead author explains in a discussion piece appended to the article, this approach broke with the contemporary practice of focally targeted photocoagulation aimed at aggressively destroying the obviously abnormal tissue, leaving scarring and visual field defects. This new technique instead involved “mild, partial destruction of the retina”.

The results are described in detail and include both patient-reported and clinician-reported outcome measures. The most important patient-centred outcome is visual acuity. In the treated Group II eyes, acuity was unchanged in 26 out of 36, whilst seven improved and three deteriorated; in those untreated eyes, 27 were unchanged, three improved and five deteriorated. For the 36 Group III eyes that were treated, 18 were unchanged whilst 10 improved and eight deteriorated; for those untreated 15 were unchanged, five improved but 16 deteriorated.

P-values were not given for these results (they were only reported on an un-pre-specified subgroup of a larger study), but when it comes to the detection of neovascularisation, and the improvements that the technique achieved in reducing the progression of neovascularisation, the results are more decisive (*Tables 1 and 2*).

Perhaps the most feared complication of diabetes is visual loss through retinopathy, a problem now known to be reduced and offset by good glycaemic control. In the first half of the twentieth century, management of this condition was aimed at alleviating advanced disease through relatively crude forms of photocoagulation and pituitary ablation (Speakman et al, 1996; Jaegers and Vanders, 2006). The best that could be hoped for was a reduction in progression of existing disability (Beetham, 1963).

Photocoagulation involved xenon-arc and other light sources prior to the development of laser technology during the 1960s. The first optic laser device, the ruby-laser, was invented in 1960 (Maiman, 1960) and by the end of this decade was widely used in diabetic eye disease. Observational evidence suggested a benefit

of early intervention to prevent rather than alleviate the advanced stages (Meyer-Schwickerath and Schott, 1968), but more rigorous evaluation was required.

The Hidden Gem

The paper by Beetham et al (1969), which is summarised above, foretells the advent of the preventive approach using these new devices and their modern successors. To apply a destructive treatment to the retina of an eye that still had normal acuity was, at the time, a brave move. It was justified by the almost inevitable progression to disability, due partly to the limited success at the time of risk factor control (including glycaemia), in those with early neovascular changes.

The screening principles of the World Health



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Hidden Gems

Table 1 and 2. Effects of ruby-laser photocoagulation therapy on the development or progression of neovascularisation and the presence of haemorrhage in Group II and Group III eyes (from Beetham et al, 1969).

Table 1. Group II eyes
Before Therapy

	N ₀		N ₁		N ₂	
	Rx	No Rx	Rx	No Rx	Rx	No Rx
N ₀		1	10		11	
N ₁		6	3	22	11	
N ₂				3	1	4
H ₂						
Total	0	7	13	25	23	4

Rx eye: Improved 32; unchanged 4; deteriorated 0
No Rx eye: Improved 0; unchanged 27; deteriorated 9

Table 2. Group III eyes
Before Therapy

	N ₀		N ₁		N ₂	
	Rx	No Rx	Rx	No Rx	Rx	No Rx
N ₀	1	2	9		9	
N ₁		3	6	13	8	
N ₂		1		5		9
H ₂			2	2	2	2
Total	1	6	16	20	19	11

Rx eye: Improved 26; unchanged 6; deteriorated 4
No Rx eye: Improved 0; unchanged 24; deteriorated 12

Rx – eye treated with ruby-laser photocoagulation therapy; No Rx – eye not treated with ruby-laser photocoagulation therapy (control); N₀ – absence of new vessels; N₁ – four or fewer discreet patches or four or fewer disc areas of new vessels; N₂ – greater than four discreet patches or greater than four disc areas of new vessels; H₂ – vitreous haemorrhage so extensive that the retina cannot be seen enough to be classified (N.B. H₀ – no vitreous haemorrhage; Beetham et al, 1969)

Organization (WHO) had been established by Wilson and Jungner (1968) just the year before, leading to increasing interest in the detection of treatable disease in pre-symptomatic individuals with progressive conditions. To fulfil the WHO criteria and justify mass screening, it was necessary in the late 1960s to establish that early intervention using this essentially destructive treatment would do more good than harm and improve longer-term outcomes.

The paper describes a key step in the move towards prevention of visual loss through early intervention in the pre-symptomatic stage, an approach later confirmed through properly randomised trials such as the Diabetic Retinopathy Studies ([DRS] Research Group, 1981).

Laser therapy has since then prevented and alleviated visual loss in many thousands of individuals at risk, and has substantially reduced the anxiety and stigma associated with diabetes itself. It represents arguably the most significant advance in the management of diabetes since the isolation of insulin in 1921.

Its historical context

This article makes a fascinating read and numerous details identify its late-1960s context. The Latin terms *oculus dexter* and *oculus sinister* (right and left eye respectively) are abbreviated to o.d. and o.s. (without the need at the time for explanation). There is no discussion over the ethics of the proposed long-term follow up of individuals with only one eye treated, even when this treated eye has shown a clear benefit. The methods lack modern rigour over randomisation and masking of outcome assessment, but this was perhaps justified by the exploratory design of this study.

Similarly, the paper perhaps dates itself through its emphasis on clinician- rather than patient-reported outcomes. Changes in visual acuity are described in the seventh table, and only after a long list of fundoscopic and other findings: refractive errors; anterior chamber depth; neovascularisation of the iris; pupil size; regularity and reaction; lens opacities;

and intraocular pressure. This again may reflect the fact that the paper is only a preliminary report of a sub-group as part of a wider project. It was designed to explore the option of earlier treatment and investigate the tissue responses to laser therapy itself, and helped to establish a basis for the randomised controlled trials of the 1970s and 80s. These later studies clarified the stage of retinopathy at which the benefits of intervention outweighed the risks, widened the use to the treatment of macular oedema, and compared alternative devices, including xenon-arc therapy, with argon laser (ETDRS [Early Treatment Diabetic Retinopathy Study] Research Group, 1985; DRS Research Group, 1994).

The recipients of photocoagulation prior to this late 1960s era had relatively advanced retinopathy and some had low life expectancy due to high cardiovascular comorbidity. The application of these techniques at the time lacked a strong evidence base and was essentially palliative. Even those at the pre-proliferative stage had a higher risk of death over the following years from coronary or cerebrovascular disease than modern populations (at least in the US where the study took place). Since 1969, improved cardiovascular mortality and increased life expectancy has further raised the importance of preventing microvascular complications in individuals likely to live long enough to make their development likely.

Why it still shines today

This paper is a hidden gem of mid-twentieth century science. In hindsight, we can see the seed from which the modern management of diabetic retinopathy grew. It developed from a palliative late-stage approach using relatively crude measures to a programme of systematic screening to identify cases early and prevent visual loss through laser technology (Yadav et al, 2014). Treatment of the eyes of pre-symptomatic individuals with normal acuity was a turning point that is so clearly described in this paper.

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