

Destructive operations for diabetes



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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this instalment of *Tattersall's Tales*, Robert Tattersall discusses some 'endocrinectomies' that were performed on people with diabetes as possible treatments for the condition, the evidence for their use at the time and the inevitable decline in their use.

*'...diseases desperate grown,
By desperate appliances are reliev'd,
Or not at all.'*
William Shakespeare. *Hamlet: act IV, scene III*

Recently, in the *New England Journal of Medicine*, I read an editorial called 'The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration' (Steinbrook, 2006). Apart from the impossibility of pronouncing or remembering the names of the two drugs, what impressed me was that they not only stopped progression of macular degeneration but improved visual acuity in the treated group.

My mind went back to the clinic in King's College Hospital, London, in 1970 when I was looking after a 19-year-old girl who had had diabetes since childhood and had become totally and irrevocably blind in the 6 months after her first vitreous haemorrhage. This was a new experience for me but such tragedies were common over the previous quarter century. In 1944 the Canadian physician, Israel Rabinowitch wrote:

'There is nothing more disturbing than the diabetic who acquires the disease in childhood; who apparently is a picture of robust health – who looks and feels perfectly well – but whose blood vessels have been degenerating insidiously for years; who, in the early 20's or 30's and probably married and with a family, is beginning to feel the effect of the degenerative changes, either because of a progressive hypertension, kidney failure, disturbance of sight due to retinitis or a sudden attack of coronary thrombosis.'
(Rabinowitch, 1944)

The first surgical attempt to affect the progression of microvascular complications was adrenalectomy. The theoretical basis was the work of the ophthalmologist Bernard Becker who suggested that retinopathy was associated with excessive adrenal cortical function and claimed to have produced retinal microaneurysms by injecting corticotrophin into alloxan diabetic rabbits (Becker, 1952). An English study of six patients was reported by John Malins in 1956 (Malins, 1956). He pointed out that the operation was safe and had no effect on diabetes control or wellbeing and that, while it had no effect on established proliferative retinopathy or nephropathy, it might stop the progression of early lesions. Selection was a problem since:

'The earliest detectable lesions [in the retina] may remain stationary for many years and only an extreme enthusiast would consider so drastic an operation as adrenalectomy at this stage.'
(Malins, 1956)

Adrenalectomy was soon overtaken by hypophysectomy. The justification was a case report by the Danish physician Jacob Poulsen at the International Diabetes Federation meeting in 1952 (Poulsen, 1953; see Poulsen, 1966, for the final course and postmortem results). His patient was 30 years old at the time of her third pregnancy in 1945 and had had at least 20 admissions with ketoacidosis in 20 years. She had been on 80–100 units of insulin daily; but, 6 months after a stillbirth and severe postpartum haemorrhage, was having frequent and severe hypoglycaemic episodes on 8 units of insulin every other day. Before the pregnancy she had complained of difficulty reading and in the sixth month an ophthalmologist found 'scattered hemorrhages formed as points, spots, and stripes, predominantly localised to the small vessels'. She was re-examined three and a half years later by a different ophthalmologist when she had 'only a few hemorrhages and a few spotty exudates'. Five years later no retinopathy could be seen.

Poulsen wondered if the 'cure' of her retinopathy might be due to a 'metabolic hormonal disorder' and that 'consideration might be given to some means of reducing the function of the pituitary gland and adrenal cortex in young patients with severe retinopathy'.

It seems likely that Poulsen had discussed this patient with his friend, the Swedish physician Rolf Luft. In any event, Luft and a neurosurgeon Herbert Olivecrona began a series of hypophysectomies in 1951. Their first patient was a 30-year-old man with diabetes since infancy who was already blind in both eyes. He had progressive nephropathy with a blood pressure of 180/100 mmHg. Postoperatively his insulin dose was dropped from 80 to 12 units/day and his blood pressure dropped to 125/80 mmHg. The next three patients, aged 20, 24, and 28 were disasters with two dying on the day of operation and the other a month later. After a 2-year moratorium they resumed operating on people with diabetes in 1953, and in 1955 reported 20 cases of whom seven had died within 19 months of the operation (Luft et al, 1955). The maximum follow-up was only 43 months but a decrease in new vessels was reported in five and 'improvement in visual capacity and/or eye ground changes' in most.

Critics pointed out the difficulty of selecting appropriate patients for what they called 'this mutilating operation' since it was known that retinopathy often waxed and waned and that new vessels regressed spontaneously in 10% of cases (Beetham, 1963). A symposium on the effect of hypophysectomy on retinopathy was held in 1962 (Symposium on the Influence of Hypophysectomy and Adrenalectomy on Diabetic Retinopathy, 1962). Postoperative mortality in 134 cases was 11.2% and a third of survivors died in the next 6 years from renal

failure, hypoglycaemia or coronary artery disease. In those who survived the operation, it was thought to be beneficial in two thirds with disappearance of new vessels and a reduction in vitreous haemorrhages.

By 1968, when another symposium was held, there were two more controlled trials (Goldberg and Fine, 1969). Knud Lundbaek from Denmark found serious deterioration of vision in 8 of 19 eyes in patients not treated by pituitary ablation compared with 2 of 17 in the operated group. The Hammersmith Hospital group headed by Russell Fraser reported that in the treated group there was an improvement in haemorrhages (50%), new vessels (30%) and venous dilatation (20%).

When he wrote his textbook in 1968 John Malins was undecided about the value of pituitary ablation saying that there was no sound reason why it should influence retinopathy and that, at worst, it could be regarded as a respectable variant of acupuncture. The results were unpredictable and at best only half would benefit. Patients who might be candidates had a limited life expectancy and both the immediate and remote complications of the operation were substantial. The debate about the value of hypophysectomy rumbled on into the 1970s but destructive operations were about to be superseded by photocoagulation.

The first report of the American Diabetic Retinopathy Study Research Group, in 1976, clearly showed that photocoagulation reduced the rate of severe visual loss in proliferative retinopathy (The Diabetic Retinopathy Study Research Group, 1976). Treatment consisted of what the Americans called 'scatter' and the British 'pattern bombing' in which burns are placed in a grid pattern to ablate the peripheral retina. After 2 years the rate of severe visual loss was reduced from 16.3% in untreated eyes to 6.4% in treated ones. The most impressive results were in patients with new vessels on the disc and I remember those in Nottingham in the late 1970s in whom proliferative retinopathy was 'stopped dead' by xenon laser photocoagulation and remained so for decades.

The results were important but The Diabetic Retinopathy Study Research Group also educated two generations of ophthalmologists on the power of the randomised controlled trial to evaluate new or existing treatments (Fine, 1984). Stuart Fine points out that the results did not necessarily confirm accepted wisdom. In 1976 many ophthalmologists were surprised to learn that destroying as much as half the retina reduced the risk of blindness from diabetic retinopathy (The Diabetic Retinopathy Study Research Group, 1976). Another even more telling example concerns the results of a study of photocoagulation for macular degeneration. When the individual investigators were told by phone that there were differences in the rate of visual loss between treated and untreated eyes, all but one guessed that laser treatment was harmful (The Macular Photocoagulation Study Group, 1982) – the result was the complete opposite!

As a postscript it should be noted that diabetes was not the only condition for which 'endocrinectomies' were used. Metastatic carcinoma of the breast and prostate were often treated by various combinations of adrenalectomy, hypophysectomy and castration from the early 1950s. Such operations were still being done in 1960 when the London surgeon Hedley Atkins described survival in disseminated breast cancer of 10.8 months after hypophysectomy and 9 after adrenalectomy (Atkins, 1960).

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