British Journal of Ophthalmology, 1981, **65**, 305–306

Editorial: The continuing challenge of diabetic retinopathy

During the last 5 years numerous publications demonstrated beyond doubt that photocoagulation is effective in maintaining vision in a high proportion of patients with the sight threatening lesions of proliferative retinopathy[1–4] and diabetic maculopathy.[5 6] Though sight may be preserved in as many as 70% of patients treated, the rapid increase in vitreoretinal surgery[7 8] sadly indicates that photocoagulation is not always possible and not always successful. Even when photocoagulation is successful in maintaining vision, thereby improving the quality of life for the diabetic, the quantity of life, often tragically short, is not influenced. Patients may still be incapacitated by renal impairment, coronary and peripheral vascular disease, and autonomic neuropathy. Clearly the challenge is to find a form of treatment which will not only preserve vision but will also affect other microvascular beds, preventing, reversing, or at least arresting the development of lesions.

It has been suggested for many years that 'good' diabetic control can reduce both the incidence and the prevalence of diabetic microangiopathy, for example, diabetic retinopathy.[9] The problem has been to prove this hypothesis, because the methods of treatment available precluded achievement of near normoglycaemia in most insulin-dependent diabetics. In this issue White *et al.* publish a case report of a young diabetic girl in whom continuous subcutaneous insulin infusion (CSII) and near normal blood sugars caused dramatic reversal of severe but nonproliferative diabetic retinopathy. The importance of this patient, and the reason why a single case warrants publication, is that she demonstrates many of the advances made in recent years in the understanding of diabetes, its control, and its microvascular complications.

At present insulin is given by subcutaneous bolus injections, which, while they reduce blood sugar levels, are not a physiological method of insulin administration. In the normal individual the pancreatic beta cell secretes insulin at a slow continuous basal rate which controls glucose homoeostasis (through its action on the liver). With each meal a burst of insulin is superimposed on the basal rate; this controls utilisation of the food taken. Indeed, as a result of feedback mechanisms linking mainly liver and pancreas the blood sugar in normal persons is kept within very narrow limits. Development of the artificial pancreas[10] (a closed loop system in which a glucose sensor in the blood stream is connected through a computer to an insulin delivery system, also in the blood stream) allows for normalisation of blood sugar in diabetic patients. At present such a closed loop system is not practicable for more than a few days because of its bulk and expense. However, continuous insulin infusion is possible through open loop systems, where insulin is delivered at 2 predetermined, basal and mealtime, rates [11–13]. The procedure became practical when instead of the intravenous route the subcutaneous route was instituted.[14–16] The more physiological method of insulin administration resulted in normalisation not only of blood sugar but also of intermediatry metabolites and lipids.[17 18]

It is therefore now possible to perform the relevant studies which will determine the role of really good control in diabetic microangiopathy. There are 2 essential, independent, but related studies. One is the effect of blood sugar normalisation on established lesions, and the other is a primary prevention study. The latter, being of at least 5–7 years' duration, will have to await availability of smaller and more universally acceptable pumps.[19]

When observing the effects on established lesions care with the selection of patients is essential. From the report in this issue, and the work by Viberti *et al.*[20] it appears that early lesions in the retina and in the kidney (microscopic proteinuria) respond to treatment. There is also increasing evidence that advanced lesions will not improve (Viberti *et al.* in preparation, White *et al.* in preparation). Proliferative retinopathy is the response to a stimulus arising from nonperfused retina. While small areas of central nonperfusion possibly of short duration can be revascularised, large peripheral areas have not been seen to do so. Normalisation of blood sugar may reduce the chances of more vessels occluding, but it can do nothing once occlusion has been established. (The case with proliferative retinopathy reported by Irsigler[21] probably improved because of the steadily increasing ischaemia preventing perfusion of the new vessels: the patient became blind from thrombotic glaucoma some 6 months later.) Similarly, when large numbers of renal glomeruli are hyalinised, good control is unlikely to be of benefit.

Since early lesions are most likely to respond, it is patients with these lesions in whom normalisation of

blood sugar should be attempted. In a rare co-operative effort between North American and British centres such a study is now in progress (supported by the Kroc Foundation). This study is aimed at determining whether CSII is acceptable over long periods to patients, whether normalisation of blood sugar can be achieved over several months, even a year or longer, and finally whether it will have an effect on early diabetic microangiopathy.

Normalisation and improvement of blood sugar by other means, such as multiple daily injections of insulin[22] or home monitoring of blood glucose,[23 24] may reduce the incidence of retinopathy in the future, and indeed of other manifestations of diabetic microangiopathy. We do not yet know how best to achieve prolonged good control, nor do we know what level of control we should aim for. But the challenge remains, and the solution is within our reach. At present photocoagulation is still needed for those who have proliferative lesions and/or maculopathy. But there is now a hope that eventually photocoagulation and vitrectomy will be as rarely needed for diabetic retinopathy as is thoracoplasty since the introduction of streptomycin and other drugs for the treatment of tuberculosis.

References

1 Diabetic Retinopathy Study Research Group. Preliminary report on the effects of photocoagulation therapy. *Am J Ophthalmol* 1976; **81**: 383–97.
2 British Multicentre Study. Proliferative diabetic retinopathy: treatment with xenon arc photocoagulation. *Br Med J* 1977; **i**: 739–42.
3 Hercules BL, Gayed II, Lucas SB, Jeacock J. Peripheral retinal ablation in the treatment of proliferative diabetic retinopathy. *Br J Ophthalmol* 1977; **61**: 555–63.
4 Diabetic Retinopathy Study Research Group. Photocoagulation in the treatment of proliferative diabetic retinopathy: 2nd report of the diabetic retinopathy study findings. *Trans Am Acad Ophthalmol Otolaryngol* 1978; **85**: 82–92.
5 British Multicentre Study. Photocoagulation in the treatment of diabetic maculopathy. *Lancet* 1975; **ii**: 110–2.
6 Townsend C, Bailey J, Kohner EM, for the British Multicentre Study. Xenon arc photocoagulation for the treatment of diabetic maculopathy. *Br J Ophthalmol* 1980; **64**: 385–91.
7 Michels RG. Vitrectomy for complications of diabetic retinopathy. *Arch Ophthalmol* 1978; **96**: 237–45.
8 McLeod D, Leaver PK, Ferelis L. Vitrectomy for severe diabetic eye disease. *Trans Ophthalmol Soc UK* 1980; **100**: 291–8.
9 Tchobroutsky G. Relation of diabetic control to development of microvascular complications. *Diabetologia* 1978; **15**: 143–52.
10 Albisser AM, Leibel BS. The artificial pancreas. *Clin Endocrinol Metab* 1977; **6**: 437–77.
11 Slama G, Hautcerverture M, Assan R, Tchobroutsky G. One to five days continuous insulin infusion on seven diabetic patients. *Diabetes* 1974; **23**: 732–8.
12 Service FJ. Normalisation of plasma glucose on unstable diabetes: studies under ambulatory feed conditions with pumped intravenous insulin. *J Lab Clin Med* 1978; **91**: 480–9.
13 Irsigler K, Kritz H. Long term continuous insulin therapy with a portable insulin dosage regulating apparatus. *Diabetes* 1979; **28**: 196–203.
14 Pickup JC, Keen H, Parsons JH, Alberti KGMM. The use of continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J* 1978; **i**: 204–7.
15 Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Eng J Med* 1979; **300**: 573–8.
16 Champion M, Sheperd G, Rodger HW, Dupre J. Continuous subcutaneous insulin infusion in treatment of diabetes mellitus. *Diabetes* 1979; **28**: 383.
17 Pickup JC, Keen H, Parsons JH, Albeti KGMM, Rowe AS. Continuous subcutaneous insulin infusion: improved blood glucose and intermediatry metabolite control in diabetics. *Lancet* 1979; **i**: 1255–8.
18 Tamborlane WV, Sherwin RS, Genel M, Felig P. Restoration of normal lipid and amino acid metabolism in diabetic patients with portable insulin infusion pump. *Lancet* 1979; **i**: 1258–61.
19 Pickup JC, Keen H, Viberti GC, Bilous RW. Patient reactions to long term outpatient treatment with continuous subcutaneous insulin infusion. *Br Med J* 1981; **i**: 766–8.
20 Viberti GC, Pickup JC, Jarret RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and beta-2-microglobulin in insulin dependent diabetes. *N Engl J Med* 1979; **300**: 638–41.
21 Irsigler K, Kritz H, Najeminh C. Reversal of florid diabetic retinopathy. *Lancet* 1979; **ii**: 1068.
22 Rizza RH, Gerich JE, Haymond MW, *et al.* Control of blood sugar in insulin dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion and intensified conventional insulin thereapy. *N Engl J Med* 1980; **303**: 1313–8.
23 Sonksen PH, Judd SL, Lowy C. Home monitoring of blood glucose. *Lancet* 1978; **i**: 729–32.
24 Waldorf S, Gale EAM, Allison SP, Tattersall RB. Self-monitoring of blood glucose. *Lancet* 1978; **i**: 732–5.