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Editorials

Insulin-like growth factor type 1—friend or foe?

Clinical trials have demonstrated a significant correlation between poor glucose control and a high incidence of diabetic complications.¹ Consequently, an intensive insulin treatment regimen is recommended to counteract the deleterious effects of chronic exposure to high levels of glucose. However, insulin is known to positively regulate the production of insulin-like growth factor type 1 (IGF-1) and evidence presented in this issue of the *BjO* (p 725) demonstrates a clear association between high levels of IGF-1 and the advancement of diabetic retinal disease.

IGF-1 may affect the progression of diabetic retinopathy directly by its mitogenic action^{2,3} on retinal endothelial cell growth, or indirectly via an increased cell survival because of the antiapoptotic properties of IGF-1.⁴ The influence of IGF-1 on the induction of other growth factors—for example, vascular endothelial growth factor,⁵ IGF-1 mediated regulation of glucose metabolism,⁶ the altered responsiveness of cells to growth factors exposed to high concentrations of glucose,⁷⁻⁹ and the mitogenicity of insulin for REC² may also be of significance. The concentrations of IGF-1 that are reported in the study presented here are well within the range that are known to promote endothelial cell growth *in vitro*² and *in vivo*.³ However, some studies indicate no real association between IGF-1 levels and the progression of retinal disease¹⁰ and a simple correlation between the level of IGF-1 and diabetic retinopathy remains elusive. Other factors compound the difficulties in drawing definitive conclusions from such studies. For example, the bioavailability and the bioactivity of IGF-1 is regulated via IGF binding proteins (IGF-BP). These proteins have been shown to be increased in patients and animal models of diabetes^{11,12} and may be of significance for the correlation of retinal disease.¹³ Furthermore, the patients in the study by Chanteleau had been restricting food intake which is known to dramatically increase the production of hepatic IGF-BP 1 and 2 (for review see Straus¹⁴). The restoration of normal food intake of the patients may be associated with a decrease in the available IGF-1-BP and the bioavailability of IGF-1 will consequently be increased. Thus, there remains a number of key questions regarding the implementation of an intensive insulin regimen and the factors that affect the balance between the deleterious actions of IGF-1 with the beneficial consequences of this treatment.

The recommendation for continuation of intensive insulin therapy, despite worsening of diabetic retinopathy represents a significant cause for concern regarding the development of diabetic retinopathy. In general, continued

longitudinal analyses of patients on intensive insulin treatment indicated a subsequent improvement of retinal disease and it is believed that the deterioration of diabetic retinopathy represents only a transient worsening. Although there is no controlled study for a gradual normalisation of blood glucose being of benefit in reducing the progression of diabetic retinopathy, clinical experience does advise this approach and it would be of great relevance to specifically address this issue given the implications that this has for the management of diabetic retinopathy. A tempered approach to the normalisation of blood glucose by insulin may be preferable and the outcome of patients may be significantly improved if a less aggressive approach to normalisation of blood glucose with insulin was embraced.

If a gradual normalisation of blood glucose is preferable for the reduction of the exacerbation of the complications of diabetes, what then is the stimulus for this adaptive response? Glucose concentration is clearly not the whole story and we need to consider how cells, in particular, how retinal cells, may adapt to the conditions in which they find themselves. The entry of glucose into a cell occurs via a facilitative transport system¹⁵ which may itself be regulated in response to changes in the glucose concentration,¹⁶⁻¹⁸ growth factors, including IGF-1 and insulin,¹⁹ with mechanisms to increase glucose transporter expression in hypoglycaemia and hyperglycaemia,²⁰ and ischaemia,²¹ all of which are conditions relating to that present in the retina of patients with diabetes. Consequently, patients chronically exposed to high levels of glucose may adapt to conditions by the regulatory processes relating to this and the rapid normalisation of blood glucose concentration may not allow for the restoration of a “non-adapted response”.

While the mitogenic and antiapoptotic properties of IGF-1 are significant, it is the metabolic properties of IGF-1 that have been exploited in the development of recombinant IGF-1 therapy for the normalisation of blood glucose levels in patients with severe insulin resistance. Although this approach has been relatively successful with respect to the reduction of HBA_{1c}(%) levels^{22,23} and clearly illustrates the metabolic potential of IGF-1, studies have shown that there are deleterious side effects resulting from the proliferative properties of IGF-1—namely, an increase in the incidence of proliferative diabetic retinopathy.^{23,24} It is unlikely that we could approach this therapy with the same rationale as we approach the intensive insulin treatment. For those patients within the latter group, the rise in the level of IGF-1 occurs as a result of insulin treatment and is often

seen to level off after a period of time. However, the continual administration of levels of IGF-1 which are known to be mitogenic represents a clear conflict and the therapeutic use of IGF-1 has to be considered in the light of the potential complications with diabetic retinopathy for patients receiving recombinant IGF-1.

In the light of the accumulating evidence regarding the role of IGF-1 in diabetic retinopathy it is clear that the normalisation of blood glucose, by intensive insulin treatment or the administration of recombinant IGF-1, should be carried out with due consideration to the impact that this will have on other regulatory responses. Thus, if we are to effectively harness the therapeutic potential of these approaches, we must first elucidate the factors that affect the balance between glucose concentration, insulin, IGF-1, and the ability of the retina to respond to the physiological demands that are placed upon it.

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Pulsatile ocular blood flow

Although the eye is the only organ in the body in which blood vessels are readily visible, a technique for the accurate and reproducible measurement of ocular blood flow and its component parts has proved elusive.¹ The increasing likelihood of a multifactorial pathogenesis for glaucoma and possible importance of optic nerve head perfusion in the pathogenesis of glaucoma has added impetus to the search for a clinical method of measuring ocular blood flow.

The pulsatile variation in ocular pressure results from flow of blood into the eye during cardiac systole. First recorded in 1850 by Wegner,² various methods have been tried to record the pulsatile variation in intraocular pressure. Langham and co-workers³ adapted the pneumotonometer to measure intraocular pressure every 30 ms thus obtaining an accurate record of the pulsatile change in pressure. They hypothesised that the pressure pulse could be converted into a volume pulse using the known relation between ocular pressure and ocular volume. By multiplying this volume by the heart rate a measure of pulsatile ocular blood flow (POBF) could be obtained. The instrument has been developed and measurements are easily and quickly performed and the reproducibility is acceptable.^{4,5}

There are, as with all techniques, problems. Knowledge of these limitations is essential if the results of studies are to

be interpreted correctly. The conversion of the pressure pulse to a volume pulse relies on limited data and will be affected by scleral rigidity and ocular volume (proportional to the axial length of the eye). Only the pulsatile component of flow is assessed and the ratio of pulsatile to non-pulsatile flow may change with alteration in the heart rate, intraocular pressure or systemic blood pressure, and a change in the compliance of the blood vessels. From this index of global ocular blood flow (largely choroidal supplied by the posterior ciliary vessels) any inference about the optic nerve head circulation, which contributes but a tiny part to total ocular blood flow, must be carefully drawn.

One must also try to distinguish between the usefulness of a technique in determining differences between groups of patients and normal controls, or groups of patients on and off treatment and its usefulness in providing clinically relevant information in an individual patient.

Fontana *et al* (p 731) provide an extensive normal database for POBF measurement in a normal population and also measure POBF in patients with normal tension glaucoma. The results confirm previous studies finding POBF to be reduced in these patients.⁶ They also report a statistically significant difference in pulsatile ocular blood flow in the affected eye compared with the unaffected eye in

patients with "unilateral" normal tension glaucoma. This finding is new and intriguing. Many of the limitations of the technique do not apply in this circumstance. There was no difference in axial length between the eyes. Intraocular pressure was slightly higher in the affected eye although the difference would have only a small effect on perfusion pressure. Systemic variables of blood pressure and heart rate are identical. Unless one proposes that there is a difference in scleral rigidity between the two eyes it appears that the difference in POBF is real and provides further evidence for the importance of compromised ocular perfusion in the pathogenesis of glaucoma. The rider about scleral rigidity is important, for although very unlikely in this study, a reduced scleral rigidity would both reduce the calculated POBF and might make the optic nerve head more susceptible to pressure damage.

On a broader plain it is still unclear whether measurement of ocular blood flow will aid the diagnosis and treatment of glaucoma. Ocular pulse analysis currently provides the easiest and most clinically acceptable means of deriving an index of ocular blood flow, albeit that there are the significant problems discussed earlier. The range in POBF values in both normal and abnormal eyes makes a

clear separation of the normal from the abnormal on an individual basis extremely difficult, but this is also increasingly true of measurement of intraocular pressure. A combination of the two measurements, which the technique gives, might provide us with additional information to aid diagnosis and monitor the effect of therapy. Great ingenuity has been shown in the many methods devised to record the pulsatile change in ocular pressure; it may prove that harnessing this record correctly, with full knowledge of its limitations, provides a good deal more information than a simple pressure measurement.

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More change at the *BjO*

The *BjO* has long been in the business of disseminating information concerning the clinical and basic research activities of ophthalmologists and ophthalmic/vision scientists within the United Kingdom. In recent years, however, the *BjO* has received an increasing number of submissions from beyond these shores and as the pages of the journal have proliferated it is becoming clear that more than 50% of published work comes from outside the UK. This is, of course, a healthy situation, and one to be encouraged. Accordingly, the journal wishes to respond to this and in so doing has introduced some changes to the editorial board which will take place in the coming weeks and will reflect this increased internationalisation of its pages and presumably its readership. These changes are not new but in fact signify a return to editorial characteristics which marked the *BjO* in earlier times in the heyday of the Commonwealth. However, today's changes better reflect the broader international ophthalmic community and in this sense will be a new departure from previous times.

The new structure will comprise an editor in chief, three associate editors, and 15 section and regional editors. The three associate editors will represent discrete global areas—namely, one for the Americas, one for Europe, and a third for the UK and rest of the world. Thus, the *BjO* will now have three offices where papers can be processed and it is intended that this should provide a more efficient service for authors from each of these regions. Authors should therefore consult the new instructions to authors before submitting their papers if they wish a fast turn around time.

The journal will continue to deal with all aspects of ophthalmology and vision science. In particular it wishes to encourage submissions in both clinical and laboratory

science. In these days of change to many areas of ophthalmic practice, there is a perception that not only is the division between the clinician and the scientist becoming wider, but that within ophthalmology different types of specialist are finding it increasingly difficult to communicate with each other because of the highly sophisticated nature of their expertise. This particularly applies to the developing separation between ophthalmic surgery and ophthalmic medicine. It is critical that channels of communication are kept as wide open as possible and thus the *BjO* will continue to encourage reviews and commentaries which deal with such issues while through its newsdesk page, it will bring to the readership any hot items in any field that even remotely impinges on ophthalmology.

Papers will be processed as before but now in one of three offices rather than solely the UK office. The normal procedure is for an initial vetting of the paper for general suitability for the *BjO*, followed by allocation of the paper to a section or region, and then review by expert referees. Much of this procedure is performed by modern communication methods such that the paper can be fully processed within a period of 4-6 weeks at the present time. This will ensure that the initial decision on papers can be made as fast as possible.

The *BjO* hopes that these changes will continue to make the journal interesting to its readership. In the process of change, several previous section editors have retired from duty and the *BjO* wishes to thank them for their tireless and painstaking efforts during the past 6 years, and for helping to forge the new look *BjO* that is on offer today.

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