overlap with the groupings of HbA_1 concentration at seven years.

At three months into the study patients with strict diabetic control showed a worsening of retinopathy relative to those receiving more casual treatment.[2] At two years strict control seemed to be of benefit,[4] but the small difference had disappeared at 3·5 years.[4] The present report at seven years is claimed to argue for a benefit of strict control (as judged by HbA_1 concentration), but the results are clearly equivocal and do not answer the question of whether a strict insulin regimen (which carries its own risks[5]) is of benefit.

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AUTHORS' REPLY,—The arbitrary values of HbA_1 concentration of 9% and 10% as cut off points for dividing the patients into three groups were chosen before any analysis was carried out. The obvious reason for doing this was to study the possible relation between the mean HbA_1 concentration during seven years and retinopathy at the seven year end point; was there any relation, was there a linear relation, or was there any threshold value? Furthermore, we plotted the relation between the progression of retinopathy and mean HbA_1 concentration during the seven years, looking for any natural steps. Most of these questions cannot be answered by correlation analysis, as Simon P Wolff suggests. If such an analysis is carried out, however, a significant result is obtained ($r=0·33$, $p=0·032$ (Spearman's correlation)). The significant relation to both HbA_1 concentration at the start of the study and reduction in HbA_1 concentration, in the multivariate regression model, is a much stronger argument for a possible causal relation between retinopathy and glucose control than the result of the correlation analysis reported above.

Wolff states that retinopathy at the start of the study is more closely related to "the inherent severity of diabetic disease than to the long term effects of hyperglycaemia." The multivariate analysis (table V) suggests that the two factors are of equal strength: the severity of retinopathy at baseline (0·35 (regression coefficient), $p<0·046$) and the difference between the baseline HbA_1 and mean HbA_1 for seven years ($-0·35$, $p<0·041$).

The second question that Wolff raises concerns the different treatment regimens given during the study. In the multivariate analysis we examined whether the treatment code had any influence on the severity of retinopathy at seven years and found that it did not. This is explained in our article (page 21). Furthermore, although treatment was allocated according to patients' preference after 41 months of strict randomisation, intention to treat analysis showed that the differences in HbA_1 concentration between the original treatment groups were sustained from 41 months to seven years (data also given in the article).

We did not include a separate analysis for progression of retinopathy in the original treatment groups because the strict randomisation was not sustained after 41 months. These data have, however, been analysed, and the figure answers this question. It shows changes in retinopathy from the start of the study to 41 months of strict randomisation in the three treatment groups and then an intention to treat basis from 41 months to seven years. The seven years mean HbA_1 concentration in each group is shown in the figure.

We believe that Wolff's concluding remarks are strongly related to the "misunderstandings" reported above. We are, however, grateful for his questions: we have become even more aware of the difficulty of explaining results from multivariate analysis of clinical data in a way that it is both correct and easy to understand.

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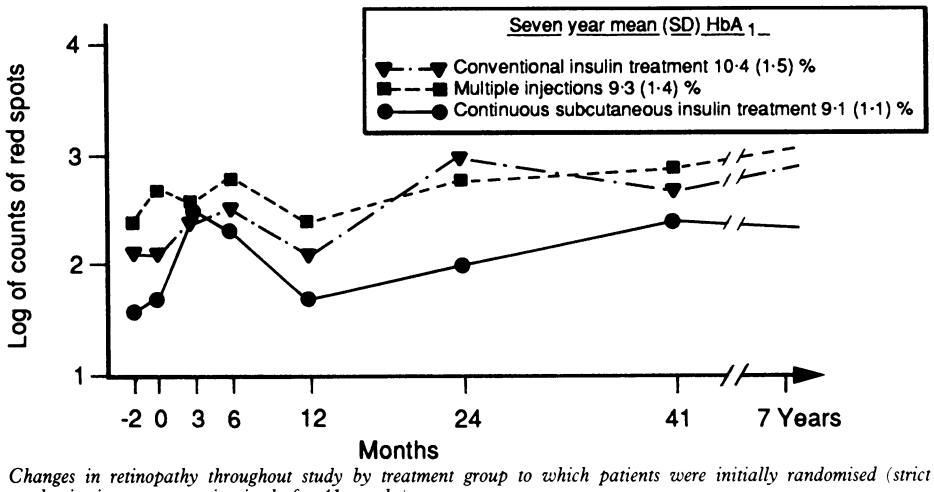

Changes in retinopathy throughout study by treatment group to which patients were initially randomised (strict randomisation was not maintained after 41 months)

High dose steroid bolus given for occlusion of central retinal artery

SIR,—N Hausmann and G Richard's report of four cases of occlusion of the central retinal artery treated by single intravenous bolus injection of prednisolone intrigued us.[1]

Firstly, the authors claim that retinal ischaemia for 105 minutes generally leads to permanent blindness. The work that they cite for this was a study of retinal tolerance time to experimental occlusion in 63 eyes of rhesus monkeys, which concluded that irreparable damage occurred after 105 minutes.[2] The relevance of this to human eyes is debatable, given that useful visual function has returned up to eight hours after the onset of occlusion in trials of fibrinolytic agents.[3-5]

Secondly, although Hausmann and Richard used prednisolone, this drug is not available for intravenous use in the United Kingdom. The preparation used in the United Kingdom is a particulate suspension. Vascular occlusion has been reported due to embolus of steroid particles.[6,7] An equivalent drug is methylprednisolone.

Thirdly, it is difficult to see how corticosteroids could achieve reperfusion of the central retinal artery within 10-15 minutes as the authors claim. The datasheet for methylprednisolone states that it can provide relief in sensitivity reactions in half an hour to two hours.[8] Glucocorticoids influence cardiovascular sensitivity to catecholamines by inhibiting the induction of mRNA responsible for the production of G protein. Coupling of adrenergic receptors and G protein is essential to transmembrane signalling in vascular smooth muscle.[9,10] This effect takes time. Corticosteroids may relieve vasospasm in this way. Adverse effects after intravenous bolus injection of massive doses of corticosteroids are rare but can be serious, including anaphylactoid reactions, tetraplegia, cardiac arrhythmias, and sudden death.[8,11]

This report repeats the classic error of extrapolation from an observed association: visual function returned after injection of steroids, therefore steroids must have restored visual function. We strongly advise against giving very high dose boluses of steroids intravenously for occlusion of the central retinal artery until the hypothesis has been verified in a randomised clinical trial.

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AUTHOR'S REPLY,—Jyotin C Pandit and Funke Tiamiyu state that fibrinolysis can restore useful visual function up to eight hours after the onset of occlusion. But Bertram *et al* gave plasminogen activator to two of 69 patients with retinal artery occlusion, only one of whom had occlusion of the central artery.[1] The outcome in this case was a central scotoma of 40° and vision reduced to finger counting. Is this useful visual function? The 67 other patients had between one and six contraindications to lysis.

In response to Pandit and Tiamiyu's second point, we used soluble steroids, not a particulate dispersion. They also say that the steroids need