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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1 Brinchmann-Hansen O, Dahl-Jørgensen K, Sandvik L, Hanssen KF. Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study. *BMJ* 1992;**304**:19-22. (4 January.)
2 Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to rapid deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *BMJ* 1985;**290**: 811-5.
3 Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, *et al*. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy and neuropathy: the Oslo study. *BMJ* 1986;**293**: 1195-9.
4 Brinchmann-Hansen O, Dahl-Jørgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol* 1988;**106**:1242-6.
5 Wolff SP. Is hyperglycaemia risky enough to justify the increased risk of hypoglycaemia linked with tight diabetes control? *Biochem Med Metab Biol* 1991;**46**:129-39.

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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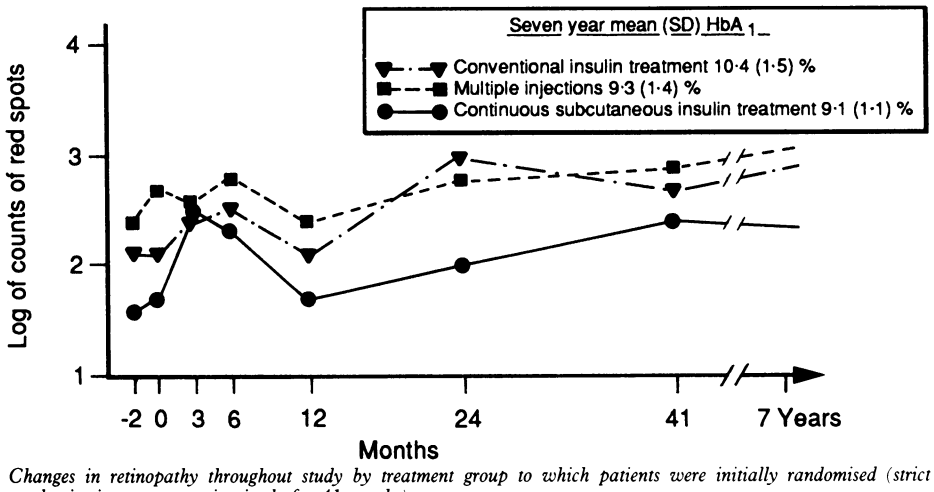

Changes in retinopathy throughout study by treatment group to which patients were initially randomised (strict randomisation was not maintained after 41 months)

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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1 Hausmann N, Richard G. Effect of high dose steroid bolus on occlusion of ocular central artery: angiographic study. *BMJ* 1991;**303**:1445-6. (7 December.)
2 Havreh SS, Weingeist TA. Experimental occlusion of the central artery of the retina. IV. Retinal tolerance time to acute ischaemia. *Br J Ophthalmol* 1980;**64**:818-25.
3 Schumacher M, Schmidt D, Wakhloo AK. Intra-arterial fibrinolysis in central artery occlusion. *Radiologe* 1991;**31**: 240-3.
4 Bertram B, Wolf S, Fisches H, Schulte K, Hoberg A, Reim M. Thrombolytic treatment of retinal arterial occlusions with plasminogen activator. *Klin Monatsbl Augenheilkd* 1991;**198**: 295-300.
5 Annonier P, Sahel J, Wenger JJ, Rigolot JC, Foessel M, Bronner A. Local fibrinolytic treatment in occlusions of the central retinal artery. *J Fr Ophthalmol* 1984;7:711-6.
6 Shorr N, Seiff SR. Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile hemangioma. *Ophthalmic Surg* 1986;**17**:229-31.
7 Wesley RE, Johnston DT, Gutow GS. Central retinal artery occlusion. *Ophthalmic Surg* 1987;**18**:123-5.
8 Walker G, ed. *ABPI datasheet compendium 1991-92*. London: Datapharm, 1991:1656-8.
9 Radomski MW, Palmer RM, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proc Natl Acad Sci USA* 1990;**87**:10043-7.
10 Haigh RM, Jones CT, Milligan G. Glucocorticoids regulate the amount of G proteins in rat aorta. *J Mol Endocrinol* 1990;5:185-8.
11 Kelly HW, Murphy S. Corticosteroids for acute severe asthma. *DICP—Annals of Pharmacotherapy* 1991;25:72-9.

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

time to take effect. Our patients described their recovery in terms of a "cracked mirror" 10-15 minutes after the injection. Angiography was performed 60 minutes after injection and showed complete reopening.

With regard to the adverse side effects mentioned by Pandit and Tiamiyu, cardiac arrhythmias were reported after longer administration of higher doses of steroids (4×30 mg/kg daily),[4] not after a single 1000 mg bolus, which is not a massive dose. Steroids are an effective measure against anaphylactic shock.[4,5] Are anaphylactoid reactions to steroids really common?

We tried to show the effect of steroids on vessel walls and offered angiographic evidence that occluded vessels became completely perfused 60 minutes later. A steroid bolus seems to us to be a suitable emergency treatment that does not interfere with other drugs for this condition. Any other treatment may be given simultaneously or afterwards.

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2 Walker G, ed. *ABPI datasheet compendium 1991-92*. London: Datapharm, 1991:1656-8.
3 Bush CA, Renner H, Boudoulas H. Corticosteroids in acute myocardial infarction. *Angiology* 1980;**31**:710-6.
4 Campbell JW, Frisse M. *Manuel de therapeutique medicale*. 3rd ed. Paris: Médecine et Sciences Internationales, 1984.
5 Madowitz JS, Schweiger MJ. Severe anaphylactoid reaction to radiographic contrast media. *JAMA* 1979;**241**:2813-9.

Side of origin of epithelial ovarian cancer

SIR,—Two studies published in the *BMJ* have been designed to test Fathalla's hypothesis that repeated trauma to ovarian epithelium caused by incessant ovulation increases the risk of ovarian cancer.[1] As ovulation reportedly occurs more often on the right side the authors hypothesised that ovarian tumours would occur more frequently in the right ovary. In one study the results were significant, with 59% of tumours occurring on the right side.[2] In the other study the results were not significant, with 53% of tumours occurring on the right side.[3]

The original report that ovulation occurs more commonly from the right ovary was based on a study of only 16 women.[4] Moreover, it conflicted with a previous report that ovulation alternated between ovaries in 80% of cycles.[5] Thus the premise that ovulation occurs more often on the right side may itself not always be correct, at least for those patients at risk of ovarian cancer.

Fathalla's hypothesis is based on much broader evidence, including both clinical and epidemiological studies. This work has been reviewed elsewhere.[6] More recently we have provided a molecular basis to support the hypothesis.[7] Studies in our department have detected loss of alleles on the long arm of chromosome 17 in specimens of ovarian tumour.[8] This loss of genetic material is thought to represent inactivation of an important tumour suppressor gene, and extensive studies are now under way to identify its precise location.

Pathologists have long recognised that most ovarian cancers arise on the surface of the ovary, not in the ovary itself. After the epithelial surface of the ovary has ruptured to release the ovum at ovulation the traumatic tears are repaired by repeated cell division. The loss of a tumour suppressor gene in a single epithelial cell may allow mitotic division to continue uncontrolled, leading to malignant change. Incessant ovulation increases the risk of promoting such malignant transformation. None the less, the main initiating event in malignancy is a sporadic or inherited mutation, not ovulation. Mutations have an equal chance of occurring on either side. Thus laterality in ovarian cancer is unlikely to emerge as a significant factor unless very large numbers of cases are analysed.

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1 Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet* 1971;ii:163.
2 Cruickshank DJ. Aetiological importance of ovulation in epithelial ovarian cancer: a population based study. *BMJ* 1990;**301**:524-5.
3 Johannes CB, Kaufman DW, Rosenberg L, Palmer JR, Stolley PD, Lewis JL Jr, *et al*. Side of origin of epithelial ovarian cancer. *BMJ* 1992;**304**:27-8. (4 January.)
4 Potashink G, Insler V, Meizner I. Frequency, sequence, and side of ovulation in women menstruating normally. *BMJ* 1987; **294**:219.
5 Marinho AO, Sallam HN, Goessens L, Collins WP, Campbell S. Ovulation side and occurrence of mittelschmerz in spontaneous and induced ovarian cycles. *BMJ* 1982;**284**:632.
6 Beral V. The epidemiology of ovarian cancer. In: Sharp F, Soutter WP, eds. *Ovarian cancer—the way ahead*. Chichester: Wiley, 1987:21-8.
7 Lowry S, Russell H, Hickey I, Atkinson R. Incessant ovulation and ovarian cancer. *Lancet* 1991;**337**:1544.
8 Russell SE, Hickey G, Lowry WS, White P, Atkinson RJ. Allele loss from chromosome 17 in ovarian cancer. *Oncogene* 1990;5: 1581-3.

Octreotide and Graves' ophthalmopathy

SIR,—T C Chang and colleagues claim that octreotide is effective in Graves' ophthalmopathy.[1] Although there are theoretical grounds why octreotide may have a place in the treatment of this disease, the question whether it is effective remains unanswered as spontaneous improvement of Graves' ophthalmopathy is common and can occur rapidly.[2] The authors might have been more convincing in their claim had they at least shown a reduction in circulating insulin-like growth factor-1 concentrations as a result of treatment.

The idea is interesting, and octreotide may indeed be useful. But only a properly controlled trial is sufficient to assess the usefulness of such an expensive drug in treating Graves' ophthalmopathy.

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1 Chang TC, Kao SCS, Huang KM. Octreotide and Graves' ophthalmopathy and pretibial myxoedema. *BMJ* 1992;**304**: 158. (18 January.)
2 Perros P, Weightman DR, Crombie AL, Kendall-Taylor P. Azathioprine in the treatment of thyroid associated ophthalmopathy. *Acta Endocrinol* 1990;**122**:8-12.

Genitourinary tract infections in pregnancy and low birth weight

SIR,—We thank Fiona Smaill[1] for referring to additional reports that support the findings of our case-control study of genitourinary infections in pregnancy and low birth weight in Australian Aboriginal women.[2] We agree that a randomised controlled trial is not required. Although there have been no randomised controlled trials in our population of Australian Aboriginal women, such a trial would not be appropriate because of difficulties with follow up and compliance and for ethical reasons.

The programme we are planning is a pragmatic attempt to instigate screening and treatment of genitourinary tract infections during pregnancy in this population. The effectiveness of such a programme in reducing the incidence of preterm birth and low birth weight will be evaluated. This should indicate whether there is a preventable relation between infection and preterm birth and low birth weight in this population of disadvantaged women, many of whom experience living conditions akin to those of less developed countries.

The results of the randomised trials conducted in other populations that Smaill cites add urgency to our proposed programme.

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1 Smaill F. Genitourinary tract infections in pregnancy and low birth weight. *BMJ* 1992;**304**:54-5. (4 January.)
2 Schultz R, Read AW, Straton JAY, Stanley FJ, Morich P. Genitourinary tract infections in pregnancy and low birth weight: case-control study in Australian Aboriginal women. *BMJ* 1991;**303**:1369-73. (30 November.)

Parent support groups

SIR,—P Morris Jones raises anxieties that "bitter and angry" parents may dominate parent support groups and so undermine their value unless a professional keeps an eye on them.[1]

From time to time Action for Sick Children receives telephone calls and letters from such parents; in most cases these parents believe that no one is listening to them and they are being labelled as difficult or hysterical. Sometimes the reality is that no one can help, but in our experience the tolerance and emotional reinforcement provided by other parents can be an important factor in coming to terms with the unacceptable—namely, having a child with severe or life threatening illness. However sensitive professionals are to the intense distress that often underlines aggression, shared experience, parent to parent, is without parallel.

For this reason we are seeking to expand our advice and support to parents. This will often be in partnership with professionals, complementing and supporting their role by providing non-clinical information and an ear to listen, but above all by providing a point of contact with our local branches and specialist groups, such as those covered in the valuable directory compiled by Contact a Family.[2]

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1 Jones PM. Parent support groups. *BMJ* 1992;**304**:55. (4 January.)
2 Annis J. Finding support for children with rare diseases. *BMJ* 1991;**303**:1154. (9 November.)

Bone banks

SIR,—I agree with H I Atrah that bone banking should be organised on a professional basis to the highest standards and that some blood transfusion laboratories would be well placed to provide this service and should be encouraged.[1] It is essential, however, that agreed minimum quality standards are adopted, and to this end the British Orthopaedic Association has, at the request of the Department of Health, formed an allograft bone working party to establish guidelines. The current advice from the Department of Health, in contrast to that given by Atrah, is that serum from all donors (living and cadaver) must be tested for HIV antibody at donation. Subsequent testing is required for living donors except women aged over 70. For fresh stored (4°C) or frozen bone bacteriological analysis of the bone surface or bone tissue is also considered to be essential.