true, but the clinical problem below that age is still just over half that of myocardial infarction. Secondly, he says that mortality statistics underestimate deaths from heart failure, but he correctly attributes that to the method of classification.

Thirdly, he says that heart failure contributes as a "pathological mechanism"; so does atheroma in the coronary arteries. The fundamental cause of atheroma still remains obscure. Finally, he points out that the epidemiology of heart failure has been largely ignored because of difficulties of definition; it is quite possible to agree a definition such as the one we have used in our work. None of these arguments are persuasive reasons for ignoring an important cause of morbidity and death.

Lives saved per 10 000 patients treated for varying periods in several studies. CONSENSUS (the cooperative north Scandinavian enalapril survival study), VHeFT I and II (Veterans Administration cooperative vasodilator heart failure trials), and SOLVD (studies of left ventricular dysfunction) were trials of enalapril in heart failure of decreasing severity. AIMS (the anistreplase intervention mortality study) tested the efficacy of thrombolytic treatment in myocardial infarction. The European CABG study (coronary artery surgery study in stable angina) investigated the benefits of cardiac surgery in patients with angina pectoris. MRFIT (the multiple risk factor intervention trial) and the WHO (World Health Organisation) study were trials in which several risk factors for coronary heart disease were modified. The LRC (Lipid Research Clinics) trial (of cholestyramine) and the Helsinki trial (of gemfibrozil) assessed the value of lipid lowering drugs in reducing mortality.

Heart failure is common, causes premature death, carries a poor prognosis, consumes considerable hospital resources, and can be identified in the population, and effective prevention and therapeutic interventions are available.⁶ Heart failure fulfils all the criteria for inclusion in *The Health of the Nation*. It is being neglected because of a belief that prevention of the main cause, coronary heart disease, is more appropriate, although current evidence suggests that proper treatment of heart failure applied to the whole population would be more effective in terms of mortality and possibly morbidity (figure). These are not mutually incompatible approaches. Proper emphasis on coronary heart disease in *The Health of the Nation* should allow interventions other than primary or secondary prevention of coronary heart disease to be included.

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Action Asthma: privatising the airways?

SIR,—A recent press release described Action Asthma as "an educational initiative launched [in January 1991] . . . to improve the management of asthma through educational programmes with hospital doctors, GPs, practice nurses and patients." It is guided by 11 doctors with a special interest in asthma. So far a national survey on asthma has collected information on how 61 000 patients feel about their asthma. There is a national telephone asthma helpline, and a leaflet with 10 questions "to ask your doctor" is being distributed. The leaflet carries the logo of Allen and Hanburys, with the company's name and the slogan "Confidence for living with asthma." The company's name appears on all Action Asthma's material, and its inhaled product packs contain a form inviting patients to enrol in the Action Asthma patient service, which offers written information and advice. Almost 180 000 patients have enrolled.

Several issues arise. Though no criticism can be made of Action Asthma's worthy aims and motives, the likely effect would seem to be the development and strengthening of patients' and doctors' loyalties to one company. This may not be in their interest or in the interest of the NHS: decisions about treatment should be independent of company loyalty. It is also, in my view, unfair to competing firms.

It would be healthier if good causes did not provide commercial benefits for their sponsors. Such relations are liable to tarnish their image.¹ If other companies, not necessarily concerned with health, had joined Allen and Hanburys in supporting Action Asthma it would be less controversial.

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1 Erlichman J. Charity logo deal breaks new ground. *Guardian* 1991 Sep 14:3.

**We sent this letter to Action Asthma, who replied as follows.

SIR,—As Andrew Herxheimer states, Action Asthma is guided by a group of respiratory physicians and general practitioners with an interest in asthma. We were pleased to accept Allen and Hanburys' invitation to develop an educational service for patients, nurses, and doctors. The aim of the service is to complement the many other initiatives to reduce suffering from asthma. We believe that various strategies are needed if that goal is to be achieved. Since its launch in September 1990 Action Asthma has provided a range of educational aids and materials and arranged various meetings for doctors and nurses.

The chairman of the education committee of the National Asthma Campaign has attended Action Asthma's programme development board, and similar initiatives from other pharmaceutical companies, to ensure that advice is standardised and duplication of effort avoided. At the first meeting there was a commitment that the materials would not be promotional and that Action Asthma's most successful educational activities would be offered to the National Asthma Campaign for continuation.

Herxheimer suggests that the aims of Action Asthma are tied in to developing patients' and doctors' loyalties to one company. This is not the case. Action Asthma's services support and encourage the guidelines for management and treatment proposed by the British Thoracic Society. We do not promote specific drug treatment produced by Allen and Hanburys or any other pharmaceutical company. We refer only to types of treatment—"relievers," "preventers"—and the

way in which they work. Membership of the Action Asthma patient service is open to all patients regardless of the treatment they receive.

Herxheimer's general concern about the funding of postgraduate education and patients' education is an important issue that extends well beyond respiratory disease. In the current climate, however, when the NHS has limited resources and the government offers little funding specifically for education about asthma, financial support for health education continues to be needed. At present this gap is often filled by pharmaceutical companies. We believe that Action Asthma's materials have been of considerable benefit to the patients who use them.

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Blood glucose concentrations and progression of diabetic retinopathy

SIR,—Olaf Brinchmann-Hansen and colleagues, reporting the progression of diabetic retinopathy at seven years in the Oslo study, suggest that improved glycaemic control is of benefit.¹ Their key data are presented in table III, which gives the score for the severity of retinopathy (mean (SD) numbers of microaneurysms and haemorrhages) at the beginning of, and seven years into, the study. The data are broken down arbitrarily into three groups: patients with "blood glucose concentration" (actually percentage glycated haemoglobin (HbA_{1c})) of <9.0% (20 patients), 9.1-10.0% (13 patients), and >10.1% (12 patients) at the examination at seven years.

Testing of these data, however, yields no difference in the severity of retinopathy at seven years between the groups with HbA_{1c} concentrations of <9.0% and 9.1-10.0% or between the groups with concentrations of 9.1-10.0% and >10.1%. A significant difference (p=0.021) exists solely between the groups with HbA_{1c} concentrations of <9% and >10.1%, but this difference is, in principle, eroded by the Bonferroni correction required for situations of multiple comparison. Spearman's or Pearson's correlation of the seven year HbA_{1c} concentration with the severity of retinopathy (which would have been a more useful test of the hypothesis than a statistical procedure based on arbitrary subdivisions) was unfortunately not given, but log linear regression analysis of the risk of retinopathy (table V) seems to enter only the difference in mean HbA_{1c} concentration between the start of the study and at seven years. The authors also show that retinopathy at the beginning of the study was not correlated to HbA_{1c} concentration at that time. As individual severity of retinopathy at seven years correlated powerfully with retinopathy at the start of the study it seems that retinopathy is more closely related to the inherent severity of diabetic disease than to the long term effects of hyperglycaemia.

The Oslo study was originally established to determine the effects of insulin pumps, multiple insulin injections, and conventional treatment on the progression of complications. At the beginning of the study 45 patients were randomised into three equal groups: 15 used insulin pumps, 15 had a multiple injection regimen, and 15 received two insulin injections a day. At seven years, however, only 10 used the pump, 29 used multiple injections (insulin pens), and only six were using conventional treatment. These groups are not analysed separately for progression of retinopathy, and it is not clear, from the data presented, how these groups

overlap with the groupings of HbA₁ 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.¹ The present report at seven years is claimed to argue for a benefit of strict control (as judged by HbA₁ concentration), but the results are clearly equivocal and do not answer the question of whether a strict insulin regimen (which carries its own risks⁵) is of benefit.

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AUTHORS' REPLY.—The arbitrary values of HbA₁ 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 HbA₁ 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 HbA₁ 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 HbA₁ concentration at the start of the study and reduction in HbA₁ 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 HbA₁ and mean HbA₁ 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 HbA₁ 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 HbA₁ 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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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.^{3,4}

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.^{5,7} 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.⁶ 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.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

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