and Monotard MC) will cause confusion and distress to many patients with diabetes mellitus.

The Department of Health and Social Security has reassured us that highly purified porcine insulin will continue to be available from Nordisk UK Ltd, but this ignores the fact that the Nordisk range does not contain an insulin zinc suspension equivalent to Monotard MC. Novo Laboratories Ltd have suggested that patients should be transferred to their brand of enzyme modified pork insulins (Human Actrapid and Human Monotard), but this ignores reports that in some patients human insulins are absorbed more quickly than the equivalent porcine preparation.[1] Many doctors currently prescribe "Actrapid" insulin without specifying species and if the pharmacist substitutes the human variety instead of porcine insulin without telling the patient about the dangers of hypoglycaemia there may be serious implications for patients who drive cars.

Actrapid MC and Monotard MC are currently the most widely prescribed insulins in the United Kingdom, so the justification for their withdrawal is difficult to understand. The work involved in changing many patients to alternative preparations will be a considerable clinical load on already overstretched diabetic clinics. The pharmaceutical industry claims to pay high regard to the needs of the patients whom it seeks to serve: in this instance it seems that narrow commercial considerations have been allowed to take precedence over duty to patients.

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MANUFACTURERS' REPLY—The substitution of Human Actrapid and Human Monotard for Actrapid MC and Monotard MC is being carried out against the background of extensive scientific evidence showing that these insulins are almost identical in clinical utility.

Pharmacokinetic studies have shown either small or no differences between the products.[1] In all eight published clinical trials, covering 282 patients, hypoglycaemic episodes have never been more frequent on transfer to the human formulations in either children or adults,[2-9] so there is no reason to believe that there is an increased risk to car drivers. In seven of these trials there was no change in total daily insulin dose, and in the remaining study a mean dose increment of 1 IU of evening Human Monotard was required to overcome the small deterioration in fasting blood glucose which was seen on transfer.[6] Hence patients can be transferred safely, dose for dose, to our human formulations, with only routine adjustments in insulin dose being required, and at identical cost to the National Health Service. Human insulin also carries with it the potential advantage of lower immunogenicity.

As a company we have the highest regard for the diabetic patient. This is evidenced by our huge commitment to basic research and development in diabetes and by the development of research links with many of the leading academic units in the UK. However, it is only by rationalising our range of insulins that we can fund further research to produce innovative products such as human insulin.

Informal discussions were held with the medical advisory committee of the British Diabetic Association in April and May 1986, and we kept the committee fully informed; it felt that we were acting in a considered and reasonable manner. To reduce any possible confusion every relevant physician, all GPs, all pharmacists, and the offices of the British Diabetic Association have been advised of this change. Every pack of Actrapid MC and Monotard MC contains a statement agreed with the DHSS about the substitution.

Many diabetologists have been aware of our intended move to human insulins for some time and have transferred large numbers of patients to Human Actrapid and Human Monotard; so far as I am aware, this has proceeded without difficulty and with little increase in clinic work. The transfer has also occurred without reported problems in Denmark, France, Portugal, South Africa, and Austria. As the insulins are being substituted over six month periods most patients can be transferred at their routine clinic visit. Nevertheless, we do apologise if any additional work arises. Special explanatory leaflets for use in the clinic have been produced. Finally, when only one species of Actrapid and Monotard is available confusion and pharmacy errors will be eliminated.

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Leucocytoclastic vasculitis and pneumonitis induced by metformin

SIR,—I am surprised that you published this short report (23 August, p 483). I have no criticism of the facts presented by Dr L Klapholz and colleagues or their conclusions, but I think that publication of this sort of adverse reaction report is wrong for two reasons. Firstly, metformin is a well established drug, and if, as the authors claim, this reaction has not been reported before despite many years of widespread use it must be extremely unusual and therefore unlikely to happen again. It is not as if the report has drawn attention to a small subgroup at risk in whom it might be reasonable to try alternative therapy.

Perhaps more importantly, however, many medical practitioners come across serious and unusual reactions that are temporally related to drug therapy but are reluctant to expose the patient to the risk of a second challenge, particularly when alternative therapies are readily available. It is unfortunate that rechallenge is often the only reliable way of confirming a suspected drug reaction, and confirmation is usually required before an article is acceptable to reviewers and editors. I cannot help wondering whether the patient in this report was exposed to the risks of recurrent cutaneous vasculitis and pneumonitis (which had previously required treatment with systemic steroids) purely in her best interests.

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AUTHOR'S REPLY,—We are unable to agree with Dr Grattan in his two objections to our short report.

It is correct that metformin is a well established drug and plays an important part in the treatment of diabetes mellitus. This fact does not interfere with our findings and, as we have mentioned, it is the first reported case of vasculitis and pneumonitis induced by metformin. Although very rare, we think that these side effects should be reported and made known. Publication of a drug induced side effect does not have the purpose of frightening medical practitioners, but any unusual and unexpected phenomenon should be reported.

Rechallenge of our case was not required by the reviewers and editors of the *BMJ*. We reintroduced metformin not as a rechallenge but for the purpose of treating the patient's non-insulin dependent diabetes mellitus with her previous regimen under strict supervision.

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Orchidectomy versus oestrogen for prostatic cancer

SIR,—The results of the trial conducted by Drs Peter Henriksson and Olof Edhag (16 August, p 413) are so strikingly in favour of orchidectomy (no serious cardiovascular sequelae) that one should perhaps suspect that another factor is responsible.

The authors have shown that the randomisation procedure produced two groups of patients which were very closely comparable in respect of 17 factors related to their cardiovascular states on entry to the trial (table I). However, patients entered the trial at widely differing stages of their disease (stages 1-4). Unless it can be shown that the randomisation has produced a similar equal distribution between the two groups in respect of severity of disease the difference in incidence of major cardiovascular events could simply be due to a preponderance of advanced cases in one group.

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AUTHORS' REPLY—We showed an increased incidence of cardiovascular morbidity during the first year of oestrogen treatment of patients with prostatic cancer.[1] The dose was the lowest recommended in the treatment of prostatic cancer.[2] The focus of the trial was cardiovascular effects, and the only known predictors of cardiovascular side effects during oestrogen treatment—that is, age over 75 years or a history of cardiovascular diseases[3,4]—excluded patients from the study. Except for those excluded because of cardiovascular criteria or age, the patients were consecutively recruited to the study and their cardiovascular characteristics were assessed. The tumour stages before treatment allocation were T_1 3%, T_2 24%, T_3 40%, and T_4 33%, which owing to the consecutive recruitment reflects the actual