4) or the duration of treatment (fig 3). However, the correlation made from the in vitro study was for data in only three patients.

No information was given as to the clinical status of the 12 patients studied in vivo, especially their vasodilator regimens, the frequency of episodes of rejection, the use of other immunosuppressive agents, etc. . . . In patients with transplanted hearts the reactivity of any particular vascular bed is likely to be influenced by several interconnected factors. Therefore, the influence of a single factor, in this case cyclosporin treatment, cannot be assessed by simple linear regression. Furthermore, the study of the effect of cyclosporin on nitric oxide release after stimulation by substance P needs a control group. There was a control group in the in vitro study but not in the vivo study.

In conclusion, we applaud O'Neill *et al* for their effort to address the important issue of vascular toxicity of cyclosporin in patients with transplants. However, we feel that both the design and the results of the study do not quite support the clear cut conclusion they made.

A TUAN DINH-XUAN
TIMOTHY W HIGENBOTTAM
Department of Respiratory Physiology,
Papworth Hospital,
Cambridge CB3 8RE

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This letter was shown to the authors, who reply as follows:

SIR,—We used three distinct models to assess the effect of cyclosporin on endothelial function in the human coronary circulation: none of them showed that cyclosporin was capable of compromising the ability of the vascular endothelium to release nitric oxide in response to an endothelium dependent vasodilator.

Dr Dinh-Xuan and Dr Higenbottam are correct in pointing out the importance of EC₅₀ values in comparing the difference in the response to low concentrations of substance P. Calculation of the EC₅₀ values shows minimal dose ratio shift of <3, but the maximum dilatory response was preserved. In our discussion we pointed out the loss in sensitivity at low concentrations of substance P, but we believe that in light of the evidence from the retransplanted patients and the in vivo study this effect is not clinically relevant. This view accords with the results from our

previously published data where therapeutic concentrations of cyclosporin had no effect on any part of the dose response curve for substance P in human coronary arteries.¹

We stated both in the abstract and the methods section that the patients in the in vivo study were clinically well and free of rejection at the time of assessment. Admittedly, these patients do form a complex group in terms of medication and clinical history. However, irrespective of "interconnected factors" the fact remains that patients who receive cyclosporin after transplantation, retain a response to substance P and isosorbide dinitrate that resembles that reported in healthy volunteers.²

Data from human studies are important in that a previous report by Dinh-Xuan *et al*³ suggests that inhibition of the release of endothelium dependent relaxing factor (EDRF) in a rat model may contribute to the underlying mechanisms of cyclosporin associated hypertension in humans. We attribute this to a genuine species difference, however, it seems that from the most recent reports the cyclosporin associated vascular dysfunction in rat aortae may also be due to an increased response to vasoconstrictors rather than to a reduction in EDRF release.⁴

The mechanisms underlying the vascular effects of cyclosporin in humans that precipitate clinically relevant hypertension and renal damage remain to be elucidated. Our findings indicate that direct inhibition of nitric oxide is unlikely to be the mechanism responsible.

GREGORY S O'NEIL
ADRIAN H CHESTER
SUDHIR KUSHWAHA
MARLENE ROSE
SAMAD TADJKARIMI
MAGDI H YACOUB
Harefield Hospital,
Harefield,
Middlesex UB9 6JH

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Antihypertensive drugs and plasma lipids

SIR,—In his editorial (*British Heart Journal* 1991;66:409-10) Professor Swales commented that a trial comparing diuretics or β blockers with one of the new classes of agents would be desirable. He also writes that "such an end point trial has not been set up and it is unlikely to be set up in the near future. . . ." The Captopril Prevention Project (CAPPP), which is now in its second year and conducted with the endorsement of the European Society of Hypertension, is precisely such a trial. Its aims and design have been reported.¹ In brief, hypertensive men and women aged

25-66 are randomised to captopril based treatment or diuretic β blocker based treatment (ACE inhibitors excluded); the aim is to detect a 20% difference in cardiovascular mortality with a power of 80% at the 5% significance level (two sided).

The study is being conducted at 275 health care centres in Sweden and Finland and the PROBE (prospective, randomised, open, blinded end point evaluation) design is used.² In September 1991 more than 6000 patients had been recruited to CAPPP. It is hoped that by 1996 enough end points will have accumulated for the study to be ended (with a significant outcome).

LENNART HANSSON
Chairman, CAPPP steering committee
BJÖRN DAHLÖF
Secretary, CAPPP steering committee,
Department of Medicine,
Östra Hospital,
CK Plan 2
S-416 85 Gothenburg,
Sweden

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Avoidance of tolerance and lack of rebound with intermittent dose titrated transdermal glyceryl trinitrate

SIR,—The study by Fox *et al* (*British Heart Journal* 1991;66:151-5) addressed an important question concerning nitrate tolerance and "rebound angina" during nitrate free periods. However, the main conclusions of the study are neither new nor entirely accurate, and leave many questions unanswered. How long do the patches remain effective? Do they last all day? When does tolerance start to develop and how long a nitrate free period is required to prevent the development of tolerance? "Rebound" might not be such a problem if the patches only need to be left off for an hour or two.

At least five previous studies have now shown that nitrate patches remain effective shortly after being re-applied after a nocturnal nitrate free period. What remains unclear, however, is how quickly tolerance develops after a patch has been applied, and therefore what is the duration of daytime efficacy during an intermittent treatment regimen. It is also not known how long a nitrate free period is required to reverse tolerance; this study does nothing to address these points.

We examined many of these questions in a previous study (the results of which were presented to the British Cardiac Society in 1987).¹ Using three active or dummy patches applied consecutively for 32-36 hours and conduction of four exercise tests over this period we assessed the effects of continuous treatment for three, eight, 12, 15, and 24 hours, and of intermittent treatment on two consecutive days using two different nitrate free periods of 12 or 16 hours. Our results showed the now familiar finding that the patches remained effective three hours after treatment was restarted.² They also showed that the length of nitrate free interval (12 hours or 16 hours) did not influence this