Inserting a large calibre cannula into a small vein is more likely to cause irritation of the intima, reduces blood flow around the cannula, and increases the risk of thrombophlebitis. Using small gauge catheters in large diameter veins reduces the incidence of thrombophlebitis.⁷ In a controlled trial Khawaja *et al* showed that 16 gauge and 18 gauge cannulas survived longer than 14 gauge cannulas.⁸ Formation of thrombus is related to the size of the intravascular device, and therefore thrombus due to a small cannula is less likely to impede blood flow.⁵

Non-steroidal anti-inflammatory gel seems to delay the onset of thrombophlebitis related to the cannula and reduces its incidence by half with no difference in bacterial colonisation between control and treatment groups.⁹

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Elderly patients with sustained hypertension

SIR,—A study and an overview in the *BMJ* referring to drug treatment of hypertension in older adults both suggest that thiazides and not β blockers should be the first line treatment.^{1,2} It is stated that β blockers may be added when special indications for their use coexist or when a second drug is needed to control blood pressure.

It is possible, however, that use of β blockers is inadvisable in elderly patients. A characteristic feature of the circulation in this age group is low cardiac output, and lowering the output still further with a β blocker might be disastrous.

I have made the following analysis, based on data from original reports. The figure shows the results of four trials of treatment of hypertension by drugs in people over 65 years of age. In each study the number of patient-years of use of diuretics has been divided by the number of patient-years of use of β blockers. When both drugs were used simultaneously, each was recorded as if they had been used separately. The Medical Research Council old adults study is divided into two parts.³ This provides a wide range of ratios for use of diuretics compared with use of β blockers. In each study these ratios have been plotted against risk ratios for total coronary events, with 95% confidence intervals. The figure shows a statistically significant positive relation between effect of treatment and use of diuretics.

Atenolol was used in all the studies included in the analysis. In one study (STOP), however, the

Coronary risk ratios with 95% confidence intervals for total number of coronary events (fatal and non-fatal) from four studies,^{1,2,4,5} one with two subgroups.¹ Diuretics and β blockers were tested against placebo and plotted with relative proportions of active drugs used in each study. Z value of difference between average of three low diuretic studies and average of two high diuretic studies = 2.303; two tailed $p=0.0212$, indicating a significant trend

participating medical centres could choose either metoprolol or pindolol. What proportions of the different drugs were used was not revealed by the authors in the publication, nor on direct request.³ However, since the outcome of the trial, in spite of wide confidence limits, accords with the results obtained from other studies, the tentatively observed phenomenon may not be restricted to atenolol but may refer to all β blockers.

My analysis suggests that the incidence of coronary disease in elderly hypertensive patients can be reduced by diuretics alone, and that this beneficial effect disappears with addition of β blockers.

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Monoclonal antibodies in sepsis

SIR,—In the editorial on monoclonal antibodies in sepsis and septic shock C J Hinds states that between 5000 and 10000 lives might be saved annually by use of HA-1A.¹ Hinds's estimate of the number of cases of Gram negative septicaemia annually is 25000. A clinical trial by Ziegler *et al* showed a reduction in mortality in this group from 49% to 30%.² From the above estimate this suggests that HA-1A would reduce mortality from 12250 to 7500, or by 4750. Where does the figure of 10000 come from?

Secondly, the author states that this would be achieved at a cost of \$5000 per life year saved. This is equivalent to one life year saved for each use of the drug. The clinical trial showed that if the drug is prescribed on purely clinical criteria at least 63% of the patients who receive it do not have Gram negative bacteraemia, so they do not benefit, and

30% of those with Gram negative septicaemia die anyway, so they gain no benefit. Of the remainder (25.9%), most would survive anyway; their survival should not be attributed entirely to HA-1A.

Surveys of the outcome of bacteraemia at this hospital show a crude mortality in Gram negative bacteraemia of 20% (unpublished data): most of the patients who die, however, have serious underlying illness, with a life expectancy of one year or less. We think HA-1A should not be used in such cases. In patients without serious background disease the local mortality from Gram negative bacteraemia is 10%.

Calculations from these figures show that 2.6% of patients who could appropriately receive HA-1A on clinical grounds might be saved by the drug; they would need to benefit by 38 years on average to achieve the cost benefit stated. As Gram negative septicaemia mostly occurs in elderly people we are not convinced that this is a realistic proposition.

The place of monoclonal antibodies in managing sepsis has yet to be clearly defined. Unanswered questions include who should get the drug and when it should be given: early, on clinical diagnosis, with the consequent threefold overuse; or late, on bacteriological confirmation. The clinical trial showed clearly that patients without Gram negative septicaemia had a slightly worse outcome with treatment despite less severe sepsis, although neither difference achieved significance. Also, the drug had no effect on mortality in the overall population when given on purely clinical grounds. It remains to be shown whether using this drug when Gram negative bacteraemia is confirmed will actually be of benefit: most deaths from Gram negative septicaemia occur early, before the result of blood culture is available, and treatment at such a late stage may have little impact on mortality.

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AUTHOR'S REPLY.—In my editorial my reference to the probable costs of using HA-1A to treat sepsis and septic shock was necessarily brief.¹

M J Sheppard and T W J Kelly correctly calculate that, based on an incidence of 25000 cases of Gram negative bacteraemia annually in the United Kingdom, 4750 (that is, about 5000) lives might be saved each year. It is extraordinarily difficult, however, to obtain an accurate estimate of the incidence of Gram negative bacteraemia in the United Kingdom, and others have therefore suggested an upper limit of 10000 lives saved each year.²

The figure I quoted of roughly \$5000 per life year saved was calculated assuming that the results of Ziegler *et al*'s study³ would be replicated in routine clinical practice (C Smith, personal communication). If 1000 patients with sepsis were selected for treatment according to the criteria used in the original study 370 would be expected to have Gram negative bacteraemia. If these 370 patients received placebo the expected mortality would be around 49% (181 deaths), whereas if they received HA-1A this would fall to about 30% (113 deaths)—that is, 68 lives would be saved. It was assumed that the average life expectancy of survivors might be 10 years. Thus 680 life years would be saved for a total of \$3750000 (\$3750 per treatment), giving a cost of \$5515 per life year saved.

A more comprehensive analysis has subsequently been published, in which the cost of HA-1A per discounted life year saved was calculated as