SIR,—Dr M E Sprackling and his colleagues conclude from their study comparing methyl-dopa treatment with observation (31 October, p 1151) that we should not embark on anti-hypertensive treatment in elderly patients. To judge by past experience this advice will be accepted all too eagerly, yet their study has serious shortcomings and cannot possibly support such a broad conclusion.

They designated elderly subjects as hypertensive or normotensive by a single casual blood pressure measurement, a method known to misclassify a large proportion of patients¹ and considered unsound at any age in ordinary practice. The criterion for entry, a diastolic pressure of 100 mm Hg (phase 4), is equivalent to a phase 5 (disappearance) diastolic of about 92 mm Hg, and the elderly hypertensives had a mean diastolic pressure of about 99 mm Hg phase 5. This is not "moderate" hypertension as the abstract says: it is mild hypertension, and benefits of drug treatment at this level are unproved at any age. We cannot be sure that the treated and observed groups were well matched, because the entry assessment was perfunctory; and we cannot be sure that methyl-dopa really lowered the blood pressure, because the measurements were open to observer bias. The sample size (120 patients) was very small given the mildness of the hypertension, and the question of type II error deserved more detailed consideration than it received. The age distribution of the population studied (83% over 74 years) was quite unrepresentative of the elderly in the general population.

The authors might have concluded that in a very old person a single diastolic blood pressure of 100 mm Hg does not deserve treatment; and this, of course, is true at any age. Unfortunately, the study tells us nothing about the pros and cons of treating a fit person of (say) 72 years with blood pressures averaging (say) 210/110 mm Hg over three visits. Careful reviews of all the evidence^{2,3} suggest that this elderly patient might well benefit from treatment. It is true that controlled studies of antihypertensive treatment have included few elderly patients, as the authors mention, but they fail to mention that older patients have benefited more than the young in these same studies. They also bolster their case by repeating anecdotal statements about the morbidity caused by antihypertensive treatment in elderly patients. In fact, adverse reactions to the drug they used, methyl-dopa, are less common in the elderly than in young patients.^{4,5}

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¹ Armitage P, Fox W, Rose GA, Tinker CM. *Clin Sci* 1966;30:337-44.

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⁵ Ramsay LE. *J R Coll Physicians Lond* 1981;15:239-44.

SIR,—Dr M E Sprackling and colleagues (31 October, p 1151) addressed the very important clinical problem of hypertension in the elderly and the value of antihypertensive drug therapy. We have some reservations about the conclusions reached.

It was stated that patients had "moderate hypertension." However, as phase 4 (muffling)

was accepted as the diastolic level with 100 mm Hg as the cut-off point, many of these patients may have had diastolic readings of 95 mm Hg or less, and would therefore be classified as having mild hypertension. Entry to the study was determined on the basis of single casual readings, but systolic blood pressure is particularly labile in the elderly and repeated estimations tend to give lower readings.¹ It is difficult to exclude observer bias because the study was open and a conventional sphygmomanometer was used.

No information on blood pressure levels is available after the first six months. There is no indication that blood pressure reduction was maintained beyond this time in the treated group, or that hypertension was sustained in the observed group. Indeed, blood pressure data are incomplete at six months, being documented in only 77% of surviving treated patients, and 72% of surviving observed patients.

We share the authors' concern that there may be a type II statistical error—that is, there were insufficient patients to refute the hypothesis that antihypertensive therapy is of value in elderly patients with high blood pressure.

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SIR,—Dr M E Sprackling and others (31 October, p 1151) failed to show that treatment of hypertension in the elderly was associated with altered survival. This is not surprising, nor is the failure of itself an indictment of methyl-dopa treatment.

An adequate trial requires of the order of 600 patients for there to be a good chance of detecting even a one-third real reduction in mortality at two years (see, for example, the trial initiated by the European Working Party on Hypertension in the Elderly¹). In contrast, the randomised controlled trial reported by Dr Sprackling and others (based on 120 patients) had only a 35% chance of detecting (at a significance level of 0.05) a true one-third reduction in mortality. In other words, even if methyl-dopa reduced mortality in the elderly from 40% to 27% at two years, 13 out of 20 similar trials would fail to identify survival in the treated group as being significantly improved relative to no treatment. "Not statistically significant" does not mean "no difference." The limited information on this trial would have been apparent in wide confidence limits or in low power² had either been noted. Freiman et al³ warned against excessive readiness to accept the null hypothesis, especially in trials of inadequate power. Contrary to the authors' claim, the strictures of Freiman et al apply to them. Not until editors and referees require the power of a clinical trial (for detecting an important treatment difference) to be reported in the methods section of a paper may readers appreciate the importance of trial size and discourage over-interpretation of differences which are not statistically significant.

The authors make some helpful comments on statistical methods (regression to the mean,

analysis by intention to treat, description of the log-rank test), but their comparison of survival at several arbitrary fixed times is ill advised¹ and could be misleading. Their explanation of significance level or p value is unfortunately incorrect: $p < 0.05$ does not mean that the probability of the result being due to chance is less than 0.05. It does mean²: if the treatment effect is nil then the probability of an outcome as extreme or more extreme than the one observed is small, less than 1 in 20.

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² Gore SM. *Br Med J* 1981;282:1687-9.

³ Freiman GA, Chalmers TC, Smith H, Kuebler RR. *N Engl J Med* 1977;299:690-4.

⁴ Peto R, Pike MC, Armitage P, et al. *Br J Cancer* 1977;35:1-39.

⁵ Gore SM. *Br Med J* 1981;283:600-2.

SIR,—From their study of treatment of moderate hypertension in the elderly (31 October, p 1151), Dr M E Sprackling and his colleagues have concluded that such a degree of hypertension was not a major risk predictor in the elderly population. Similarly the interim report of the European working party on hypertension in the elderly has failed to show any statistically significant reduction in mortality or morbidity in the elderly by substantially reducing their blood pressure.

Older patients are more likely to have their blood pressure recorded than the younger ones¹ and it is known that the treatment for hypertension is one of the main causes of drug-induced illness in the elderly.² Further, in hypertensive elderly patients the auto-regulatory mechanism is altered and even quite small reductions in blood pressure may significantly affect cerebral blood flow,³ resulting in reduced cerebral perfusion that causes dizzy turns, lightheadedness, falls, transient ischaemic attacks, and strokes. All physicians confronted with elderly hypertensives are almost constantly facing this dilemma, and are eagerly awaiting the full results of the European working party's report (which I understand has been delayed for two more years); but until contrary concrete evidence comes out of that report it appears quite appropriate to spare the elderly from potentially harmful drugs such as diuretics, methyl-dopa, vasodilators, alpha-blockers, and beta-blockers.

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² Williamson J, Chopin J. In: Crooks J, Stevenson IH, eds. *Drugs and the elderly*. London: Macmillan, 1979.

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Pulmonary oedema in acute myocardial infarction

SIR,—I read with interest the article by Dr A D Timmis and others (5 September, p 636) about pulmonary oedema in acute myocardial infarction and would like to make a few points.

Firstly, the correlation between clinical and radiological evidence of pulmonary oedema has been shown to be poor in patients with "increased-permeability," or low-pressure, pulmonary oedema.¹ Although chest x-ray examination is still the most frequently used method of diagnosing pulmonary

oedema, many factors make it unreliable, such as differences in body position, level of inspiration, tube-to-object distance, current and voltage, and the existence of prior lung disease. Furthermore, we have noticed that the x-ray appearances may lag behind the clinical state of the patient, as judged by respiratory function, by as much as 36 hours during both the development and the resolution of pulmonary oedema. A more accurate diagnosis may be made by using lung functions such as the alveolar-to-arterial oxygen-tension gradient or the shunt fraction, which would be easy to measure with a pulmonary artery catheter in place.

Secondly, although the patients in the Brighton study had normal serum albumin concentrations, this is only one determinant of the colloid osmotic pressure, accounting for 65-70%.² The remaining 30-35% comprises the other serum proteins and any colloidal fluids used in therapy. Moreover, temperature elevation, pH, position of the patient, and anticoagulant therapy may all affect the colloid osmotic pressure, and the application of a tourniquet to collect the blood sample will increase the measured value. Therefore it would be more accurate to measure the actual colloid osmotic pressure from an arterial or central venous blood sample. The colloid osmotic pressure has been shown to fall, often dramatically, in patients with acute myocardial infarction with circulatory shock,^{3,4} and the majority of patients with normal hydrostatic (pulmonary capillary wedge) pressures but with low colloid osmotic pressure have developed pulmonary oedema.

Thirdly, one has to interpret the measured hydrostatic pressures with care. If the transducer is placed at the level of the sternal angle, and the catheter tip is in the dependent region of the lung, as it often is, there may be a hydrostatic pressure difference of 20 cm H₂O, equivalent to about 15 mm Hg. The value obtained for the pulmonary artery end-diastolic pressure would be an under-reading by this amount for the dependent region of the lungs, and it is there that the oedema often forms. Furthermore, the use of the pulmonary artery end-diastolic pressure as an index of left atrial filling pressure may not be accurate in these clinical circumstances. It has been shown that the pulmonary vascular resistance rises early in the formation of pulmonary oedema with different causes, and this creates a gradient between the pulmonary artery end-diastolic and the pulmonary capillary wedge pressure.⁵ Therefore if clinical pulmonary oedema is present, the pulmonary artery end-diastolic pressure may give a higher reading than the left atrial filling pressure. In this situation the pulmonary capillary wedge pressure would be a more accurate representation of the left atrial filling pressure.

I completely agree with the authors that careful pressure monitoring is important in the management of these patients, and therefore feel that attention to detail in these respects may improve the outcome for these critically ill patients.

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Pulmonary hypertension and fenfluramine

SIR,—I read with interest the paper by Dr J G Douglas and others (3 October, p 881), in which the authors seek to demonstrate a parallel between fenfluramine and aminorex

in the pathogenesis of pulmonary hypertension. Cardiopulmonary pathology resulting from the use of aminorex appeared as an epidemiological phenomenon shortly after the drug was marketed. Aminorex is an amino-oxazoline, unlike fenfluramine, which is a phenylethylamine; contrary to the authors' statement, the compounds are not chemically related.

On the two cases reported, I should like to offer the following observations. In the first case the patient was a non-obese woman (61 kg) taking a large dose (160 mg/day) of fenfluramine nearly three times that usually recommended for mild obesity (60 mg/day). The admission to hospital occurred four weeks after she first started to take oral contraceptives. The disappearance of her symptoms was temporally related to administration of the thiazide diuretic as well as withdrawal of the oral contraceptive and fenfluramine. In the second case the woman was also being treated for hypothyroidism. The findings on cardiac catheterisation indicated a global cardiac insufficiency, with left and right heart failure. She received bendrofluazide and this may well have been the major contribution to the improvement in her symptoms, rather than withdrawal of the drug.

Oral contraceptives have been implicated in the aetiology of pulmonary hypertension in young women,^{1,2} and pulmonary hypertension has been described in obese patients without significant alveolar hypoventilation, reflecting left ventricular insufficiency.^{3,4} In both cases reported, a known aetiological factor for pulmonary hypertension and an immune disease (ulcerative pancolitis, hypothyroidism with thyroid antibodies) was present.

The relevance to man of the observations in dogs by Engelhardt *et al*⁵ is doubtful, and Prime⁷ showed the stability of pulmonary pressure in man following administration of fenfluramine for up to three months. It is noteworthy that no cases of this nature have been previously published since the drug was first marketed in 1963, and the relationship between pulmonary hypertension and fenfluramine in the two cases described is by no means clear.

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² Kleiger RE, Boxer M, Ingham RE, Harrison DC. *Chest* 1976;69:143-7.

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Tricyclic antidepressant poisoning and prolonged external cardiac massage during asystole

SIR,—I am grateful to Drs D A Orr and M G Bramble for their article emphasising the potential for resuscitation from tricyclic antidepressant overdose even after prolonged periods of asystole (24 October, p 1107). I am, however, somewhat concerned that their comment, "Asystole caused by a drug overdose does not carry the same prognosis as asystole secondary to acute myocardial infarctions," might suggest less heroic efforts in resuscitating patients with organic heart disease. We know that life-threatening arrhythmias complicating angina pectoris or

acute infarction do not necessarily predict long-term survival and need not correlate with the extent of myocardial damage—possibly the best long-term prognostic factor.¹

I have personally resuscitated a patient with acute myocardial infarction after two hours of asystole. His subsequent course in hospital was uneventful and he has returned to a vigorous lifestyle without brain damage. The presence of extensive cardiopulmonary disease, advanced age, malignancy, etc might well suggest less heroic resuscitation measures; however, since the majority of patients we will see with asystole or other malignant arrhythmias will probably have ischaemic heart disease, not tricyclic drug overdose, we must be committed, within reason, to salvage as many of these lives as possible. The Seattle experience certainly indicates the potential for aggressive resuscitation efforts.² We must also not forget other young adults with "healthy myocardiums"—for example, victims of mitral valve prolapse, coronary artery spasm, electrocution, and others who die suddenly—whose potential for recovery mandates intensive efforts in resuscitation. These efforts may save many useful lives, and even ultimately unsuccessful efforts at resuscitation might provide badly needed organ donors to salvage other young lives from the suffering of blindness, renal failure, congestive heart failure, and other diseases amenable to transplantation therapy.

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¹ Myerberg RJ. In: Hurst JW, Logue RB, Schlant RC, et al, ed. *The heart*. New York: McGraw-Hill, 1978: ch 49.

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Non-steroidal anti-inflammatory drugs and frusemide-induced diuresis

SIR,—I was interested in the three case reports of Drs A C Yeung Laiwah and R A Mactier (12 September, p 714) relating to use of ibuprofen and naproxen in older patients with congestive heart failure and diuretic therapy. They describe the antagonistic effect on the diuretic by these non-steroidal anti-inflammatory drugs. They rightly point out that this effect is likely to be seen in patients in whom renal prostaglandins assume clinical importance (for example, those with compromised renal function, systemic lupus erythematosus, severe cardiac failure, etc). They conclude that non-steroidal anti-inflammatory drugs should be avoided in such patients.

Although no one will disagree with this suggestion, it is worthy of note that one such non-steroidal anti-inflammatory drug, sulindac, may not have this deleterious effect. Sulindac is considered a pro-drug since it is absorbed in its inactive sulphoxide form. Only the reduced sulphide is effective in inhibiting prostaglandin synthesis. Although it is well recognised that the precise relationship between prostaglandins and renal function is controversial,¹ Ciabattini and colleagues have shown that the renal prostaglandin system is probably not inhibited by sulindac in humans at doses which inhibit platelet cyclo-oxygenase.² Likewise, sulindac has a paradoxical effect in Bartter's syndrome, a condition that responds to other non-steroidal