Placental weight:birth weight	No of infants	Weeks of gestation			Birth weight (g)		
		<37	37-40	>40	<2500	2500-4000	>4000
-0.164	57 (20)	2 (17)	37 (18)	18 (24)	1 (9)	48 (21)	8 (17)
-0.177	57 (20)	0	45 (22)	12 (16)	2 (18)	45 (19)	10 (22)
-0.191	60 (21)	1 (8)	42 (21)	17 (22)	0	45 (19)	15 (33)
-0.209	60 (21)	2 (17)	43 (21)	15 (20)	1 (9)	53 (23)	6 (13)
>0.209	55 (19)	7 (58)	34 (17)	14 (18)	7 (64)	41 (18)	7 (15)
All	289	12	201	76	11	232	46
p Value			0.044			0.007	

the relation between birth weight and placental weight we analysed data on 289 second born male infants collected as part of a study of psychosocial factors in pregnancy. Whereas the association between birth weight and gestation could be modelled by the familiar logistic growth curve, passing through the origin, the relation between placental weight and gestation was linear (again passing through the origin). If placental weight is fitted to the difference between observed birth weight and that expected according to the growth curve model then the intercept is indeed significant; if, however, gestation and placental weight are fitted simultaneously then the expected values again pass through the origin. This difference means that the effects of gestation and placental weight on birth weight are not independent. A slight improvement on the use of placental weight is the square of this value, which implies that the relative contribution of placental weight to birth weight is greater for larger placental weights (and hence for longer gestations).

This model, which implies different, or at least differently timed, fetal and placental growth, also has consequences for the interpretation of Barker and colleagues' finding of a relation between the ratio of placental weight to birth weight and fibrinogen concentration. As would be expected given the relations described, this ratio tends to decrease with increasing gestational age or birth weight (table). This systematic decrease does not reflect the appropriateness of birth weight to gestation but is, rather, explained by the different patterns of fetal and placental growth. While the groups with high ratios of placental weight to birth weight do include infants born at term, infants born at lower gestations are overrepresented. The association between ratios of placental weight to birth weight and haemostatic factors in later life might be explained by poor fetal growth or as one of the sequelae of immaturity at birth (or a more subtle combination of the two). Our understanding of the relation between early development and health in later life would be enhanced if we knew which explanation was the most likely.

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Low dose oxybutynin for the unstable bladder

SIR,—Oxybutynin was licensed by the Committee on Safety of Medicines at the beginning of last year. Since the withdrawal of terodiline oxybutynin has been used increasingly to treat urinary incontinence secondary to detrusor instability or detrusor hyperreflexia.

The datasheet for oxybutynin recommends a dose of 5 mg three times a day. This reflects published reports on the efficacy and safety of the drug at the time the licence was issued.¹ The drug is a powerful anticholinergic and has side effects.

Although oxybutynin has a short plasma half life (about three hours),² our clinical experience leads us to believe that a lower dose given less frequently—2.5 mg twice daily—may be effective and associated with fewer side effects. We acknowledge that this should be submitted to a double blind controlled trial. Fifty patients have been recruited into such a study in our department, but this has yet to finish. We thought, however, that our clinical experiences may be helpful to those using the drug for the first time.

We have analysed the records of 271 patients (210 female, 61 male) treated in our incontinence clinic who were established on oxybutynin as part of their treatment for detrusor instability or detrusor hyperreflexia. Our patients included young and old patients (mean (SD) age 52.8 (19.9) years, median 52, range 6-89). Patients initially take 2.5 mg twice daily, and they are encouraged to titrate this dose in response to efficacy and side effects. We always use a bladder retraining regimen. We found that the optimum dose with regard to clinical effect and side effects was 2.5 mg twice daily in 119 of the 271 patients, 5 mg twice daily in 84, 5 mg three times a day in 27, 5 mg once daily in 19, 2.5 mg three times a day in 11, and various other schedules in 11. The condition of 11 patients deteriorated and of 24 remained unchanged; 92 patients improved but continued to experience some symptoms, and 144 became asymptomatic. There were no relations between age, dose, diagnosis, and outcome.

We have probably underestimated the frequency of side effects that were not mentioned by the patients. We recorded a dry mouth in half the patients, constipation in 41, and dry skin and oesophageal reflux in 14.

At the doses that we used the drug was well tolerated and clinically helpful. We suggest starting treatment in all patients, regardless of age, at a dose of 2.5 mg twice daily and then titrating this accordingly.

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Exploding microwaved eggs

SIR,—Recently, three cases of ocular injury due to exploding microwaved eggs have been reported.^{1,2} In one case seven eggs were microwaved in their

shells and six exploded spontaneously on removal from the oven.² In the two other cases eggs without their shells were cooked in the microwave oven without the yolk sac having been pierced.¹ In all three cases return to normal visual acuity occurred. We report a more severe case, in which vision was still reduced four months after the injury.

A 22 year old woman cracked an egg into a bowl of water and heated it in a microwave oven. Immediately after she removed the dish from the oven the egg exploded in her face. She sustained first degree burns to the skin on the malar areas and the lower lids. There was epithelial loss affecting the conjunctiva and cornea in both eyes: all corneal epithelium was lost in the left eye. It took two weeks for the left cornea to re-epithelialise. The peripheral cornea became vascularised and inflamed, and the epithelium remained unstable.

The patient required treatment in a special corneal clinic and also by the burns team. The right eye and skin of the lid rapidly healed within 10 days of the injury. Four months later the left malar skin remained erythematous and had to be camouflaged with cosmetics. The left cornea remained inflamed and vascularised at the periphery. The eye was still partially closed, and the vision remained reduced to 6/12 owing to abnormal corneal epithelium. Topical steroid treatment was continued.

Microwaved eggs explode owing to rapid expansion of gas within closed compartments formed by the chorioallantoic and shell membranes and the yolk sac. Eggs can be safely cooked in a microwave oven if the shell is cracked open and the yolk sac is punctured before heating. Alternatively, eggs can be scrambled. Up to now reported eye injuries due to this cause have not been serious and have resolved fully. The case we describe shows that more serious eye injuries may also occur. Eggs should not be cooked in a microwave oven unless the yolk sac has been pierced, and we additionally suggest that they should not be cooked in water as the combination of hot water and egg yolk seems to have caused a more severe injury.

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Survival of peripheral intravenous infusions

SIR,—J F Hecker fails to address well established factors that play an important part in the survival of peripheral intravenous infusions—namely, trauma at the site of the infusion, the size of the cannula and the material from which it is made, and the use of topical non-steroidal anti-inflammatory gel.¹ The skill of the operator inserting the cannula is important: Cosentino found that greater experience in performing venepuncture decreased the incidence of infusion thrombophlebitis.² In response to this problem, many North American hospitals employ intravenous therapy teams for routine insertion of cannulas.³

Recent advances in polymer technology have resulted in improved materials for cannulas. Polyurethane is less thrombogenic than Teflon, which in turn is less thrombogenic than polyethylene and polypropylene.^{4,6} Comparison of Teflon and polyurethane cannulas showed that the material from which the cannula was made was the single most important factor in the incidence and severity of infusion thrombophlebitis, polyurethane cannulas being associated with a 46% lower incidence.⁶

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} 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