perhaps fewer are ventilated in other hospitals. As computed tomographic scanners become available in more general hospitals, fewer hopeless cases of head injury (and cases of intracranial haemorrhage) are likely to be referred to neurosurgeons. That could mean more potential donors in other hospitals. International comparisons of brain stem death and organ donation should allow for the fact that the incidence of fatal head injuries is two to three times greater in the United States, Canada, Australia, France, and Germany than in Britain and that the number of intensive care beds per head is 10 times greater in the United States. We hope that the further planned audits of deaths in intensive care units in England may throw more light on the factors that influence the yield of organ donors.

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- 1 Bodenham A, Berridge JC, Park GR. Brain stem death and organ donation. *Br Med J* 1989;299:1009-10. (21 October.)
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SIR,—Dr A Bodenham and his colleagues undertook a prospective audit of potential organ donors in Addenbrooke's Hospital, Cambridge, and found only three cases where consent to a donation was not sought.¹ They concluded that required request would not increase the supply of donor organs.

Several points make this conclusion invalid. The survey was conducted in a large teaching hospital heavily committed to liver, kidney, and pancreatic transplantation and therefore more aware than most of the needs of transplantation. The survey was not carried out by a group that was independent of the donation process, and the fact that it was prospective and known to be in progress could well have influenced decisions. No attempt was made to see whether the number of brain stem dead individuals identified within the hospital was complete. This could have been done by examining the case notes of all patients dying within the hospital.

A point of concern is that a pair of kidneys was not removed because of lack of a suitable recipient. Cambridge is a signatory to the national sharing agreement, and if there were no suitable local recipients there would have been plenty nationally.

We believe that potential organ donors are frequently overlooked, particularly in smaller, non-teaching hospitals where intensive care facilities may be limited. Required request could well have an impact in such hospitals, and it is unfortunate that the authors should attack the concept using questionable data obtained within one specialised institution.

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Organ donation from intensive care units in England

SIR,—We wish to point out that the first sentence in the conclusion of our abstract can be misinterpreted if read without the qualifications given

in the discussion.¹ This sentence could be read as implying that we recommend formal testing of brain stem function whenever brain stem death is a possible diagnosis. We do not. Although the results of the audit showed that tests for brain stem death were not performed in 26% of those in whom this was a possible diagnosis, we suspect that in many of these cases formal testing of brain stem function was, for various reasons, clearly inappropriate. Accordingly, a supplementary inquiry has been initiated to determine the reasons why tests for brain stem death were not performed in these cases and to estimate the proportion of these patients who could have been potential donors.

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Acute renal failure after infusion of gelatin

SIR,—We wonder whether the article by Drs S F Hussain and P J T Drew could be more simply entitled "Acute renal failure after aortobifemoral graft surgery."¹

The data provided are incomplete and do not confirm their contention that Gelofusine was a causative agent. The only circumstantial evidence is one measurement of plasma oncotic pressure, which could relate to accumulation of any fluid at a time when renal failure was more or less established.

The report as presented suggests that the only fluids given over the 48 hour perioperative period were blood and Gelofusine to a total of 3.5 litres, together with 330 ml of mannitol. Over the same period the urine output was 2.2 litres, thus leaving 1.3 litres to cover all losses, including significant "3rd space" losses into the areas of surgical dissection. The fall in serum albumin concentration would seem to indicate that the losses into this "3rd space" were considerable. It would seem probable, therefore, that the use of mannitol and frusemide together with a diminished intravascular volume, which this treatment could have worsened, were the major contributory factors to the acute renal failure.

Whatever the cause in this case it is clear that preventing renal failure depends on adequate organ perfusion, and this is best achieved by having an appropriate circulating volume and hence cardiac output. A fall in urine volume should not be treated by a diuretic in patients who are likely to have a reduction in circulating volume after major vascular surgery. Uncertainty over the state of the intravascular compartment needs measurement of the appropriate vascular pressure and trials of fluid. In this context it has been shown that central venous pressure can be unreliable in predicting change in blood volume² and that it is better to use pulmonary capillary wedge pressure and urine output as guides to fluid replacement.³

We therefore cannot support the contention that Gelofusine caused renal failure in this patient.

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- 1 Hussain SF, Drew PJT. Acute renal failure after infusion of gelatins. *Br Med J* 1989;299:1137-8. (4 November.)

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SIR,—The implication in this paper that the Gelofusine caused the renal failure in this patient is highly debatable.¹

The most well documented cause of renal failure after aortic vascular surgery is prerenal in origin. The pronounced haemodynamic changes that occur—particularly with aortic cross clamping and unclamping—cause changes in cardiac output and hence renal blood flow. For instance, infrarenal cross clamping causes redistribution of blood flow and hence cortical ischaemia.² Moreover, central venous pressure monitoring is an unreliable indicator of left ventricular end diastolic pressure. Pulmonary capillary wedge pressure is a more accurate indicator for volume expansion,³ particularly in the face of coronary artery disease, which frequently coexists with aortic atherosclerotic diseases. It is also conflicting to say on the one hand that blood loss was minimal and on the other that 3.5 litres of colloid were required. Finally, the problems of prerenal failure may be compounded by direct nephrotoxins—antibiotics, radiocontrast media, haemoglobinuria (from blood transfusion reactions)—in the pathogenesis of acute tubular necrosis.

No mention is made of the postoperative monitoring of the patient, and it is at this time when hypovolaemia may occur, particularly during re-warming.

The implication that Gelofusine has accumulated is at odds with the known pharmacology of Gelofusine. Gelofusine has a mean molecular weight of 35 000 and even in anephric patients it would redistribute to the entire extravascular space by 48 hours (when plasma oncotic pressure was measured). In any case as it is renally excreted and the urine output was satisfactory for the first two days after operation most of the Gelofusine would have been excreted.

In my department Gelofusine is used precisely for the circumstances in which we are now advised to avoid it—that is, low perfusion pressure and low rates of urine flow—and when titrated accurately against the patient's needs it is most successful at restoring cardiac output and urine flow.

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- 1 Hussain SF, Drew PJT. Acute renal failure after infusion of gelatins. *Br Med J* 1989;299:1137-8. (4 November.)
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SIR,—As medical adviser to the manufacturers of Gelofusine, Hausmann Laboratories of St Gallen, Switzerland, I was surprised and dismayed to read a case report suggesting that Gelofusine was potentially nephrotoxic.¹ My surprise was based on the apparent breach of the longstanding practice whereby, before publication of such reports, the manufacturer's comments are invited by the author.

Such a policy of consultation is of value, for, while it is essential that clinically important reactions are speedily drawn to the attention of potential prescribers, it is also essential that the report should discuss other information available so that the risk:benefit equation can be meaningfully reassessed.

Although there are published references on the effects of Gelofusine on renal function, not one was cited. Had the authors so chosen they could have discussed the evidence that operations on the aorta are associated with the development of acute renal failure¹; that the fall in urine output was noted before the Gelofusine was infused (and therefore a cause preceding Gelofusine administration required exclusion); and the longstanding belief that, rather than being nephrotoxic,^{2,3} the gelatins promote an osmotic diuresis⁴ and help maintain renal blood flow.⁵ There is no discussion of the logic behind the jump from showing that Gelofusine will accumulate in renal failure (as with other substances dependent on intact renal function for excretion) to concluding that Gelofusine is nephrotoxic.

It does the rational analysis of drug associated reactions no service when a paper is published that contrives to avoid mention of any published reports.

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- 1 Hussain SF, Drew PJT. Acute renal failure after infusion of gelatins. *Br Med J* 1989;299:1137-8. (4 November.)
- 2 Wilkins RG, Faragher EB. Acute renal failure in an intensive care unit. *Anaesthesia* 1983;38:628-34.
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* We have received several letters making similar points, and the authors reply below.—ED, BMJ.

AUTHORS' REPLY.—Restriction on the length of our original article meant that some information had to be excluded from the case history.

The operation was performed by a consultant vascular surgeon, and estimated blood loss was 200 ml. Total clamp time was one and a half hours, but the aorta was clamped for less than three quarters of an hour with sideclamps placed well below the renal arteries. Fluorinated anaesthetic agents and aminoglycoside antibiotics were not used (cefotaxime and metronidazole were given). Blood pressure on admission was 140/70 mm Hg and perioperative systolic blood pressure was always greater than 100 mm Hg. A dopamine infusion was started at induction of anaesthesia together with low dose fentanyl and bupivacaine epidural analgesia, and three litres of crystalloid solution was given during the early part of the operation; mannitol (200 ml 20%), suspended red cells, and Gelofusine were given because of the poor urinary response (50 ml), and the central venous pressure at the end of surgery was 8 cm H₂O. Large volumes of fluid were given postoperatively to maintain the central venous pressure recording during rewarming, and during the first 24 hours there was a positive fluid balance of 7283 ml, including 1920 ml of Gelofusine. Infusions of 20% human albumin were given during the second postoperative day with no urinary response and it was clear at the end of this day that renal failure was established since urine was isotonic with respect to plasma. The physical signs were of volume overload. The stepwise increase in serum creatinine concentrations led us to believe that renal failure developed at the time of operation, notwithstanding the moderate urine output in the first 24 hours, but measurements of urine osmolality were not made until the second day. Blood pressure was well maintained during subsequent haemodialysis and no radioccontrast material was given until six weeks after operation.

The fall in serum albumin was apparent 24 hours after operation and was far outside the range normally seen after major surgery. We accept that there were probably significant "3rd space" losses, but a rise in acute phase proteins sufficient to preserve oncotic pressure seems unlikely since there was an increase in total globulin of only 3 g/l. We were unable to measure serum gelatins in this case but made such measurements in another recent case in which 3.5 litres of gelatin had been infused during resuscitation of a man presenting with circulatory collapse and oliguric renal failure. Twenty four hours later the serum albumin was 12 g/l and the plasma was calculated to be 23% gelatin solution (Hoechst, West Germany). (The patient died, anuric, 16 days later with a diagnosis of multisystem failure secondary to culture positive legionnaires' disease.)

Had the patient described in our case report recovered renal function we would doubtless have reasoned that he had suffered acute tubular necrosis secondary to a perioperative decrease in renal perfusion pressure. There have been some studies showing the safety of gelatin solutions given to hypovolaemic animals that rapidly regain normal renal function and urine output,¹ which is the usual clinical outcome, but we are unaware of any studies looking at the safety of gelatin solutions in the early phases of acute tubular necrosis, when urine flow rates may be relatively low and back diffusion of the smaller filtered molecules² could lead to a concentration of larger molecular weight gelatins and a very rapid rise in the viscosity of the tubular fluid.³

We take issue with some of the points raised by Dr Wilkins. We reported this case in detail to the Committee on Safety of Medicines but regret that we did not send a copy of that report to Hausmann Laboratories. We did contact the suppliers of the Gelofusine (Consolidated Chemicals) as soon as we considered the possibility of nephrotoxicity and were informed that there were no previous reports. They kindly supplied us with the available reports concerning the effects of gelatins on renal function including the relevant papers cited by Dr Wilkins and the paper of Michie *et al*,⁴ which was the first detailed account in the human, showing lack of any apparent nephrotoxicity, and which we quoted in the opening paragraph of our case report. We did discuss alternative explanations for the renal failure and the fact that urine output fell before administration of Gelofusine, and we believe we have provided a cogent argument why gelatins may be potentially nephrotoxic under such circumstances if the fall in urine output is sustained as a result of acute tubular necrosis.

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Risks and benefits of prophylactic antimalarial drugs

SIR,—In his recent editorial on the risks and benefits of prophylactic antimalarial drugs Professor Alasdair Breckenridge made no mention of the potential risk to patients with psoriasis of acute exacerbation of their disease.¹ We have recently seen a patient who exemplifies this risk.

A 47 year old man with chronic plaque psoriasis since 1970, maintained with topical 5% tar in quarter strength Betnovate ointment, was treated

with chloroquine sulphate 400 mg weekly and proguanil 200 mg daily before a trip to Nigeria. Two weeks after the first dose he experienced an acute exacerbation of his psoriasis, leading to erythroderma, which required hospital admission and subsequent treatment with systemic methotrexate.

Since 1956 there have been several reports of patients having acute exacerbation of psoriasis associated particularly with chloroquine and mepacrine.^{2,3} These patients often need hospital admission to control their disease. This is a potentially serious problem and should always be considered when prescribing antimalarial prophylaxis for patients with psoriasis.

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- 1 Breckenridge A. Risks and benefits of prophylactic antimalarial drugs. *Br Med J* 1989;299:1057-8. (28 October.)
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Symptoms of oestrogen deficiency in women with oestradiol implants

SIR,—The interest shown in the report by Dr Kevin Gangar and colleagues of 12 women with supraphysiological concentrations of oestradiol after treatment with implants shows the importance of publishing even those papers with an obvious sampling bias as they generate worthwhile discussion.

These observations are not new. Cardozo *et al*, Savvas *et al*, and Studd and Magos showed the cumulative effect of repeat oestrogen implants on plasma oestrogen concentrations.^{1,2} Brincat *et al* reported that climacteric symptoms returned although the plasma hormonal profiles were still in the premenopausal range.³ Furthermore, these symptoms, even in the presence of normal or high concentrations of oestradiol, responded to a further oestradiol implant and not to a placebo implant. Climacteric symptoms are related to changes in plasma concentrations of oestradiol rather than absolute low concentrations.^{4,5} This applies to all climacteric symptoms but particularly to the cyclical symptoms of depression, irritability, mood fluctuations, loss of energy, and headaches that are characteristic of the premenstrual syndrome in women approaching the menopause. This explains why in placebo controlled trials percutaneous oestrogens, either by implants⁶ or patches,⁷ eliminate these symptoms.

We need to know more about the population from which Dr Gangar and colleagues derived their patients. What is the incidence of supra-physiological oestradiol concentrations among women with returning symptoms? How many are young women who have had their ovaries removed? How many had a psychiatric history, and how many had depression or premenstrual syndrome as their primary problem? Our experience is that these patients need high oestradiol concentrations to relieve symptoms and to allow them to overcome any dependence on psychoactive drugs. If these issues are investigated we have little doubt that tachyphylaxis will be found to be an unusual event found mostly in women with psychiatric pathology. These women are better served by percutaneous oestradiol implants⁶ than ineffective oral treatment.

We therefore seriously question the management proposed by Dr Gangar and colleagues of withholding further therapy until oestradiol concentrations fall to 200 pmol/l. This is inadequate