is usually appointed. I should be grateful if any of your readers with such qualifications would inform me, adding a note of their present occupation.

T D WHITTET

Department of Health and Social Security,
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London SE1 6BY

Arsine toxicity aboard the Asiafreighter

SIR,—We are the managing agents to the owners of the above vessel, on whose behalf I now write, and have read with interest the article by Dr S P Wilkinson and others (6 September, p 559). In relation to the section headed "The incident and initial symptoms" the following should be pointed out in order to keep the record straight.

(1) It might be understood from the wording of the article that the double bottom tanks were examined as a result of heavy weather. The examination was in fact of a routine nature.

(2) The cylinders of arsine were stowed in the second tier from the top and not in the second from the bottom.

(3) The cause of the escape of the gas from the cylinder is open to some doubt and to attribute it to a previous storm can be little more than supposition.

P J F HENDERSON
Manager-Insurance,
Denholm Ship Management Ltd

Glasgow

Serum creatine phosphokinase and malignant hyperpyrexia

SIR,—I was interested in the paper by Dr F Richard Ellis and others (30 August, p 511) in which they concluded that serum creatine phosphokinase (CPK) estimations were of no value in screening for susceptibility to malignant hyperpyrexia. This conclusion was based on the assumption that halothane-induced muscle contracture in vitro was a specific test for susceptibility to malignant hyperpyrexia. Unfortunately this assumption is invalid, as we have already pointed out that halothane-induced contracture can occur in normal individuals.¹ More recently we have found that among 54 normal persons 30% had muscle fibres that responded to halothane treatment with contracture.

Individuals susceptible to malignant hyperpyrexia have muscle with heightened sensitivity not only to halothane but also to caffeine, succinylcholine, potassium chloride, and temperature change. Increased sensitivity to all these pharmacological agents must be shown in order to be certain that a patient is affected by the myopathy predisposing to malignant hyperpyrexia.

Using this more detailed in-vitro muscle test we have found that serum CPK levels are usually reliable in screening relatives of patients who have suffered from malignant hyperpyrexia for the presence of the predisposing myopathy. In particular, we have yet to find a relative with a normal serum CPK level who gave an abnormal muscle contracture response in vitro. If the serum CPK result is equivocal affected individuals must be identified by testing their skeletal

muscle for increased pharmacological sensitivity to caffeine, succinylcholine, and potassium chloride as well as halothane. Halothane-induced muscle contracture alone is a less reliable index of susceptibility to malignant hyperpyrexia than is the serum CPK.

M A DENBOROUGH

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John Curtin School of Medical Research,
Australian National University,
Canberra

¹ Moulds, R F W, and Denborough, M A, *British Medical Journal*, 1974, 2, 245.

Oral contraceptives and premenstrual tension

SIR,—I am writing to protest at the advice given in "Any Questions" (27 September, p 761) for the most suitable oral contraceptive for a woman suffering from premenstrual tension and irritability.

The general advice given by your expert over assessing the woman's own hormone balance/imbalance and choosing a suitable combination pill to alter it as required is sound, although, as the writer of the article referred to, my advice would be the opposite in such a case—that is, to give a pill which is on balance progestational rather than oestrogenic. However, there is a more major error. The articles to which the reader is referred classified all available oral contraceptives according to hormone balance, but your expert, quoting products from this list, has taken no account of the important findings and guidance since then over the amount of oestrogen in the pill—and all those named by your expert except one contain more than the recommended amount of oestrogen and some of them are rightly discontinued. This is quite unnecessary. The hormone balance of the pill does not depend on the dose of oestrogen or progestogen but on the balance of both. It is perfectly possible using newer low-dose oral contraceptives containing not more than 50 µg of mestranol or ethinyl oestradiol to attain the same effect on hormone balance without the added risks associated with the use of more than this amount of oestrogen.

ELEANOR MEARS

Grimsby, South Humberside

Transport of infants for intensive care

SIR,—In table I of their paper Miss A M Blake and her colleagues (4 October, p 13) seemed to show that the best chance is offered to seriously ill babies if they are born in a hospital with an intensive care baby unit. Much as we have appreciated the help that Dr Reynolds and his colleagues have given us on many occasions, their figures are incomplete unless they include the number of babies they have had to refuse from our and other district general hospitals. We have no foreknowledge on any one occasion when—with our inadequate staff—we will have to provide the only intensive care available to a particular infant. Up to the time of writing, since 1 January this year, University College Hospital has been able to accept only three of the 12 infants we have thought justified referral; seven of the remaining nine were

also refused admission at the other designated intensive care unit in our region.

Could Dr Reynolds and his colleagues publish details of the numbers of cases they have had to refuse over the period reviewed, so that the DHSS may begin to realise that No 127 of their Reports on Public Health and Medical Subjects remains a hollow mockery and that no provision is yet made for many of these babies either in the hospital where they are born or at designated centres?

SHEILA LEWIS
MARY ROSSITER

North Middlesex Hospital,
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** We showed this letter to Miss Blake and Dr Reynolds, whose reply is printed below.

SIR,—We agree with Dr Lewis and Dr Rossiter that it is a matter for great regret that insufficient facilities are available in the UK for the intensive care of sick newborn infants. Our own unit always runs at more than 100% bed occupancy and we have to operate on a first-come first-served basis. Our data for the number of babies refused admission in 1972-4 are incomplete. During the past 12 months, however, more were refused than admitted, as implied in Dr Lewis and Dr Rossiter's letter.

ANTHEA M BLAKE
E O R REYNOLDS

Paediatric Unit,
University College Hospital,
London WC1

Clonidine overdose

SIR,—We read with interest the report by Dr S N Hunyor and others (4 October, p 23) describing two cases of clonidine overdose associated with severe hypertension.

The mechanism which they propose for the observed paradoxical hypertension in these cases is a dominance of the peripheral alpha-agonist action of the drug over its central hypotensive effect in the presence of high serum levels of the drug. In preliminary studies of clonidine pharmacokinetics and concentration-effect relationships in man, using a specific and sensitive mass fragmentographic assay for clonidine developed in our laboratory,¹ we have demonstrated an unusual relationship between plasma clonidine concentration and the effect on blood pressure. At low plasma concentrations the fall in arterial pressure is related to the plasma level. With high plasma concentrations, however, there is considerable reduction in the expected hypotensive effect. We think that this represents a predominance of the peripheral alpha-agonist effect of the drug at higher plasma concentrations and is probably seen only clinically immediately following intravenous bolus injection, when transient hypertension occurs. Our finding would support the proposed mechanism for the hypertension observed in Dr Hunyor and his colleagues' cases.

It was surprising to read that diazoxide and not alpha-adrenoceptor blocking agents had been used to lower blood pressure in these patients, as alpha-adrenoceptor blocking agents block the peripheral hypertensive action of clonidine.² We would suggest that

an alpha-blocker such as phentolamine should be the first choice in the management of hypertension complicating clonidine overdose.

We should also like to take issue with the recommendation that forced frusemide diuresis is an effective means of removing clonidine. In normal individuals given 300 µg of clonidine either orally or intravenously we have found that 39-48% of the dose is excreted unchanged in the urine in the first 24 hours. In addition, a variable amount of extrarenal elimination occurs. In the first case described by Dr Hunyor and his colleagues 47% of the ingested dose was excreted in the first 24 hours, and this is what we would have expected without the use of frusemide. Although we have no experimental data on the effect of frusemide on clonidine excretion, we doubt if it would alter the rate of elimination if an adequate urine flow was maintained.

L M H WING
D S DAVIES
J L REID
C T DOLLERY

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- 1 Dollery, C T, *et al*, *Clinical Pharmacology and Therapeutics*. In press.
2 Kobinger, W, and Walland, A, *Arzneimittelforschung*, 1967, 17, 292.

Enteric-coated aspirin overdose and gastric perforation

SIR,—The report by Dr R J Farrand and others (11 October, p 85) of a case of gastric perforation following the ingestion of an overdose of Safapryn suggests that sufficient aspirin may leach out of enteric-coated aspirin cores in the stomach itself to cause irritation of the gastric mucosa, erosions, and perforation. The post-mortem photograph illustrating the case clearly shows erosions of the gastric mucosa at points where enteric-coated aspirin cores were in contact with it, but I feel that attention should be drawn to the fact that mechanical factors were operating in this case which would not be present in the more usual situation of a patient taking 2-4 tablets of Safapryn at a time.

The post-mortem report on this patient stated that "67 intact whole tablets were present in the stomach. The tablets were all of similar plain white appearance, but showed varying degrees of bile-staining and seven were slightly thicker. One 1913 silver threepenny coin was also found, showing heavy bile-staining." The pathologist's comment was as follows. "Coins pass through the gastrointestinal tract without delay, so the threepenny piece must have been taken with the tablets. The Safapryn would have been ingested 6-48 hours before death. They could not have accumulated at six a day over 11 days. The chest and abdominal pains she had in the early hours of 18 April could have been caused by irritation of the stomach by the ingested tablets."

The number of tablets taken was large and they were in the stomach for many hours before death. During this time they must have been exposed to a certain amount of attrition by mutual friction and by friction against the silver coin. This could have been

enough to chip the protective enteric coating off many of them, exposing small areas of aspirin which, while insignificant for the purpose of absorption (no free aspirin was found in the stomach), nevertheless presented sites where contact could be made between the gastric mucosa and concentrated sources of aspirin. The conditions were not the same, therefore, as those found following the therapeutic administration of Safapryn.

In a recent study 10 patients were given four tablets of Safapryn and a marked tablet consisting of a barium sulphate core with an enteric coating identical with that used in Safapryn. The course of the marker tablet was followed by serial x-ray examination, and in none of these 10 patients did the marker disappear until it had reached the ileum or jejunum. By inference, therefore, no aspirin was released in the stomach or duodenum. This suggests that release of aspirin in the stomach from Safapryn tablets is unlikely in the absence of other factors such as the mechanical one mentioned above. In the case reported by Dr Farrand and his colleagues still other factors may also have played a part: the patient had been, for an unspecified time, treated with phenylbutazone, which is a well-known gastric irritant and may have modified the state of the gastric mucosa.

F J A BATEMAN
Medical Director,
Pfizer Ltd

Sandwich, Kent

** We showed this letter to Dr Farrand, whose reply is printed below.

SIR,—How much room for speculation is there in a "short report"? I consulted Pfizer Ltd but did not think a small coin was of significance. Likewise, I did not report tests carried out by the Manchester Regional Quality Control Laboratory on Safapryn tablets from the batch used. The tablets failed the BP disintegration test as they did not disintegrate completely at pH 6.8. Pfizer Ltd confirmed the results and commented on a tendency for intestinal disintegration time to lengthen with storage. Perhaps there is significant variation in the enteric coating. The coats of the tablets from this patient still appear intact and, once exposed, aspirin is rapidly soluble. We have filled a mixer with Safapryn tablets, the coin in question, and simulated gastric juice, and after 24 hours mixing the enteric coats remain intact.

I might envy Dr J M Gumpel (1 November, p 287) his clearcut assumptions, but if patients were simple there would be no call for thought. We enjoyed speculating about possibilities in the case reported and are sorry that Dr Gumpel seems immediately to jump to conclusions. We hesitated to blame paracetamol for gastric perforations because inquiries indicated that the overdose was taken about 24 hours before death and the liver appeared normal. After a fatal paracetamol overdose most patients appear well for the first three days, after which signs of liver failure develop.¹ The plasma half life of paracetamol, even in overdose, has been found to be only about four hours,² so that the toxic blood level is gone long before death occurs due to paracetamol. We should like to know when Dr Gumpel has seen gastric perforation following acute para-

cetamol overdose: his apocrypha of paracetamol toxicity is more extensive than ours. We hesitated to blame phenylbutazone because none was detectable in the stomach or blood, there was no history of phenylbutazone intolerance, and we did not accept the overdose as mere coincidence.

I am grateful to your correspondents' contributions to a complex case. We tried to eliminate the impossible and what remained, however improbable, I think must be the truth.

I am grateful to Mr N W Blacow for the pharmaceutical results.

R J FARRAND

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Hope Hospital,
Salford

- ¹ Clark, R, *et al*, *Lancet*, 1973, 1, 66.
² Proudfoot, A T, and Wright, N, *British Medical Journal*, 1970, 3, 577.

A safer antidepressant?

SIR,—Tricyclic antidepressants are among the most toxic of the commonly used psychotropic drugs.¹ The first recorded fatal overdosage of imipramine took place within a year of its introduction in 1959, while in 1973, out of 2914 deaths from suicidal, accidental, and "undetermined" poisoning, some 9% were attributable to tricyclic drugs.² A study of the figures for previous years³ indicates that, at a conservative estimate, the proportion of suicidal poisoning due to tricyclics increased by more than seven times between 1965 and 1973, while antidepressant prescribing during the same period increased by only 2½ times. It seems that depressed and suicidal patients are more aware of tricyclic toxicity than are many doctors.

Viloxazine (Valan) is a new antidepressant chemically unrelated to tricyclic compounds and apparently much less toxic than them. In the year since its general release no fatalities have been reported, and an uneventful recovery from an overdose of 6.5 g is on record.⁴ In contrast, according to Brophy,¹ the largest recorded non-fatal ingestion of amitriptyline is 4.7 g. Animal studies also indicate the relative safety of viloxazine, for which the median lethal dose (LD₅₀) by mouth in mice is 1000 mg/kg⁵ compared with 289 mg/kg for amitriptyline.⁶

It is not my purpose to suggest that viloxazine should be used with the abandon which characterises much current tricyclic prescribing. Indeed, I remain rather sceptical of the value of antidepressants, which have had no obvious beneficial effect on either the suicide rate or the number of admissions for depression. I do believe, however, that if viloxazine were prescribed a little more and tricyclics a good deal less we might be spared the sad and ironic spectacle of patients killing themselves with tablets which have been prescribed in order to make them happy.

COLIN BREWER

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- ¹ Brophy, J, *Archives of General Psychiatry*, 1967, 17, 652.
² *Pharmaceutical Journal*, 1975, 214, 249.
³ Brewer, C, *Psychology Today*. In press.
⁴ Hanning, C D. Personal communication, 1975.
⁵ Mallion, K B, *et al*, *Nature*, 1972, 238, 157.
⁶ Barnes, C D, and Etherington, L G, *Drug Dosage in Laboratory Animals*, 2nd edn. Berkeley, University of California Press, 1973.