following four groups:¹ (a) Serogenetic neuritis (patients inadvertently vaccinated in spite of egg allergy); (b) anaphylactoid reaction (within hours after the vaccination in patients with no egg allergy); (c) Guillain-Barré syndrome or encephalopathies (starting five days after influenza immunisation); (d) damage of sensory dermal nerves of the upper arm by jet injection.²

The incubation time of these neurological complications in our 11 published cases was always the first week after vaccination.¹ Since anaphylactoid accidents may occur within 1 hour after the first immunisation, a toxic factor must be considered in the aetiology. Poser and Fowler³ have stressed similarities between the Guillain-Barré syndrome and complications of serum sickness, which are manifestations of hypersensitivity. The pattern of the incubation time (peak in the second and third week) in the American cases follows mainly that known from serum polyneuritis. We therefore think a similar mechanism of hypersensitivity against components of the vaccine may work in these patients. The frequency of Guillain-Barré syndrome in the American data is disturbing (1 case per 100 000 vaccinees⁴). We calculated the risk as 1 neural complication per 0.7 and 1.3 million, respectively, distributed doses of two German influenza vaccines (period 1968-76).¹

W EHRENGUT

Hamburg,
W Germany

¹ Ehrengut, W, and Allerdist, H, *Münchener medizinische Wochenschrift*, 1977, **119**, 705.

² Ehrengut, W (in preparation).

³ Poser, C M, and Fowler, C W, *Acta Neurologica Scandinavica*, 1963, **39**, 187.

⁴ Schonberger, L B, personal communication.

New strategies for drug monitoring

SIR,—I would like to comment on the leading article "New strategies for drug monitoring" (2 April, p 861), in which voluntary reporting schemes for drug monitoring are seriously compromised. Recently in this journal Professor C T Dollery and Professor M D Rawlins too have denied the value of a voluntary reporting scheme for the early detection of previously unrecognised adverse drug effects (8 January, p 96).

Drug monitoring—that is, the surveillance of adverse reactions to drugs—is an empirical study which should be based on a number of distinct methods, including comprehensive hospital monitoring, national voluntary reporting schemes, international monitoring (World Health Organisation), epidemiological surveys, systematic literature study, and, if necessary, specific investigations to clarify particular problems. These various approaches are complementary. If a voluntary reporting scheme is to contribute effectively to the early detection of adverse reactions to drugs, there must be a close collaboration and a continuous exchange of information with monitoring projects of other types.

The crucial statement in the leading article is that "the chief defect of voluntary reporting schemes . . . is that reactions are never reported until doctors suspect that they may be caused by a drug." This suggests that one cannot rely upon the doctor's ability to recognise the possibility of the drug-induced origin of a symptom or a syndrome. Clearly the extent of this "chief defect" is entirely dependent on

the alertness and co-operation of the individual practitioners in any country. In contrast to the leading article I believe that the observations of "the man in the field"—that is, the practitioner—are of utmost importance and that his contribution is the very element which makes a voluntary reporting scheme an indispensable part of drug monitoring.¹ In the Netherlands the voluntary reporting scheme has on several occasions pointed to new adverse reactions to drugs before the effects in question had been mentioned in the medical literature, most recently aprindine agranulocytosis.² Moreover, our reporting scheme has proved to be a valuable source of information in the assessment of the significance of pointers to adverse reactions reported in the literature or elsewhere.

I would suggest that in the case of a failure of a voluntary reporting scheme we should, prior to blaming the practitioners, consider the possibility that the agency involved has for some reason functioned inadequately. In a number of Continental countries, for instance, adverse reaction agencies are insufficiently developed or even still in the experimental stage of the 1960s.

National monitoring centres should be well equipped and well organised to ensure that doctors are motivated and accustomed to report cases of adverse reactions. Each individual case report should be fully evaluated and followed up, and the resulting conclusions should be promulgated without delay. There is indeed an increasing awareness in many countries of the shortcomings of current drug monitoring procedures. For the above reasons I believe that, while searching for new methods, the improvement of drug monitoring should involve the further development of the existing methods, including voluntary reporting schemes.

R H B MEYBOOM

Netherlands Centre for Monitoring
of Adverse Reactions to Drugs,
Ministry of Health,
Leidschendam, The Netherlands

¹ Meyboom, R H B, "Spontaneous reporting—National Monitoring—Centres." Paper read at the Fifth European Symposium on Clinical Pharmacological Evaluation in Drug Control (World Health Organisation), Deidesheim, October 1976.

² Leeuwen, R van, and Meyboom, R H B, *Lancet*, 1976, **2**, 1137.

Alkaline phosphatase isoenzymes in dialysis bone disease

SIR,—We read with interest the article by Dr R B Naik and his colleagues (21 May, p 1307) on alkaline phosphatase isoenzymes in dialysis bone disease. We have recently determined serum alkaline phosphatase isoenzymes in 69 patients with chronic renal failure, and our results support the authors' view that increased total serum alkaline phosphatase activity in chronic renal failure may result not only from an increase of bone isoenzyme but also from the presence of other isoenzyme fractions. In addition our findings suggest that changes in bone alkaline phosphatase rather than in total enzyme activity are related to the duration of regular dialysis treatment.

Polyacrylamide gel electrophoresis was used for separation of serum alkaline phosphatase isoenzymes. Sixteen of the patients were not undergoing haemodialysis, 30 patients were treated by regular haemodialysis for not longer than one year, and 23 patients were on regular haemodialysis treatment for 14-63 months. Forty-six normal subjects served as a reference group.

A bone isoenzyme was found in 94%, an intestinal isoenzyme in 26%, and a liver isoenzyme in 88% of the patients. The incidences of bone and liver isoenzymes were similar to those reported by Dr Naik and his colleagues (94% and 85%, respectively). However, a lower incidence of intestinal isoenzymes was noted in our patients. This difference could be attributed to differences in methodology, since we did not use inhibition by L-phenylalanine. Of 37 patients with a raised total alkaline phosphatase activity, a predominant bone isoenzyme was present only in 21 (56.7%). Furthermore, the presence of such an isoenzyme generally corresponded to roentgenographic evidence of renal osteodystrophy.

In contrast to previous reports^{1,2} we did not find any significant correlation between total serum alkaline phosphatase and duration of regular dialysis treatment. However, a prominent bone isoenzyme was detected in 43.5% of the patients in whom the duration of regular dialysis treatment was longer than one year. This incidence was significantly higher than that found in the patients undergoing regular dialysis for less than one year (13.3%; $P < 0.05$) and in the control group (2.2%; $P < 0.001$). The difference from the group of the patients not on dialysis (12.5%) was not statistically significant, presumably because of the small number of observations in this group.

It is of interest to note that a similar distribution among the different groups was found to exist for serum calcium levels. Mean ($\pm$ SEM) serum calcium in the patients treated by regular dialysis for more than one year (8.91 ± 0.17 mg/100 ml (2.23 ± 0.04 mmol/l)) was significantly higher than that in the patients not undergoing dialysis (8.09 ± 0.13 mg/100 ml (2.02 ± 0.03 mmol/l); $P < 0.001$) and in those who were on regular dialysis for less than one year (8.58 ± 0.17 mg/100 ml (2.14 ± 0.04 mmol/l); $P < 0.05$), while it did not differ significantly from control values (9.02 ± 0.07 mg/100 ml (2.26 ± 0.02 mmol/l)). This rise in serum calcium with increasing duration of regular dialysis treatment might indicate autonomy of parathyroid glands.^{1,3} Hyperparathyroidism could then be responsible for the preponderance of bone alkaline phosphatase in patients with a long duration of regular dialysis treatment.

TH MOUNTOKALAKIS
C VIRVIDAKIS
A NICOLAOU
O MANOUSOS

Second Department of Internal
Medicine,
Athens University,
Athens

¹ Massry, S G, *et al*, *Archives of Internal Medicine*, 1969, **124**, 431.

² Oreopoulos, D G, *et al*, presented at the meeting of the Royal College of Physicians and Surgeons of Canada, 1971, Ottawa, 20-23 January.

³ Ogg, G M, *Kidney International*, 1973, **4**, 168.

Chronic urticaria after vasectomy

SIR,—I have recently seen two patients with chronic urticaria in whom the condition started one week following vasectomy. In both the urticaria has persisted for 1-2 years and appeared to be of the ordinary type of chronic urticaria, with some angio-oedema swellings from time to time. I have not been able to make a complete check of the literature, and it may well be that this finding has been noted before.

The association may be just a coincidence, or even psychological factors may have been operative. However, there could be an immunological explanation. For example, it is well known that antisperm antibodies may

develop after vasectomy, and also a glycoprotein contained in the seminal plasma has also been shown to have been an antigen responsible for urticaria in a female partner.

Until now I have not sought information after vasectomy in the male patients with chronic urticaria, and the purpose of this letter is to draw attention to the possible association, and find out if it has already been noted by any of your readers.

ROBERT P WARIN

Bristol

Sexually induced headaches

SIR,—I recently saw a 32-year-old man with a severe form of the type 2, sexually induced headaches described by Lance.¹ His headaches begin occipitally explosively as he reaches orgasm, radiating then to the rest of his head. In view of the proposed vascular nature of this problem I first tried my patient on clonidine (and diazepam) without success, but am happy to report that propranolol 20 mg bd has completely abolished his symptoms.

It would seem that this admittedly uncommon syndrome may respond to β -blockade, and that this is yet another indication for this valuable group of drugs. I should add that the patient (and his wife) are considerably happier with this state of affairs than the total abstinence that was suggested to me as the only way to help their problem.

N R NUTT

Swindon

¹ Lance, J W, *Journal of Neurology, Neurosurgery and Psychiatry*, 1976, **39**, 1226.

Psychologically mediated abdominal pain

SIR,—Surely Dr Joan Gomez and Dr P Dally (4 June, p 1451) are not suggesting that 85% of patients referred with abdominal pain require psychiatric management of their symptoms. It is true that tension, depression, and stress may precipitate abdominal pain, but usually when a basic pathological state exists which is exacerbated by these specific causes. The irritable colon syndrome, for instance, is extremely common and the cause of a good deal of abdominal pain frequently precipitated by psychogenic factors. Nevertheless, in these patients a basic colonic motility disorder exists which will require treatment even though all the investigations may be unhelpful. It is possible that these patients are depressed and tense because of the recurrent abdominal pain and bowel symptoms from which they have suffered for many years.

I TAYLOR

Department of Surgery,
University of Liverpool

Management of the stove-in chest with paradoxical movement

SIR,—The leading article on the above subject (14 May, p 1242) very admirably described the most recent concepts in this difficult and problematic area. It is, however, unfortunate that the last paragraph should have commenced "Taxing as these cases are, they are few and far between. . . ." Few and far between they certainly are in accident depart-

ments, but not in mortuaries. Severe chest injury is one of the commonest reasons for death before transport to hospital.

A recent study¹ has shown that wearing a seat belt results in an 86% statistically significant reduction in life-threatening serious injuries, among which stove-in chest injuries would be included. Your leading article would have been an excellent occasion to have mentioned, as a final point, the value of seat belts in this context and possibly to have urged the profession further to advocate their use to patients. It is my belief that the distinctions between curative and preventive medicine have been sufficiently blurred in recent years to make this not inappropriate in a journal such as yours, which speaks to the whole profession.

C P DE FONSEKA

Royal United Hospital,
Bath

¹ Transport and Road Research Laboratory, Leaflet L.F. 633, *Alleviation of injuries by use of seat belts*, January 1977.

Transient hypotension following intravenous ethamsylate (Dicycne)

SIR,—We are naturally concerned as a company to read the report by Dr L Langdon of a fall in blood pressure following intravenous injection of our product ethamsylate (Dicycne) (4 June, p 1472). Dr Langdon refers to slight transitory hypotension having been reported. This in fact refers to one case contained within the Committee on Safety of Medicines register of adverse reactions covering the period from January 1964 to October 1971. No other authenticated cases are included in our adverse reaction file. Internationally no confirmed reports of such occurrences have been received. During animal toxicity experiments the only species that showed hypotension was the cat at a dose in excess of 500 mg/kg. This again was of a transitory nature. I fail to follow the statement that the giving of slow intravenous injection is not facilitated by the use of the "theatre pack." Further investigation of this report will be carried out with Dr Langdon's permission and assistance.

B WATSON

Technical Manager,
Delandale Laboratories Limited

Canterbury

Peritoneal fibrosis

SIR,—In reply to Mr M A Morris's letter (21 May, p 1355) concerning adhesions following the use of noxytiolin, I should like to draw his attention to the results of many workers who have shown just the opposite.

Stoller¹ remarked how pleasing it was to find no adhesions when reoperating on patients who had recovered from faecal peritonitis following noxytiolin lavage. Since that time I have used noxytiolin for faecal peritonitis with similar results. Pickard² showed it was effective in detaching fibrinous plaques from the bowel wall. Any adhesions that did form in the study carried out by Cleaver *et al*³ were few and flimsy and were significantly less than the controls. Last year also Gilmore and Reid⁴ carried out a controlled trial to study the effect of noxytiolin on adhesion formation and showed that the total and the mean number of adhesions formed as well as the mean length

of attachment were significantly reduced if noxytiolin peritoneal lavage was used. Finally, I presented at the Surgical Research Society earlier this year the results of an experiment in which we used topical noxytiolin prior to colonic anastomosis, and among other findings we discovered the formation of adhesions were inhibited, which bore out our clinical impressions.

R D ROSIN

Kingston Hospital,
Kingston upon Thames

¹ Browne, M K, and Stoller, J L, *British Journal of Surgery*, 1970, **57**, 525.

² Pickard, R G, *British Journal of Surgery*, 1972, **59**, 642.

³ Tolhurst-Cleaver, C L, Hopkins, A D, and Kee Kwong, K C, *British Journal of Surgery*, 1974, **61**, 601.

⁴ Gilmore, O J A, and Reid, C, *British Journal of Surgery*, 1976, **63**, 978.

Tetracycline and toxoplasmosis

SIR,—The article by Dr A Fertig and others (23 April, p 1064) entitled "Tetracycline treatment in a food-borne outbreak of toxoplasmosis" is an example of the misleading literature which has appeared on toxoplasmosis.¹ The authors report what they interpreted as a case of acquired toxoplasmosis which they treated with oxytetracycline, yet the dosage is not stated. The antibiotic was used for a second course, but again no dosage was given. The authors state, "A final month's course of oxytetracycline and prednisolone was given." As corticosteroids may decrease lymph-node size and cause a sense of clinical well-being, it is impossible to attribute either clinical or symptomatic improvement in their patient to oxytetracycline.

The authors cite the study of Garin *et al*² as evidence that acute toxoplasmosis responds to tetracycline. Garin *et al* studied demethylchlortetracycline, not oxytetracycline, in their mouse model. There are no data to suggest that the different tetracyclines are equally efficacious. In fact Eyles and Coleman³ point out, "tetracycline is inferior to chlortetracycline in activity against toxoplasmosis in the mouse model."

In the studies by Garin *et al* 200 mg/kg/day resulted in 60% survival. In other studies Eyles and Coleman found that the mean curative dosage of chlortetracycline and tetracycline in acute murine toxoplasmosis was approximately 1240 mg/kg/day and concluded that tetracyclines are probably of no practical value in acute toxoplasmosis.³ Expression of dosage in mg/m², rather than mg/kg, has been suggested as a means of more realistically comparing doses in man and laboratory animals. (A formula for this purpose has been discussed by Freireich *et al*.⁴) For example, a dose of 2 g tetracycline/day (33.3 mg/kg/day in a 60-kg man), when corrected for dose/m² of body surface, corresponds to 410 mg/kg/day in a 20-g mouse. Although extrapolation of tetracycline efficacy in murine toxoplasmosis to acquired human toxoplasmosis may be hazardous, the corrected figures for dose/m² for the data of Garin *et al* suggest that this dose of demethylchlortetracycline might indeed be therapeutic in man. In contrast, from the data of Eyles and Coleman 6 g/day of a tetracycline might be required in man. Thus from the limited information and the one case provided in their article it would seem premature for Fertig *et al* to "suggest that an adequately long course of tetracycline should be considered." Although oxytetracycline may have been