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

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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.

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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.

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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