clinical, and therapeutic aspects. If the disease is shown to be an irreversible one, then ancillary workers are most helpful in assisting with the difficult and important skills of subsequent psychosocial adjustment and management.

But please, Sir, when we are discussing illness (as opposed to the more vague, pure social maladjustments of contemporary society) let us not be falsely persuaded by the fashionable soft sciences into abrogating our inalienable role as leader of the clinical team.

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¹ Anderson, W F. and Carlton-Ashton, J R, eds, *Age and Ageing*, 1977, suppl.

² Harrison, M J G, and Marsden, C D, *Archives of Neurology*, 1977, **34**, 199.

³ Pearce, J, and Miller, E, *Clinical Aspects of Dementia*. London, Baillière Tindall, 1973.

Cholestyramine in uraemic pruritus

SIR,—Most renal physicians find uraemic pruritus difficult to treat, so the report of Dr D S Silverberg and his colleagues (19 March, p 752) of a favourable response to cholestyramine will excite interest and encourage others to try this treatment.

The authors realise that cholestyramine has the potential to cause acidosis but found no evidence of this in their patients. The absence of acidosis was probably the result of haemodialysis three times a week, which would return the acid-base state to normal and prevent cumulative hydrogen ion retention. But dialysed patients are less liable to this complication than uraemic non-dialysed patients, and the latter would be particularly at risk from the acidifying effect of cholestyramine, as the following argument makes clear.

Cholestyramine is a strongly basic anion-exchange resin in the chloride form, with an exchange capacity of 4.1 mEq/g. A study of several similar anion-exchange resins some years ago found that after oral ingestion the resin was excreted in the stool predominantly with organic anion and bicarbonate, and only 15% in the chloride form.¹ By extension of this finding to cholestyramine, every gram of resin taken would contribute 3.5 mEq of chloride to body fluids and remove in exchange 3.5 mEq of bicarbonate or bicarbonate-precursor from the body. Loss of bicarbonate from the body is equivalent to a gain in hydrogen ion, so the 10 g dose of cholestyramine used daily by Dr Silverberg would donate 35 mEq of hydrogen ion to body fluids, an amount which is only a little less than the daily excretion of hydrogen ion by healthy kidneys. It might be argued that this would not occur in a uraemic subject because of a change in the ionic pattern of intestinal juices; however, a study of this point has been made and showed no significant difference in the anion pattern of faeces from uraemic and normal subjects.² There are therefore strong a priori grounds for predicting progressive hydrogen ion retention in non-dialysed uraemic subjects given cholestyramine. Although Silverberg referred to *hyperchloraemic* acidosis, the resultant acidosis might not be accompanied by hyperchloraemia because of the retention of unmeasured anion, which is usual in renal failure.

This problem would not arise if the manufacturers marketed cholestyramine in acetate or lactate form rather than as chloride. The necessary conversion can easily be carried out

in a laboratory with the simplest equipment, such as exists in hospital pharmacies, but this would remove the added flavouring which is important for palatability, and the conversion would therefore be best incorporated during manufacture. Cholestyramine modified in this way would be just as effective as the present chloride form for the other therapeutic purposes for which it is used.

Incidentally, the name "cholestyramine" is misleading, as it implies a particular mode of action (binding of bile anions); whereas the approved names of most modern drugs are derived from the chemical structure of the drug alone. Anion exchange resins remove much more from the body than bile anions, which are not retained in renal failure, and any effect they may have in relieving uraemic pruritus is likely to be mediated by some other action.

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¹ Hurst, P E, *et al*, *Clinical Science*, 1963, **24**, 187.

² Wilson, D R, *et al*, *Clinical Science*, 1968, **35**, 197.

Aerosols containing neomycin

SIR,—I refer to your "Warning on Aerosols containing Neomycin" (21 May, p 1360). May I draw your attention to two illustrations, 19.1 and 19.2 (pp 454 and 455), in my textbook,¹ which show the extensive damage to Corti's organ and its innervation caused by neomycin aerosols in two children with cystic fibrosis treated in a neomycin atmosphere for several months.

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¹ Friedmann, I, *The Pathology of the Ear*. Oxford, Blackwell, 1974.

Side effects of sodium valproate

SIR,—While we agree that sodium valproate (Epilim) is a most useful anticonvulsant in childhood, we should like to report an apparent side effect not mentioned in your leading article (16 April, p 986).

A 14-year-old Asian boy was born in hospital in Kenya. Delivery was apparently normal, birth weight 3 kg. From the age of 6 months he started attacks of eye rolling, rigidity, and shaking, which lasted about three minutes and occurred about every two weeks until he was 5 years old, when they became less frequent. He came to the UK in 1969 and now attends a boarding school for educationally backward children. Clinical assessment revealed bilateral optic atrophy, clumsy gait, but no obvious syndrome. Head circumference was at the 10th centile and skull x-ray was normal.

Since 1973 he has had occasional brief episodes of loss of vision and jerking of the head followed by intermittent "blackouts." Electroencephalography showed epileptic features, and he was prescribed phenobarbitone. The convulsions became more frequent, occurring two or three times a week, and treatment has included various combinations of anticonvulsant drugs, including sodium valproate, with no definite success. The regimen was changed recently to sodium valproate alone at a dose of 42 mg/kg (1600 mg) per day. After 14 days free from convul-

sions he became confused and had recurrent episodes of bizarre behaviour in which he stared vacantly, shouted gibberish, and had frightening hallucinations. He was visited by a general practitioner deputy, who stopped the drug. Two days later he was seen at hospital, when he was still moderately confused and appeared frightened though apparently had steadily improved since the sodium valproate had been stopped. Plasma valproate level at that time was 13 µg/ml. The drug was recommenced at half the previous dose (800 mg per day). Ten days later his behaviour had returned to normal and he remained free from convulsions.

The clinical course of this patient's acute episode of psychotic behaviour in relation to his medication is suggestive of a drug reaction. The plasma level two days after discontinuing sodium valproate is surprisingly high. Considering the average half life of the drug in epileptic patients to be about six hours, the level at the time of the reaction would have been far above the expected therapeutic range. Careful questioning did not suggest that an overdose had been taken (this would have been unlikely as the patient had been on anticonvulsant drugs for many years under the supervision of the excellent nursing sister and medical officer at his special school). We have found no other reports of similar side effects of sodium valproate when given on its own and suggest that a watch should be kept for psychotic changes in patients on this drug.

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Basal body temperature

SIR,—In their paper "Problems in using basal body temperature recordings in an infertility clinic" (26 March, p 803) Dr Elizabeth A Lenton and others are trying to achieve the impossible. They asked "experts" and "non-experts" to diagnose a small mixed sample of BBT curves from healthy volunteers (8), infertility patients with ovulatory cycles (14), with anovulatory cycles (24), and pregnant cycles (4). Such a hodgepodge of variables cannot be analysed statistically and meaningfully. Further, the authors did not provide definitions according to which the BBT curves should be examined, nor were the experts and non-experts asked to spell out their own diagnostic criteria. Thus, the results reflect the participants' guesses but not the diagnostic value of the BBT curve.

The elevated phase of the biphasic BBT curve indicates corpus luteum activity, and consequently an ovulatory menstrual cycle. However, the BBT curve does not allow us to time precisely the day of ovulation.

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Guillain-Barré syndrome and influenza vaccine

SIR,—Your leading article on Guillain-Barré syndrome and influenza vaccine (28 May, p 1373) stimulates me to consider the various possibilities of neural disturbances after influenza immunisation. We differentiate the

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