drug on respiratory function¹ was prominent cardiac rhythm was unaffected. Chlormethiazole toxicity is not confined to excessive oral administration but has been reported after parenteral use¹ and recently we have seen two patients who had cardiac arrests during chlormethiazole infusion at the recommended dose.

Case 1—A 65-year-old man with a history of alcohol abuse was drinking heavily until one day before admission following a haematemesis. There was no clinical evidence of hepatic decompensation although serum enzymes were markedly elevated. Vital signs and concentrations of serum electrolytes and haemoglobin were satisfactory. Delirium tremens developed 24 hours after admission. When treatment with parenteral diazepam and chlorpromazine proved unsuccessful, satisfactory control of symptoms was achieved by chlormethiazole 0.8% infusion alone. Sixteen hours after the infusion was commenced he developed ventricular tachycardia, from which he was resuscitated and made an uneventful recovery.

Case 2—A 54-year-old man was admitted with severe facial bone fractures following an assault outside a bar. His clinical state was stable although biochemical studies revealed raised serum enzymes and low serum albumin. Soon after admission he became increasingly restless, parenteral diazepam and chlorpromazine again proving ineffectual. Intermittent infusions of chlormethiazole 0.8% controlled his symptoms but cardiac arrest followed a one-hour infusion of 100 ml, its only administration for 24 hours. Resuscitation was unsuccessful. The only other drug treatment was diazepam 10 mg in divided doses over the six hours before death. Necropsy revealed an insignificant pulmonary embolus and fatty hepatic degeneration consistent with chronic alcoholism.

These cases demonstrate that potentially lethal cardiac dysrhythmias may complicate chlormethiazole infusion at the manufacturer's recommended maintenance dose (333-1333 mg/h). At the times of cardiac arrest the infusion rates were 667 mg/h and 660 mg/h respectively. There was no evidence, prior to arrest, of the respiratory depression noted by Dr Illingworth and his colleagues and by others.¹

The extensive hepatic biotransformation of chlormethiazole² should be emphasised. Although neither of our patients nor those of Dr Illingworth and his colleagues had clinically overt liver dysfunction, hepatic enzyme activity might be expected to be abnormal in chronic alcoholics, as in our patients and in the six alcoholics in their series. Presumably as a result of age-related changes in hepatic clearance,² the terminal phase half-life of chlormethiazole is longer in the elderly² than in healthy young adults.³ Acute ingestion of alcohol, which accompanied the overdose in at least six of the subjects reported, might also be expected to inhibit the metabolism of drugs with high presystemic extraction, such as chlormethiazole, when they are taken orally.⁴ The likely influence of alcohol on chlormethiazole toxicity has previously been reported in animals⁵ and in man.¹ The plasma half-life in the patients described by Dr Illingworth and colleagues was rather longer than in previously reported cases,^{2,3} from which it may be inferred that the above factors were indeed relevant.

Chlormethiazole is a useful drug which may be employed successfully in the management of the acute symptoms of alcohol withdrawal when other drugs are less satisfactory, as in our cases. However, this report and other recent case studies^{1,6} emphasise that the drug should be administered with caution. Particular attention should be paid not only to the patient's respiratory function and age but also

to alcohol intake and hepatic and cardiac function when chlormethiazole is prescribed for oral or intravenous use.

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¹ Pentikainen, P J, Valtanen, V V, and Miettinen, T A, *International Journal of Clinical Pharmacology*, 1976, **14**, 225.

² National, R L, et al, *European Journal of Clinical Pharmacology*, 1976, **10**, 407.

³ Moore, R G, et al, *European Journal of Clinical Pharmacology*, 1975, **8**, 353.

⁴ Bircher, J, and Zysset, T, paper presented to International Conference on Drug Absorption, Edinburgh, 1979.

⁵ Vapaatalo, H, and Karppanen, H, *Agents Act and Actions*, 1969, **1**, 43.

⁶ Horder, J M, *British Medical Journal*, 1978, **1**, 693.

SIR—In his discussion of severe poisoning with chlormethiazole (13 October, p 902) Dr R N Illingworth and others question its safety in elderly patients and in patients with chronic bronchitis.

Having acquired wide experience in the use of chlormethiazole, orally as a premedicant, intravenously for sedation during surgical procedures under local anaesthesia, and in combination with a variety of narcotics as a general anaesthetic for minor surgical procedures, I feel Dr Illingworth has overstated his case.

The patients who received oral premedication and intravenous sedation with chlormethiazole were invariably elderly with some degree of pulmonary dysfunction and at no time have I experienced any untoward respiratory complication. Even in combination with narcotics the degree of respiratory depression has never exceeded that expected from the narcotic alone. The conclusions drawn from Dr Illingworth's case histories should include: (1) caution should be employed whenever any pharmacological preparation is prescribed for the elderly; (2) the long-term prescription of large doses of chlormethiazole to outpatients is contrary to the manufacturer's advice; (3) despite massive overdosage with chlormethiazole all the patients survived.

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Neutropenia associated with metronidazole

SIR—It is not without astonishment that I read the letter by Drs M W McKendrick and A M Geddes (29 September, p 795) describing a patient who developed neutropenia while taking metronidazole. Since azathioprine was given simultaneously, it is highly questionable whether the warning against metronidazole in connection with neutropenia has a shred of evidence to support it. Azathioprine is well known as an agent capable of inducing neutropenia—alone. In this country a general warning is included in the annual prescriber's handbook, including all pharmaceutical products accepted by the Norwegian authorities, to the effect that haematological side effects (leucopenia, thrombocytopenia, and pancytopenia) are so important that regular monitoring must be carried out at least weekly during the first eight weeks of azathioprine treatment.

Metronidazole—or any other agent—given together with a drug which regularly may precipitate leucopenia cannot be incriminated

on the basis reported by Dr McKendrick and Dr Geddes. If you observe leucopenia in a patient who has received chloramphenicol and distilled water, would there be any reason to suspect the water to be the cause?

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SIR—It was with interest that we read that a combination of metronidazole and azathioprine was found to cause neutropenia¹ (29 September, p 795). We believe that a combination of metronidazole and fluorouracil may also give rise to such an effect.

In a trial of adjuvant chemotherapy with fluorouracil in this department, patients with colorectal cancer have received 12 mg/kg fluorouracil intravenously after surgery and on the first two postoperative days followed by weekly fluorouracil at a dose of 15 mg/kg. An initial pilot study performed one year ago demonstrated no adverse side effects of this regimen in the 20 patients included. However, of the 12 patients admitted to the present trial four have developed a leucopenia with leucocyte counts of $1 \times 10^9/l$ or less. This has been caused by a reduction in neutrophils and was not observed earlier than eight days after commencement of therapy. The neutropenia lasted from one to three weeks. The time of onset led us to believe that the dose of fluorouracil at one week was responsible, but withdrawal of this dose has not eliminated the occurrence of neutropenia. The only difference in therapy between the two studies has been our recent use of metronidazole at a dose of 400 mg orally three times daily for three days before surgery and 500 mg intravenously three times daily for five days after surgery.

Reversible neutropenia has been reported following the use of metronidazole alone,² and McKendrick and Geddes¹ suggested that the neutropenia may be akin to that observed following treatment with levamisole because of their like chemical structures. However, we have not observed a greater incidence of neutropenia in patients who have received in addition to fluorouracil and metronidazole 150 mg of levamisole on the first three postoperative days. In addition, a combination of levamisole and fluorouracil (without metronidazole) has not, in our hands, been found to cause neutropenia.

The mechanism of the neutropenia remains obscure; however, our findings suggest that caution must be exercised in giving metronidazole with fluorouracil to postoperative patients.

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¹ McKendrick, M W, and Geddes, A M, *British Medical Journal*, 1979, **2**, 795.

² George, R H, *Prescribers' Journal*, 1979, **19**, 18.

Withdrawal of cyanocobalamin

SIR—Dr A H Goodspeed (3 November, p 1142) misses my point, which is that occasional patients with cyanide toxicity syndromes may be harmed by the use of cyanocobalamin, whether incidental or therapeutic (but erroneous).

The chance that a patient who has had a sensitivity reaction ("rare," according to the data sheet) or anaphylaxis ("exceptional") will not be equally sensitive to hydroxocor-

balamin seems remote, unless the sensitivity is to other components. Why not, then, abandon the less safe, and less effective, of two equivalent and equally priced preparations, other than for commercial reasons?

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*Dr Davidson sent a copy of his letter to Dr A H Goodspeed, medical adviser to Glaxo, whose reply is printed below.—ED, *BMJ*.

SIR,—I am afraid that Dr Davidson has also missed my point, which is that, while he is suggesting that cyanocobalamin should be withdrawn because occasional patients with cyanide toxicity syndromes may be harmed by its use, there are occasional patients who do display hypersensitivity following the administration of cyanocobalamin or hydroxocobalamin. For example, I am currently awaiting further developments in a case of "brisk anaphylactic reaction" to hydroxocobalamin which occurred earlier this year in Scotland. This is the second case of hypersensitivity to hydroxocobalamin of which I have learned this year. As I said in my previous letter, we have no reports of cross-sensitivity between the two cobalamins so far, and since the other constituents of both marketed preparations are identical I am afraid that sensitivity to one cobalamin is not so remote as Dr Davidson would seem to suggest.

So, again, why should cyanocobalamin be withdrawn simply because some doctors do not apparently read data sheets? And can Dr Davidson suggest an appropriate course of action for the above cases of hydroxocobalamin hypersensitivity which have actually happened other than to transfer them to cyanocobalamin, which he would have us withdraw?

A H GOODSPEED

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Treatment of tumours in children

SIR,—The paper by Dr E L Lennox and others on the treatment of nephroblastoma (8 September, p 567) serves to illustrate very clearly how important it is that children with cancer should be treated in centres specialising in paediatric oncology, and that their therapy should be given following well-defined protocols. The results achieved in the first Medical Research Council nephroblastoma trial, quoted in that paper, are somewhat out of date now; and the second trial organised by the Working Party on Embryonal Tumours in Childhood closed last year. The interim results of the second trial show survival rates of 90% for all children with disease confined to the kidney or with local or regional nodal spread—that is, without distant metastases.

Despite the remarkable improvement in survival achieved for children with Wilms's tumour there are still many who do not benefit from these advances, either because surgery is carried out by individuals not regularly concerned with treating cancer in children or because the radiotherapy and chemotherapy given after surgery do not follow the modern accepted guidelines. Children are still seen whose tumours have

been removed though loin incisions, making accurate staging impossible.

The United Kingdom Children's Cancer Study Group, which has been established to enable interested and active clinicians in the field to participate in therapy programmes for a wide variety of different children's tumours, has just started a new trial for nephroblastoma. It is hoped that all eligible children will benefit from the lessons learnt in previous trials both in the UK and in other countries.

JOHN MARTIN
Chairman

JILLIAN MANN
Secretary

United Kingdom Children's Cancer Study Group,
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Clinical photographs of children

SIR,—It is common in clinical meetings to be faced with slides of children without clothes. It seems to me that for anyone to be stood against a wall and photographed in the nude is a potentially degrading and embarrassing thing. I would like to suggest that children should never be subjected to this indignity unless there is a compelling reason for it—and then only with the consent of the parents and, if he is old enough, the child himself.

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Putting children first

SIR,—The international Year of the Child is drawing to a close, and I should like to ask what in particular we as a profession have contributed to this important aspect of social medicine. I read with interest the leading article "Putting children first" (15 September, p 623), but I should like to see more emphasis given to the child before it is even conceived.

Sex education is now a recognised part of the school curriculum and I understand that marriage guidance counsellors are giving helpful instruction to children at the school level. General practitioners, however, have a unique opportunity for enlightening potential parents of the difficulties and problems, often painful ones, of successful family life. If we could convince ourselves, and young people in particular, that the child comes first; that family life is absolutely basic for the welfare of that child; that successful family life is not easy—that in fact it is all the more successful when difficulties, conflict, and even suffering, are part of it, for it is by facing problems together that growth and progress occur—then I believe that we should have made a real step forward. The child is father to the man, but man and woman, boy and girl, are parents to the child. Both of these views are equally true and equally important.

JEAN WEST

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Accidental injury in children and interrogation of families

SIR,—I write in response to the letter from Drs J M English and Patricia A Sutcliffe (20 October, p 1003) on accidental injury in

children and interrogation of families. This is a particularly sore point with my partners and I as in our practice a particularly unpleasant and unhappy case has arisen where the damage done by a social worker interrogating the family was far in excess of any damage that might have been done by parental abuse of one of the children.

Two points caused us considerable pause for thought—the first was that the whole attitude taken by the social workers and those who ran the non-accidental injury register was of guilt until innocence was proved. They have maintained, and still maintain, this attitude, despite exhaustive research and the absence of any cumulative suspicious evidence apart from one child in the family displaying bruises, which are of the normal nature but of remarkable frequency. The second point is the vigour and the persistence of the inquiry. The result of the ill-considered zeal in the particular case has been: (1) depression for father; (2) repeated consultations for support by mother; (3) the removal of a long-term foster child (to that foster child's considerable detriment—this child was not the subject of the original interest); (4) the inevitable knowledge in a small community that this family is the subject of inquiry and the equally inevitable belief by some that there cannot be smoke without fire.

Surely it is time for the pendulum to swing a little in the other direction—for the families to be considered, and for some system to be arrived at where if confirmatory evidence of child abuse has not been forthcoming after a certain while attention is focused away from that family and that family's name removed from the black book. The family in question have been told that they will be the subject of continual supervision and inquiry until the boy is 16 in some 10 years' time. They have also been warned that this will follow them about the country if they decide to move.

NORTH OF ENGLAND GP

Circumcision and cruelty to children

SIR,—I must take issue with Dr J E Oliver (13 October, p 933) who looks at circumcision from a very polarised point of view. As a general surgeon, I am well aware of the dangers, both physical and mental, that surround circumcision, particularly if performed without anaesthesia, but he does not mention the consequences of leaving the foreskin until 16 years of age or such time as the patient decides he wants something done.

I know remarkably little of the natural history of the foreskin; certainly I recognise the extremes, but I cannot predict the outcome of the large group who may or may not later develop paraphimosis or even a ballooning foreskin. In this group the challenge is to assess the advisability of doing a circumcision versus adopting a wait-and-see policy. My own view is that circumcision at 10 days on religious grounds alone cannot reasonably be refused. After this I do circumcision for complications only until the child is dry, around the age of 3 years, because of the dangers of meatal ulcer. Beyond 3 years I have swung towards circumcision rather than away from it, though I still discourage those with a wide opening. My reasons for so doing are that eventual circumcision at a later age entails yet more discomfort and perhaps an absence from school. A paraphimosis with all