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, Valtonen, 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-