referred to by Dr Prescott and his colleagues^{2 3} are unsuitable for patients with mixed poisoning, as it has been established that oxyphenbutazone interferes with the Routh method⁴ and the same drug and others—for example, salicylates and barbiturates—may interfere with the Dordoni procedure. Although, as we stated, measurement of total paracetamol may have been a poor index of the need for treatment, the pretreatment serum alanine aminotransferase (SGPT) values show that many of our patients were severely poisoned.

As to our claims for the efficacy of late cysteamine treatment, Dr Prescott and his colleagues appear to have misread our paper. Our last paragraph states that we do not claim to have proved that cysteamine is effective, only that it is safe. We argue that consideration of the mechanism of its action would lead one to anticipate that cysteamine would prevent further liver damage as long as any unconjugated paracetamol remains in the circulation and there are liver cells still undamaged.

Dr Prescott and his colleagues state that the course of paracetamol poisoning is uninfluenced by cysteamine administered later than 10 h after overdosage, because it does not change the number of patients who suffer severe liver damage. However, our paper showed, and our current figures confirm, that liver damage was known to be already moderate or severe before treatment in eight out of the 11 patients who developed severe liver damage in the late cysteamine group (see table). Our hypothesis is that cysteamine may prevent these patients progressing to more severe, even fatal liver damage.

Late cysteamine group—current results

No of patients	Mean ingestion-treatment interval (hours)	Severe liver damage	Death from fulminant hepatic failure
20	17.8	11 (55%)	0

The numbers in our published series are not large enough to refute or confirm this hypothesis. In the meantime, therefore, we feel that it is entirely reasonable to assume that late cysteamine may indeed protect the liver from further damage. Only series large enough to show significant differences in mortality rates will clarify this point.

We have scrutinised Dr Prescott's list of references but can find no evidence that the lethal potential of cysteamine approaches, let alone exceeds, that of untreated paracetamol poisoning. We find that most of the references state, as we did, that cysteamine is unpleasant. No death has been reported and we feel that slower injection might have prevented the one case of ventricular tachycardia. We have seen no electrocardiographic changes during this regimen.

We should be happy to change to a less unpleasant antidote if any were shown to be equally harmless in patients with severe liver damage. Methionine has been found to induce hepatic coma in some patients with cirrhosis.⁵ N-acetylcysteine may be as safe as cysteamine in late paracetamol poisoning, but this remains to be proved—the manufacturers are unhappy about its intravenous use.⁶

The Edinburgh workers describe our study as indefensible, but they also used "late" cysteamine in 13 patients. We think their work

is readily defensible, although we disagree with their conclusions (for the reasons stated above).

We found their criticism of our preparation of cysteamine confusing, as our "home-made" solutions were prepared according to their own original recipe.⁷

Finally, we would support the suggestion of James⁸ that a multicentre trial is necessary to determine the effectiveness of any treatment in reducing the mortality from paracetamol poisoning. Studies of a number of patients developing severe liver damage cannot help us to decide the effectiveness of treatment in a group of patients many of whom have moderate or severe liver damage before treatment is commenced. We need to see significant differences in recovery from this liver damage in the treated and untreated groups. Our series is as yet too small for this purpose.

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- ¹ Glynn, J P, and Kendal, S E, *Lancet*, 1975, **1**, 1147.
- ² Routh, J I, et al, *Clinical Chemistry*, 1968, **14**, 882.
- ³ Dordoni, B, et al, *British Medical Journal*, 1973, **2**, 86.
- ⁴ Weiner, K, Longlands, M G, and Tan Bha, *Annals of Clinical Biochemistry*, 1976, **13**, 452.
- ⁵ Phear, E A, et al, *Clinical Science*, 1956, **15**, 93.
- ⁶ Fish, L J, *Lancet*, 1977, **2**, 610.
- ⁷ Prescott, L F, et al, *Lancet*, 1974, **1**, 588.
- ⁸ James, O, *Journal of International Medical Research*, 1976, **4**, suppl 4, p 151.

*Mercaptamine is preferred to cysteamine both in the WHO's list of recommended international non-proprietary names and in Martindale's *Extra Pharmacopoeia*. We agree, however, that the name cysteamine is much more commonly used in Britain and that the substitution of mercaptamine in the original paper was an error of editorial judgment.—Ed, *BMJ*.

Cannabis and the cardiovascular system

SIR,—In the UK cannabis is usually smoked in the form of resin (hashish) mixed with tobacco, in the US as herbal cannabis (marihuana); all the health warnings which refer to tobacco should apply with equal force to these practices. The principal additional physical effects attributable to inhalation of volatile cannabinoids are congestion of the conjunctivae and a dose-related tachycardia,¹ neither of which seems unduly to concern young smokers.² An average "joint" contains 5 mg of tetrahydrocannabinol (THC), of which approximately half is absorbed and produces a blood concentration of 20–70 µg/l.³

Much of the work quoted in your leading article (25 February, p 460) refers to herbal cannabis, which contains many active substances. Direct measurement of the mechanical properties of isolated driven papillary cardiac muscle from cat and rat⁴ has shown that THC has a negligible effect on contractile force, its time course, or elasticity in a concentration 1000 times greater than that achieved in man by a smoke. Measurement of these parameters in humans can only be by inference from indirect observation. This is not to deny that smoking herbal cannabis or resin in tobacco will disturb the heart's action by modifying the autonomic regulators, but such an effect is likely to be transitory in persons who do not

suffer from disease of the cardiovascular system.

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- ¹ Graham, J D P, and Li, D M F, in *Cannabis and Health*, ed J D P Graham, pp 162–178. New York, Academic Press, 1976.
- ² Graham, J D P, *Cannabis Now*. Aylesbury, HM and M Publishers, 1977.
- ³ Teale, J D, et al, *Lancet*, 1974, **2**, 553.
- ⁴ Graham, J D P, et al, *British Journal of Pharmacology*, 1978, **62**, 153.

Indomethacin and alclofenac in rheumatoid arthritis

SIR,—We have recently had occasion to review a summary in our possession of the data relating to a paper reported by Dr M Aylward and others in the *British Medical Journal*.¹ Although we are of the opinion, through other studies, that alclofenac is efficacious in the treatment of rheumatoid arthritis, we must, with regret, disassociate our company from the above-mentioned publication.

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- ¹ Aylward M, et al, *British Medical Journal*, 1975, **2**, 7.

Outpatient chemotherapy for breast cancer

SIR,—We are writing in regard to the paper by Drs J H Goldie and L A Price (22 October, p 1064) and the subsequent letter from Mr B V Palmer (19 November, p 1354) and the reply from Drs Price and Goldie (17 December, p 1603) regarding the use of methotrexate with folinic acid rescue.

In the past three years we have administered oral high-dose methotrexate (400 mg) with folinic acid rescue on an outpatient basis to 51 patients in a total of 282 courses of treatment. The diagnoses include head and neck cancer, small cell cancer of the lung, breast cancer, lymphatic leukaemia, and lymphoma. The technique requires the patient to take 25 mg (10 tablets) of methotrexate every hour for 16 h. The folinic acid is started at 24 h and continued in a dose of 7.5 mg every 6 h for a total of eight doses. Parenteral folinic acid 6 mg is given in a single intramuscular injection in the period from 24 to 48 h and again from 48 to 72 h in the patient's home by a visiting nurse. No patient has died of the technique and complications have been acceptable. Mucositis occurred in 13 of 215 courses in which methotrexate was the only agent given. Rash occurred in one patient and photosensitivity in another. No patient has had significant neutropenia or thrombocytopenia, and nephrotoxicity has not occurred. Nausea and vomiting is common but rarely severe, and has resulted in abandonment of outpatient treatment in three cases.

The advantage of this approach includes a saving of hospital bed days, reducing the cost of the procedure and the dislocation of the patient's life. The visiting nurse ensures that folinic acid is given even to the patient who may be vomiting. In some cases folinic acid rescue has been extended for several days as a result of the nurse's assessment of the patient on the first visit. We have evidence that with this technique methotrexate blood levels are similar to those achieved with infusions.