noxythiolin-free control. A 10- μ l sample from each tube was plated on blood agar at 0, $\frac{1}{2}$, 1, 2, 4, and 24 h. The results for one of the organisms tested with 10^6 bacteria added to 1 ml of solution are shown in the table. It can be seen that 2 h exposure was required for killing by a 10 g/l solution of noxythiolin, although the MBC as previously determined was 2 g/l. Two other organisms (MBC 1 g/l) when tested with 10^6 organisms/ml showed complete killing by 20 g/l in 1 h, by 10 g/l in 2 h and by both 5 g/l and 2.5 g/l in 4 h.

Presence of persisting *Bacteroides fragilis* after exposure to noxythiolin

Time of exposure (hours)	Noxythiolin concentration (g/l)					
	20	10	5	2.5	1.25	0
0	+++	+++	+++	+++	+++	+++
$\frac{1}{2}$	+++	+++	+++	+++	+++	+++
1	+	+++	+++	+++	+++	+++
2	—	—	+	+++	+++	+++
4	—	—	—	+	+	+++
24	—	—	—	—	—	—

The results of our own studies on *B. fragilis* and those of Dr Chattopadhyay on *Ps. aeruginosa* lead us to believe that the disc sensitivity test or determination of MIC or MBC as routinely applied to the study of antibiotics may be of limited value. We feel that assessment of the rate of killing is the only method likely to give a meaningful result for topical agents which may otherwise be instilled for too short a period of time, with long periods of time between treatments during which regrowth could occur. We doubt, however, whether laboratories could devote the time needed to assess the rate of killing in every case.

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¹ Haler, D, and Aebi, A, *Nature*, 1961, **190**, 734.

Drinking behaviour

SIR,—Your leading article entitled "Drinking behaviour" (8 October, p 914) is rather misleading in its emphasis. Alcohol is rarely a main cause of the conditions attributed to its abuse¹; only a tiny minority of British drinkers (perhaps 0.05-0.1%) develop serious complications. Where there is an association with cirrhosis, marital strife, dementia, work-time lost, etc, the alcohol ingestion may well be a correlate or even a consequence rather than a cause.

Mental, physical, and social illnesses cause alcoholism rather than the other way round. Thus even when alcoholics abstain totally they tend to be overtly disturbed.⁴ If nuclear alcohol dependency is usually a symptomatic phenomenon the crucial lesson is that we must search exhaustively for underlying, often treatable, pathology. If alcoholism is disease-based the present expensive educational drive by David Ennals in the north-east to reduce the Geordies' intake is doomed to failure.

Excessive drinkers might wreak even more havoc on themselves or society without the refuge of the bottle⁵ which serves as a "sinister but effective" peacemaker. This pain-relieving model suggests a more heuristic, treatment-oriented typology than the rather ineffective WHO restatement of Jellinek's excellent descriptive classification:

(Ia) Those "normals" whose life problems, leading to excessive intake, may be soluble by a

non-organic approach—for example, family counselling. This type, often a middle-class minority, has traditionally and, I feel, most unfortunately been confused with the following categories.

(Ib) Those "normals" for whom sociopsychological measures alone are insufficient and who therefore need pharmacological help while their underlying stress continues. A relevant analogy is the snoker who starts smoking much more when subjected to stress. Both may continue to indulge out of habit when the stress is removed, but not to excess any more. This group can return to "social" drinking, as an increasing number of studies is now showing.⁷

(II) The "core" alcoholics needing long-term drug help in their effort at tension-discharge. They typically suffer from chronic physical and/or psychiatric illness. Female alcoholics are over-represented here in that they tend to be more psychologically disturbed.⁸

Oral medication is usually unsuitable for maintenance treatment.⁹ The obvious answer is the depot phenothiazine,^{10,11} which is not only our most effective anti-aggressive agent but may even block a possible toxic-addictive complex of dopamine with a tetrahydroisoquinoline derivative of ethanol.

If this tension-reduction approach should prove scientifically fruitful we will have achieved a breakthrough in the exorcism of a very nasty "demon." The bell may toll only for those not given the chance of treatment with a depot neuroleptic.

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¹ Benjamin, I S, Inrie, C W, and Blumgart, L H, in *Alcoholism: New Knowledge and New Responses*, ed G Edwards and M Grant, p 198. London, Croom Helm, 1977.

² *World Health Statistics Annual*, 1973-1976. Geneva, WHO, 1976.

³ Galambos, J T, in *Progress in Liver Diseases*, ed H Popper and F Schaffner, vol 4, p 567. New York, Grune and Stratton, 1972.

⁴ Gerard, D L, Saenger, G, and Wile, R, *Archives of General Psychiatry*, 1962, **6**, 83.

⁵ *Sunday Express*, 18 September 1977, p 21.

⁶ Proudfoot, A T, and Park, J, in *Alcoholism: New Knowledge and New Responses*, ed G Edwards and M Grant, p 224. London, Croom Helm, 1977.

⁷ Litman, G K, *Once an Alcoholic, Always an Alcoholic: A Review and Critique* (Addiction Research Unit paper). London, Institute of Psychiatry, 1977.

⁸ Beckman, L J, *Quarterly Journal of Studies on Alcohol*, 1975, **36**, 797.

⁹ Proudfoot, A T, and Park, J, in *Alcoholism: New Knowledge and New Responses*, ed G Edwards and M Grant, p 222. London, Croom Helm, 1977.

¹⁰ Kinnell, H G, *Lancet*, 1977, **2**, 659.

¹¹ Bartholomew, A A, *Quarterly Journal of Studies on Alcohol*, 1966, **27**, 510.

Cimetidine and gastric ulcer healing

SIR,—Dr R J Machell and his colleagues suggest (15 October, p 1023) that the great effect of cimetidine found in our double-blind gastric ulcer trial (24 September, p 795) may partly have been due to unsuccessful randomisation, especially because the healing rate in the placebo group was very low. We should of course have been happier if the retrospective stratification had not shown that the treatment group and the control group were, by chance, not comparable in all respects, but as discussed in the paper this fact probably does not bias the results in favour of cimetidine. Also properly conducted randomised therapeutic trials are subject to stochastic variation, but it is worth pointing out that our findings are in very good agreement with those of the only previously published complete trial.¹

It is necessary that we learn the truth about the effect of cimetidine in a disease which is as common as gastric ulcer disease, but the full truth will emerge only when more trials have been published. Dr Machell and his colleagues

mention that their trial is not complete and that a significant effect of cimetidine "has yet to emerge." This statement worries us because usually it is assumed that the results of a randomised trial are not known until the completion of the study. Otherwise it may be difficult to decide when to stop the trial.

We agree very much with Mr R S Arnot (15 October, p 1022), who states that treatment with cimetidine may lead to an increased incidence of missed gastric carcinomas if the patients are not examined sufficiently early.

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¹ Multicentre Trial (France), in *Cimetidine*, ed W R Burland and M Alison Simkins, p 287. Amsterdam and Oxford, Excerpta Medica, 1977.

Depression in men and women

SIR,—Your recent leading article on this subject (1 October, p 849) very rightly focused attention on the significantly higher incidence of depression in women during their reproductive years as compared with men of comparable age and also older women. The two articles which are discussed in detail^{1,2} make some mention of the possible reasons for this, but come to no very firm conclusions on the relative importance of endocrine and other factors.

We should like to support the view that depression occurring in a cyclical manner during the premenstrual days has an endocrine component in many cases, and to advance the hypothesis that subtle neuroendocrine imbalance may well exist in the cases in which it is at present not possible to detect endocrine abnormality. Recent work from this department on patients with the premenstrual syndrome (PMS) has demonstrated a deficiency of plasma progesterone during the luteal phase in 40% of the patients investigated^{3,4} and preliminary studies suggest a tendency to increased prolactin levels when progesterone levels are significantly decreased.⁵ Serum oestradiol levels may also be slightly increased in the late luteal phase.⁶ These findings are in general agreement with those of Carstensen in Uppsala.^{7,8} A tendency to increased prolactin levels in PMS has also been reported by others.^{9,10}

It is encouraging that several recent approaches to the treatment of PMS have given beneficial results which are clearly well above the maximum (30%) placebo effect likely to be encountered. These various approaches have recently been discussed¹¹ and their rationale in PMS considered. They include the use of dydrogesterone, especially in patients with a luteal deficiency of progesterone,¹² and high-dose pyridoxine therapy.¹³ Both these treatments may give complete or partial relief of symptoms in about 75% of selected cases. Research currently in progress suggests that further improvement in relief of symptoms can be obtained by individualising dose regimens and sometimes by combining dydrogesterone and pyridoxine therapy. A single-blind trial on the use of dydrogesterone in PMS is now almost completed and a similar trial using pyridoxine is about to start.

We therefore feel that there are grounds for

continuing and expanding research on the treatment of this condition, which is at present responsible for considerable personal distress and social disruption. In view of the large numbers of women between the menarche and the menopause who suffer from PMS any significant reduction in its overall incidence will be welcome and we hope that family doctors will be encouraged to treat PMS by these new approaches. Further help and support from specialised clinics in teaching hospitals and other centres will be required for some time yet, but we hope soon to publish further observations on the clinical presentation of PMS which will minimise this need.

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- ¹ Weissman, M M, and Klerman, G L, *Archives of General Psychiatry*, 1977, **34**, 98.
- ² Pollitt, J, *Proceedings of the Royal Society of Medicine*, 1977, **70**, 145.
- ³ Munday, M R, et al, *Journal of Endocrinology*, 1977, **73**, 21P.
- ⁴ Munday, M R, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 16.
- ⁵ Brush, M G, et al, Abstract, International Symposium on Prolactin, Nice, France, 1977.
- ⁶ Munday, M R, and Brush, M G. Unpublished observations.
- ⁷ Backstrom, T, and Carstensen, H, *Journal of Steroid Biochemistry*, 1974, **5**, 257.
- ⁸ Backstrom, T, et al, *Journal of Steroid Biochemistry*, 1976, **7**, 473.
- ⁹ Benedek-Jaszmann, L J, and Hearn-Sturtevant, M D, *Lancet*, 1976, **1**, 1095.
- ¹⁰ Halbreich, U, et al, *Lancet*, 1976, **2**, 654.
- ¹¹ Brush, M G, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 9.
- ¹² Taylor, R W, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 35.
- ¹³ Kerr, G D, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 29.

Anaphylaxis after dichloralphenazone treatment

SIR,—The case of anaphylactic response to the ingestion of dichloralphenazone (Welldorm) tablets (reported by Dr Steven Perl, 5 November, p 1187) is by no means unique.

Two Welldorm tablets were administered as night sedation to a 55-year-old man awaiting a minor surgical operation. Within minutes he developed severe bronchospasm and a widespread bullous skin eruption. The bronchospasm responded readily to injection of hydrocortisone and aminophylline. By the following morning there was no evidence of any lesion.

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Silk sutures in the common bile duct

SIR,—Having twice had a similar experience to that described by Mr B I Rees and Mr G Jacob (12 November, p 1265)—although on both occasions the recurrent common bile duct stone contained a thread rather than a silk suture—I was interested last year to remove three stones from the common duct of a woman who had had a cholecystectomy eight years before. Each stone contained a thread suture, and reference to the excellent original operation note produced the explanation: the cystic duct and two cystic arteries had been tied with thread.

I agree that it is important that no unabsorbable suture should be used in the vicinity of the common duct. It is not uncommon to

find that surgeons in training recognise this risk so far as the cystic duct ligature is concerned, but many are unaware that the cystic artery tie also may discharge itself into the common duct. The chances of this happening are presumably greater if an exploration of the common duct has been performed, but a small abscess around the foreign body on the artery can undoubtedly discharge into the lumen of the nearby common duct even when its wall is surgically intact.

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Anaphylactoid reactions to dextran 70

SIR,—I read with interest the report by Dr L H Fanous and others of two cases of anaphylactoid reaction to dextran 70 (5 November, p 1189).

The cases which we reported last year¹ had no history of asthma and did not develop urticarial rashes. Investigation of the immunological aspects of these cases did not reveal the cause. It is peculiar that in our hospital there have been no cases of this type reported in the general surgical or medical wards and that the syndrome appears to be associated with maternity cases.

The question of particles in the dextran solutions and bacteriological contamination of these solutions were investigated with negative results at the time. As an anaesthetist I have meanwhile continued to give dextran as a prophylaxis against deep venous thrombosis in orthopaedic cases, but more recently there has been apprehension about dextran as a precipitating factor in postoperative acute renal failure, as a result of a paper by Feest,² and the practice here now is to not give dextran to those orthopaedic patients who have a blood urea concentration higher than normal for their age.

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- ¹ Fothergill, R, and Heaney, G A, *British Medical Journal*, 1976, **2**, 1502.
- ² Feest, T G, *British Medical Journal*, 1976, **2**, 1300.

Lichen-planus-like eruption: a marker for chronic graft-versus-host reaction

SIR,—In regard to your leading article (23 July, p 211) on skin changes after bone marrow transplantation we would like to make the following comments. Since our initial report¹ of four patients with lichen-planus-like eruption (LPLE) after bone marrow transplantation we have seen seven additional cases.² We have found that the clinical spectrum of LPLE may be compared to the various clinical aspects of idiopathic lichen planus (ILP). The occurrence of LPLE after bone marrow graft not only would throw light on the pathogenesis of ILP^{2,3} but also has a practical interest in the management of patients after grafting.

Indeed, we have found that: (1) a graft-versus-host reaction always precedes development of the LPLE; (2) LPLE never occurs if the graft is rejected; and (3) LPLE always occurs in a context of "persistent graft-versus-host reaction." These data strongly support the concept of LPLE actually representing a skin manifestation of graft-versus-host disease.³ In every case the first

symptoms of LPLE were found in the mouth. This oral involvement was very similar to ILP; it can be easily recognised by a dermatologist and is quite different from drug-induced erosive leukokeratosis and from candidiasis. The oral LPLE represents, therefore, a useful early marker of chronic graft-versus-host disease and a tool for clinical evaluation and therapeutic guidance in patients undergoing bone marrow transplantation.

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- ¹ Saurat, J H, et al, *British Journal of Dermatology*, 1975, **92**, 591.
- ² Saurat, J H, et al, *British Journal of Dermatology*, 1975, **93**, 675.
- ³ Saurat, J H, and Gluckman, E, *Clinical and Experimental Dermatology*. In press.

Adverse reactions to intravenous thiopentone

SIR,—We were interested to read the article by Drs J M Evans and J A M Keogh (17 September, p 735) in which they reported three histaminoid-type reactions to the intravenous use of thiopentone. In view of the relative rarity of adverse reactions to this agent¹ we would like to report a further case.

A 33-year-old White man underwent a routine repair of a right inguinal hernia. Routine premedication with atropine plus Omnopon was given and intravenous thiopentone and suxamethonium used for induction of anaesthesia. The operation was uneventful. Postoperatively the patient developed severe bronchospasm, generalised erythema, pruritus, and gross facial oedema. His white cell count remained normal but showed a 6% eosinophilia. Treatment was instituted with high-dose steroids and the antihistamine chlorpheniramine. The bronchospasm settled rapidly, but the erythema and oedema gradually resolved over the following 72 h.

This patient had a known hypersensitivity to penicillin and tetanus toxoid and eight years previously had undergone an operation for treatment of a compound fracture of his right lower leg. In view of the common use of thiopentone for induction, it is likely that previous use had sensitised the patient to this agent, resulting in a type I hypersensitivity reaction on re-exposure.

As noted by Drs Evans and Keogh, histaminoid-type reactions are probably encountered more frequently than reported and it would seem justified to advocate the prophylactic use of an antihistamine in patients known to be hypersensitive to exogenous agents.

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- ¹ *British Journal of Anaesthesia*, 1976, **48**, 57.

Bell's palsy and herpes simplex

SIR,—Dr B E Juel-Jensen (22 October, p 1086) has taken exception to the evidence that I presented (24 September, p 829) which appeared to support the hypothesis that Bell's palsy may be associated with herpes simplex virus (HSV) infection. While his own studies, to which we are given no reference, resulted in a conclusion contrary to three of the references I cited, he is correct to confirm that there is no definite proof of the association. However, in his determination to demonstrate that the patient in my report did not have