favourable groups of alcoholics (such as single, divorced, or widowed men and women) is as yet unknown but may appear doubtful to the practising clinician.[3] The statement that, "Treatment may actually make some alcoholics worse" by protecting them from the consequences of their drinking or by fostering inactivity surely applies only to utterly inadequate "treatment." The risks arising from the behaviour of well-meaning "enablers" who shelter the alcoholic from experiencing the painful effects of his drinking on himself (and others) and the importance of fostering the patient's responsibility for his recovery, his own initiative, and active participation in the therapeutic programme are surely nowadays well known to every experienced therapist. The finding of some community-based studies that sociopathy did not predict outcome is surprising; it contrasts with most clinicians' observations[1-3] and also with the statement in your leading article that "the best predictor is stability in one's own job and marriage." Social stability (with its link with "good outcome") is hardly a characteristic feature of sociopathy.

M M GLATT

University College Hospital
Alcoholism Teaching Centre,
St Pancras Hospital,
London NW1

[1] Glatt MM. *Br J Addict* 1955;**52**:55-92.
[2] Glatt MM. *Lancet* 1959;ii:397-8.
[3] Glatt MM. *Alcoholism*. London: Teach Yourself Books, 1982.
[4] Orford J, Edwards G. *Alcoholism*. London: Oxford University Press, 1977.

Benoxaprofen

SIR,—In analysing the suspension of the product licence of a drug linked to at least 61 deaths and 3500 adverse reactions in the past two years, the author of your leading article (14 August, p 459) has raised serious but necessary questions about the roles of the manufacturer, pharmaceutical companies in general, the Committee on Safety of Medicines, the lay press, practising doctors, and even the public at large. No mention was made, however, of the role of editors and advertising managers of medical journals, under whose aegis Opren (benoxaprofen) was provided with a credible context from the outset.

The influence of pharmaceutical advertising directed at prescribing doctors—and the responsibility of those persons at medical journals who approve an advertisement for publication—must also be considered. In this instance, two-page and three-page advertisements for benoxaprofen appeared prominently in no fewer than 20 issues of the *BMJ* alone in the two years since the introduction of the drug. One such advertisement favourably compared the five-letter brand-name product with the more unwieldy generic name counterparts: diclofenac, flurbiprofen, indomethacin, and piroxicam. As in many pharmaceutical advertisements, the prescribing information was obscurely placed, and included vague sentences such as "Peptic ulceration has occured (sic) only rarely."

Practising doctors and medical editors alike may resent the implication that frequency and prominence of advertisements for a drug increase the number of prescriptions. I believe most doctors would say they pay little attention to the advertisements, much less prescribe a drug on the basis of one. None the less, the irony is inescapable that while manuscripts, including those dealing with clinical drug trials and post-marketing surveillance programmes, often undergo extensive revision before acceptance for publication, paid advertisements extolling only the virtues of various products generally are accepted without modification.

In the face of the need to maintain fiscal viability while upholding the highest editorial standards, what is a medical journal to do in regard to advertising? The issue needs to be explored by both editors and medical associations at their meetings. One proposal has been raised[1] and seconded[2] for a "physician boycott" of drugs that are unethically promoted. Alternatively, I would propose that medical journals reject advertising for prescription products that are also promoted and advertised in the lay press. In addition, as a way of discouraging the rush to prescribe new drugs, I would propose that journals either wait for a period of time after the introduction of a drug before accepting an advertisement for it, or confine the content of the advertisements to prescribing information.

In my opinion, the benoxaprofen affair points out the need for more careful "peer review" by medical editors and other doctors of pharmaceutical advertisements submitted for publication.

ALAN BLUM
Editor

Medical Journal of Australia,
Glebe,
New South Wales,
Australia 2037

[1] Solomon SD, Grimmett BL, Maurer KH, Levin NW. *N Engl J Med* 1979;**300**:203.
[2] Mallace AH. *N Engl J Med* 1979;**300**:734.

**The *BMJ* has a code which it applies to all advertisements; the prime requirement is that: "Statements of fact should be supported by trustworthy evidence." We do reject advertisements or ask the advertiser to modify the wording or presentation on grounds of accuracy or taste. For us to object to an advertisement on the grounds of frequency would, however, be unduly quixotic.—ED, *BMJ*.

SIR,—While we generally agree with the thoughtful leading article on benoxaprofen (14 August, p 459), there is one correction which is germane to your query as to whether the Committee on Safety of Medicines acted too slowly in banning the drug.

In a letter to the *BMJ* (29 May, p 1630) Lilly vice-president Ian Shedden stated that "no jaundice" had been seen "in approximately 2200 carefully followed patients who participated in clinical trials in the USA." This statement is repeated in the leading article. In fact five cases of reversible jaundice, including four cases with concomitant (also reversible) renal disease, occurred in patients in US clinical trials prior to the US marketing of benoxaprofen in May 1982.[1] The first case occurred in 1978.

Although the US cases occurred in younger patients, they bear a striking similarity to many of the fatal cases reported in the UK. Until we know whether Lilly informed the Committee on Safety of Medicines promptly about these cases, we cannot determine whether the Committee on Safety of Medicines acted too slowly in banning benoxaprofen.

The best mechanism for early warning of side effects, especially those occurring more frequently than once in a thousand patients, is the carefully controlled and monitored clinical trial. Unless there is prompt reporting of the results of such trials by the sponsoring drug company to all governmental agencies in countries marketing or planning to market a particular drug, the Committee on Safety of Medicines, the Food and Drug Administration, and similar agencies in other countries will not be acting on the best available information.

SIDNEY M WOLFE
EVE BARGMANN

Health Research Group,
Washington DC 20036

[1] July 2, 1982. Submission by Lilly to the Food and Drug Administration.

Prescription-event monitoring

**The following is a draft of a letter to be sent to all GPs in England.—ED, *BMJ*.

SIR,—In my letter of 26 February this year I described the preliminary results of our pilot study of prescription-event monitoring. Your response was excellent and I felt that the rapid feedback, less than one month after the "green forms" had been distributed, would be appreciated. Although this was only a small-scale study designed to test the system, some interesting and fairly reassuring data on the two drugs—fenbufen (Lederfen) and benoxaprofen (Opren)—were also obtained.

Among approximately 6000 green forms returned for benoxaprofen, there were eight in which jaundice had been reported as an "event." Further inquiries eliminated some patients with alternative causes and others who were not taking the drug, and there remained only three cases in which benoxaprofen was a possible cause. Prescription-event monitoring had thus signalled a potential risk, but I considered that these few reports did not justify raising an alarm, at least until the hypothesis had been tested in a larger series.

Four months later, a small cluster of reports of benoxaprofen-associated jaundice appeared in the journals. They tended to strengthen our earlier signal, and defined the problem as one which mainly affected elderly patients. The manufacturers circulated a warning to prescribers on 21 June recommending that elderly patients should take no more than 300 mg daily. On 3 August, it was announced that the licence for benoxaprofen had been temporarily suspended by the Department of Health and Social Security.

The following preliminary statistics from the pilot study may be of interest:

(1) Ninety-five per cent of benoxaprofen and 96% of fenbufen patients had been prescribed daily doses of 600 mg or more.

(2) Fifty-six per cent of both groups had been treated for osteoarthritis. Twenty per cent of the benoxaprofen and 11% of the fenbufen group had been treated for rheumatoid arthritis.

(3) Thirty-six per cent of the benoxaprofen group were under 60 years of age, 29% were aged 60-69, and 35% were over 70. Corresponding figures for fenbufen were 33%, 25%, and 42% respectively.

(4) About 40% of patients on benoxaprofen and 43% of those on fenbufen continued their treatment beyond the 12 months of the study. Of the remainder, the mean duration of treatment was approximately 18 weeks for benoxaprofen and 15 weeks for fenbufen.

(5) In both groups the overall mortality during the 12 months of the study was 3%.

Excepting that relatively fewer patients with rheumatoid arthritis were treated with fenbufen, the two groups were very similar in other respects. Although the questionnaires were not designed to test efficacy, a number of doctors volunteered the information that patients taking benoxaprofen

who had developed photosensitivity insisted on continuing treatment rather than sacrifice pain relief or mobility.

The 61 deaths reported to the Committee on Safety of Medicines may underrepresent the mortality attributable to benoxaprofen but, if the widely quoted estimate that more than half a million patients have received it is correct, it is likely that at least 10 000 patients died from natural causes while taking benoxaprofen. The deaths attributed to benoxaprofen probably account for only a very small fraction of the total mortality in this predominantly elderly population.

We had already commenced a new and larger study of benoxaprofen designed to test whether or not the new instructions about the treatment of elderly patients had been effective. Two anti-arthritic agents not previously included in prescription-event monitoring had been selected as controls. The suspension of the licence for benoxaprofen halted this study, but, fortunately, we had already identified a large number of patients who started treatment last year. Less than 10% of them had been included in the pilot study, and we hope soon to be able to test various hypotheses in a large population.

To avoid disturbing the progress of 10 other drugs currently in the prescription-event monitoring pipeline we propose to introduce the expanded benoxaprofen study in one region at a time. This is not merely an academic exercise. It is as important to determine the characteristics (for example, age or diagnosis) of patients for whom the benefits may outweigh the risks as it is to confirm the extent of the risk in vulnerable groups.

I do hope that we can count on your help in this extension of the benoxaprofen study and in other prescription-event monitoring studies. Once again I would like to thank several thousand colleagues who have already helped in the pilot study.

W H W INMAN
Director

Drug Surveillance Research Unit,
University of Southampton,
Southampton SO2 3FL

Chest radiography as a marker of alcoholism

SIR,—Further to the findings of Dr D R M Lindsell and others (28 August-4 September, p 597) I would like to furnish the following data. I have described the medical morbidity of 235 consecutive admissions to a detoxification centre,[1] and part of that study involved a chest *x*-ray examination and serum liver function tests. The detoxification centre at the University Hospital of South Manchester was opened in October 1977. A man or woman found by the police to be "drunk and incapable" or "drunk and disorderly" and known to have had similar convictions in the past could be taken by a police officer directly to the detoxification centre. Once there, all criminal charges were dropped, and the patient was immediately examined by a doctor. Of the 235 chest radiographs taken, 24 showed rib fractures and four showed clavicular fractures, giving a total of 28 (or 12%). Only one patient had any disturbance of liver function tests.

These findings may indicate that in a population of "binge" drinkers the periods of sobriety enforced either by imprisonment or by poverty serve as a protective mechanism against the development of liver damage, which often occurs in the "chronic imbibers." These results also confirm that fractures on a chest radiograph are still more common in any population of problem drinkers than in the normal population, even in the absence of liver disease.

The drinking pattern of the group I studied was loss of control "binge" drinking, which inevitably led to drunkenness. It was felt that the fractures occurred due to injuries sustained while drinking, and this was supported by discussions with the individuals.

A D REDMOND

Intensive Care Unit,
Royal Preston Hospital,
Preston PR2 4HT

[1] Redmond AD. *The medical morbidity of 235 individuals admitted to Britain's first hospital based, purpose-built, detoxification centre.* Manchester: Victoria University, 1979, MD Thesis.

Diabetic complications: retinopathy

SIR,—While I wholeheartedly agree with Dr Peter Watkins (7 August, p 425) when he says that diabetic retinopathy needs to be actively sought if it is to be detected early enough to prevent blindness, I would take issue with his further statement that diabetic maculopathy should be treated when visual acuity begins to decline—that is, a decrease of two lines on the Snellen chart. This seems to me to be rather closing the stable door after the horse has bolted.

The British multicentre photocoagulation trial showed that the patients who do best from treatment with photocoagulation in relation to maculopathy are those with exudates encroaching on the macula but in whom the vision remains at 6/5 or 6/6. These patients had one eye treated and the other eye was left untreated and there were four further lines of deterioration in the untreated eye compared with the treated eye over five years. If one waits until these exudates have reduced the vision to 6/12 or 6/18 then the difference in deterioration between the two eyes is reduced to the order of two lines over five years. This evidence therefore suggests that exudative maculopathy should certainly be treated in the premaculopathy phase. In addition, I have noticed as a complication of treatment that hard exudates can enlarge immediately after treatment. If one waits until the hard exudates are poised on the edge of the macula there is therefore a greater risk of morbidity from treatment—another indication for earlier treatment.

It is essential that a situation is created in which the retinas of people suffering from diabetes mellitus are examined at regular intervals, especially once they are into the danger zone for diabetic retinopathy chronologically, so that their retinal lesions may be treated before they become symptomatic. It is often too late to treat disc new vessels once the symptoms of vitreous haemorrhage have begun to develop or maculopathy once the symptoms of reduced central visual acuity have begun to develop. This is because a patient may have the most severe form of proliferative retinopathy or the most devastating hard exudates poised on the edge of the fovea without having any symptoms or being aware of any serious problem.

C TOWNSEND

Western Ophthalmic Hospital,
London NW1

ABC of Diabetes: diabetic emergencies

SIR,—I refer to the letter of Dr O M P Jolobe (14 August, p 509) and his suggested programme for managing diabetic emergencies. The point that insulin should be withheld until the potassium result is known is well made, but he loses my support with his "counsel of safety."

My point is that, although probably merely an oversight, it is not specified in the letter which diabetic emergency one is dealing with. Should the stated "counsel of safety" happen to be followed in a patient in a hyperosmolar, non-ketotic state the resulting hypernatraemia might be disastrous—rather more disastrous and irreversible than the hypokalaemia he fears. Especially so if one is prepared to follow Dr Watkins' regimen for the stated two hours while waiting for the electrolyte results to be phoned through, by which time two to three litres of normal saline may have been infused.

The diagnosis of the hyperosmolar aketotic state is not difficult—once it has been thought of. With dehydration making urine unavailable for testing and plasma ketostix testing by no means universal, the diagnosis might well be overlooked by the house physician.

None of the above, of course, is earth-shattering information, but I would not want a newly qualified colleague to come away from Dr Jolobe's letter with the idea that a fast saline infusion may be given with impunity to any patient with "diabetic precoma."

In practice it is unusual for the biochemist to take two hours to give the results of blood sugar, electrolytes, or even blood gas estimations. Since it seems to me that this length of time would be unlikely to be critical in the outcome, if one is to wait for two hours a safer counsel of safety might be to do absolutely nothing in the meantime.

PAUL BAKER

Warrington General Hospital,
Warrington WA5 1QG

SIR,—Discussing with colleagues here the timing of insulin and potassium in diabetic ketoacidosis (14 August, p 509), I agree that two hours is too long to wait for a potassium result before commencing insulin. Because the vast majority of diabetics in ketoacidosis will have levels of serum potassium verging on hyperkalaemia, it is safer to commence insulin without waiting for the potassium result if one expects laboratory delays.

O M P JOLOBE

Dudley Road Hospital,
Birmingham B18 7QH

The arms race and health care

SIR,—Dr D J Holdstock (7 August, p 421) has indicated the scale of current diversion of resources into armaments. A proportion of that expenditure is devoted to weapons which if used are likely to cause very extensive civilian mortality and morbidity. The BMA Board of Science will provide next year an assessment of these possible effects, but it has not been asked to comment on the ethical aspects of supporting use of weapons with mass destructive capability developed as a result of technological progress in the last few decades. In view of the nature of the destructive effects of such weapons, these ethical issues require adequate evaluation by the profession.

Although wars in the past often had adverse and at times devastating effects on civilians, in general it could have been argued that maintaining the integrity of a nation state and safeguarding its resources by armed conflict served the interests