alcoholic liver disease than in healthy people. Thus dextropropoxyphene is not a recommended analgesic for alcoholics. When the drug alone has been taken in excessive doses in other patients saturation of the first-pass metabolism may take place.⁴

The authors further suggest that the dangers of dextropropoxyphene outweigh the analgesic activity of the drug. They cite Miller's review of the drug⁵ in support of their argument. However, in their introduction mention is made of the fact that Distalgesic is by far the most commonly prescribed drug. Recently Dr C I T Cruickshank (7 June, p 1378) suggested that Distalgesic was the drug of first choice for analgesia among his consultant colleagues. To us it would appear clear that the analgesic efficacy of the drug is responsible for its widespread use. Dextropropoxyphene finds its greatest use in musculoskeletal disorders and as an adjunct in rheumatoid arthritis; only a few trials dealing with these are found in Miller's reviews.^{5,6} Moreover, many of the papers reviewed by Miller were single-dose studies, whereas studies indicate greater analgesic activity in multiple doses.⁷

Dextropropoxyphene addiction has been reported in Britain by Whittington⁸ and in a recent short report by Dr Robert Wall and others (17 May, p 1213). The two patients concerned were, however, taking 27 and 32 Distalgesic tablets daily respectively (recommended maximum dose eight tablets per day). Moreover, there was a previous history of abuse of other drugs. We have found no reports of addiction to dextropropoxyphene at recommended therapeutic doses. A preliminary survey of rheumatoid outpatients⁹ showed no evidence of tolerance or addiction to Distalgesic.

The emotive issue of fatalities where dextropropoxyphene is said to be implicated is certainly a case for dispassionate and objective investigation and further research. Current reports, important as they are, which highlight the self-poisoning issue do tend to conceal the fact that probably a million or more patients in the United Kingdom alone safely take the drug for effective relief of pain.

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- ¹ Fraser DM, Lawson AAH. *Health Bull* 1975;33:1.
- ² Lawson AAH, et al. *Health Bull* 1979;37:121-7.
- ³ Perrier D, Gibaldi M. *J Clin Pharmacol* 1972;12:449-52.
- ⁴ Schou J, et al. *Arch Toxicol* 1978; suppl 1:343-6.
- ⁵ Miller RR, et al. *JAMA* 1970;213:996-1006.
- ⁶ Miller RR. *Am J Hosp Pharm* 1977;34:413-23.
- ⁷ Waife SP, et al. *Int J Clin Pharmacol* 1975;12:301-4.
- ⁸ Whittington RM. *Lancet* 1979;ii:743-4.
- ⁹ Farrell J, Brown AW, Sturrock RD. *Br Med J* 1979; i:1284.

Lithium and the kidney

SIR,—In an intensive investigation¹ on renal function in 101 patients treated with lithium for periods ranging from 1 to 12½ years we found, like Drs N J Birch and R P Hullin (3 May, p 1148), little evidence of serious impairment of renal function attributable to lithium therapy. Creatinine clearance, serum creatinine, maximum urine osmolality after desmopressin (DDAVP) administration, urine and plasma β_2 -microglobulin, and the urinary excretion of *N*-acetyl- β -glucosaminidase were not significantly different between patients on lithium and depressed patients never treated

with lithium. Only 1% had a urine volume greater than 3.5 litres.

Our dosage regimen, however, was different to that used by Drs Birch and Hullin. Our patients were treated with lithium carbonate (Priadel), given once a day in late evening to give a mean plasma level of 0.86 mmol/l (0.59 mg/100 ml) 12 hours after the last dose (the mean daily lithium dosage was 23.5 ± 0.8 mmol (16.2 ± 0.55 mg/100 ml) for women and 30.9 ± 1.0 mmol (21.32 ± 0.69 mg/100 ml) for men). We agree with Drs Birch and Hullin that the optimum prophylactic level may well be lower than those previously advanced but we would suggest caution before reducing 12-hour serum levels to 0.4 mmol/l (0.28 mg/100 ml) until we have further evidence.

The data indicate that our regimen is safe, provides effective prophylaxis, is convenient for the patient, and ensures good compliance.

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- ¹ Coppen A, Bishop M, Bailey J, Cattell WR, Price RG. *Acta Psychiat Scand* (in press).

Progesterone, fluid, and electrolytes in premenstrual syndrome

SIR,—In all my writings and lectures on premenstrual syndrome I find it is essential to begin with a clear definition of the syndrome to avoid confusion with menstrual distress and because progesterone therapy is only effective in correctly diagnosed cases of premenstrual syndrome.

Mr P M S O'Brien and his colleagues (10 May, p 1161) give no definition and it appears that they are confusing it with menstrual distress, as other authors have done recently.¹ Premenstrual syndrome is defined as "symptoms which recur regularly in the same phase of each menstrual cycle, followed by a symptom-free phase in each cycle."² A minimum of seven days free from symptoms is required, although many women experience two or three weeks each cycle free from symptoms. Thus the diagnosis depends on the timing of the symptoms rather than the mere presence of characteristic symptoms or their duration. Symptoms which increase during the premenstrual week but are present throughout the cycle come under the diagnosis of "menstrual distress," not premenstrual syndrome. Many, if not most, women afflicted with endogenous depression and anxiety neurosis experience a premenstrual exacerbation; this is not premenstrual syndrome. Approximately half of all newly referred patients attending the premenstrual syndrome clinic at University College Hospital, although presenting with characteristic symptoms, are found *not* to be suffering from premenstrual syndrome according to the above quoted definition when their symptoms are properly charted.

There is no relationship between the severity and duration of symptoms present in premenstrual syndrome. The explosion of symptoms in cases of epilepsy, baby battering, and overdose attempts may last only a day or two and may be unaccompanied by bloatedness or alteration in libido and so would

merit a low score on the daily change of mood scores used by Mr O'Brien and his colleagues.

No mention is made in the paper of the ages, parity, or social class of the subjects, although one may assume that they possessed a fair intelligence to enable them to differentiate on a daily linear scale depression from sadness and anxiety from tension. Libido may alter, in both the positive and the negative direction, in premenstrual syndrome and change of libido can hardly be considered characteristic of the syndrome; but no indication is given of whether increased or decreased libido rated higher on the visual analogue scales.

Endocrinologists are increasingly recognising that it is the free proportion, as opposed to the bound fraction, of the hormone which is of clinical significance. Mr O'Brien and his colleagues have reached their conclusion from a study of measurements of total serum progesterone without waiting for reliable estimations of free progesterone.

Ever since Dr Raymond Greene and I published the first paper in 1953 on the use of progesterone injections for the treatment of premenstrual syndrome, with a success rate of 83%,³ a steadily increasing stream of correctly diagnosed patients has been successfully treated with progesterone pessaries and suppositories as well as by injection. This has proved to be the most successful form of treatment for premenstrual syndrome. Menstrual distress, however, is a completely different problem.

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- ¹ Sampson G. *Br J Psychiatry* 1979;135:209-14.
- ² Dalton K. *The premenstrual syndrome and progesterone therapy*. London: Heinemann Medical Books, 1977.
- ³ Greene R, Dalton K. *Br Med J* 1953;ii:1007-14.

Anorexia nervosa in diabetes mellitus

SIR,—We were interested in the report by Drs C G Fairburn and J M Steel (10 May, p 1167), although their third case would not meet our criteria for anorexia nervosa.¹ They do not state the size of their diabetic population, but since the prevalence of anorexia nervosa is about one in 100 in the most vulnerable group—that is, girls of 11-18 in schools of good academic standing—the number of cases reported is probably that to be expected in a large diabetic clinic. The prevalence of insulin-dependent diabetes in the general population of the United Kingdom is about 1 in 400² and is probably slightly higher in the age range at risk for anorexia nervosa, 11-35 years. Our series of 400 anorexics includes two with insulin-dependent diabetes, both of whom had a history of long-standing personality problems, more characteristic of secondary than of primary anorexia nervosa, and used vomiting (and laxatives) as well as dieting to control weight.

Our first patient developed anorexia nervosa at 16, and presented in diabetic coma four years later. At 29, this girl remains 15% underweight, amenorrhoeic, depressed, and unable to break away from her mother. She manages her diabetes competently, and this does not seem a major factor in her restricted life style. The two disorders in this case are coincidental. By contrast, in the other patient diabetes appears to have been a partial determinant of anorexia nervosa. She developed diabetes at nine; it interfered with school activities, to her distress, and family attitudes towards her altered. At 13, after menarche, when she weighed 56 kg, she took a small overdose; 18 months later she developed anorexia

nervosa. She was subject to recurrent hypoglycaemia and on one occasion had a grand mal fit. After a joint medicopsychiatric admission she was followed up in both clinics in conjunction. She remained at about 42 kg (standard 50 kg) until just after taking O levels at 16; she lost 4 kg in a few weeks, and was subsequently found dead in bed.

A few missed periods and fluctuations in weight are commonplace in adolescence. Primary anorexia nervosa is liable to arise when lack of menses and weight loss come specifically to assuage high levels of adolescent anxiety. The combination of the illusion of self control, the safety of emotional regression, and reaffirmation of parental concern may be rewarding enough to maintain and intensify weight-reducing behaviour. In our second patient the strains of puberty and adolescence were added to the psychological disturbance common in unstable diabetes³—leading to overdose, wristcutting, and finally anorexia nervosa. The reason for her death was uncertain but she did not have autonomic neuropathy, which can predispose to cardio-respiratory arrest in diabetes.⁴ It seems that the association between anorexia nervosa and diabetes mellitus is neither excessively rare nor particularly common, but what would be expected by chance. However, since the secondary forms of anorexia nervosa merge into various neurotic reactions it is probable that a search among diabetics would produce an appreciable number with neurotic behaviour which included an obsession with weight.

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¹ Dally P, Gomez J, Isaacs AJ. *Anorexia nervosa*. London: Heinemann, 1979.

² Jarrett RJ, Keen H. *Lancet* 1976;ii:1009-12.

³ Gale E, Tattersall R. *Hospital Medicine*. 1979;22:589-97.

⁴ Page M, McB, Watkins PJ. *Lancet* 1978;ii:14-6.

Guar crispbread in the diabetic diet

SIR,—In 1978, largely from hospital metabolic ward studies, we concluded that guar crispbread was likely to be a useful adjunct to diabetic treatment.¹ Later, Cohen and Martin reported that they had failed to find any beneficial effect when feeding supplements of guar or bran to poorly controlled obese diabetics.² We replied³ that the form of supplement and its relationship to the meal may be all important—that is, the fibre should be taken mixed with the carbohydrate portion of the meal.

Subsequently Mr Nathan Mantel (15 December, p 1589) stated that he found some "disturbing aspects" in our original report with "several numerical discrepancies in the data."

Firstly, he notes that the large mean reduction in urinary glucose output (38%, $p < 0.002$) was due largely to a fall in one individual. However, exclusion of this individual still results in a mean fall of 33% ($p < 0.01$) for the remaining eight patients. Secondly, he comments that smaller urinary glucose concentrations were seen in a patient prior to hospital admission than were measured on the metabolic ward. It is well recognised that some patients, especially those who lead active lives, show greatly increased glycosuria when such activity is

restricted by a period of hospitalisation. Thirdly, he suggests the possibility that our very limited follow-up study was terminated when individual patients showed an improvement. The follow-up data in our original paper were preliminary and we gave the most up-to-date figures we had at the time. Not all patients were started synchronously; hence the disparity in times.

We are also asked for data on "the entire course of the results for each patient," and these have now been published (7 June, p 1353).

Though we acknowledge deficiencies in our studies, we would not wish Mr Mantel's comments to obscure what we consider to be a major problem of ensuring that guar is distributed throughout the day with the carbohydrate portion of the meals. To this end, if guar is to be used successfully, further guar products will have to be developed to supplement the crispbread.

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¹ Jenkins DJA, Wolever TMS, Nineham R, et al. *Br Med J* 1978;ii:1744-6.

² Cohen M, Martin FIR. *Br Med J* 1979;i:616.

³ Hockaday TDR, Jenkins DJA, Wolever TMS, Nineham R, Taylor RH, Bacon S. *Br Med J* 1979;ii:1353.

Dietary management of maturity-onset diabetes

SIR,—Ms E Anne Wilson and others have recently described their very considerable experience in Belfast with low-carbohydrate diets for diabetic patients (7 June, p 1367). Such diets seem to have been recommended almost universally for diabetics in Western countries at least since the eighteenth century; and many authorities, at least in the United Kingdom, are clearly still recommending them. We would agree with Ms Wilson and her colleagues that achieving ideal body weight (preferably by means of a "simple approach") is undoubtedly the most important aim of a diet for maturity-onset (type II) diabetes, and that if it is achieved this obviates the need for drug therapy in the great majority of cases. However, we wonder whether in 1980 a low-carbohydrate diet is still the best means of achieving this.

Research done elsewhere¹ and in Oxford^{2,3} has suggested that diets relatively high in total carbohydrate (derived chiefly from cereal and vegetable sources) and dietary fibre result in lower fasting and preprandial blood glucoses and lower cholesterol levels than a low-carbohydrate diet. There is still much to be learned about the long-term acceptability of such diets, but in Northern Ireland, where

intake of starches is usually high, it may be that a simple diabetic diet could be based on the "high" rather than the "low" carbohydrate principle.

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¹ Kiehlm TG, Anderson JW, Ward K. *Am J Clin Nutr* 1976;29:895-9.

² Simpson RW, Mann JI, Eaton J, Moore RA, Carter R, Hockaday TDR. *Br Med J* 1979;i:1753-6.

³ Simpson RW, Mann JI, Eaton J. *Br Med J* 1979;ii:523-5.

Pseudomonas septicaemia

SIR,—The failure of antibiotic therapy to reduce the mortality of *Pseudomonas* bacteraemia (discussed in your leading article of 24 May, p 1240) could be the result of too enthusiastic therapy, producing too much endotoxin for debilitated subjects.

This possibility was first put forward, even before the discovery of penicillin, in 1936 by the late James Reilly¹ in the course of his researches into typhoid fever and confirmed following the introduction of chloramphenicol.² In several instances patients receiving loading doses of this antibiotic suffered severe cardiovascular collapse, which in some cases was fatal. The possibility that this might arise from endotoxin released from the typhoid bacilli was suggested by Galpin in 1949.³ A few years later Reilly confirmed his hypothesis by showing that animals infected with Gram-negative organisms that received a weight-equivalent loading dose of chloromycetin consistently underwent fatal cardiovascular collapse although all the organs were sterilised.⁴

A summary of this work appeared in 1978,⁵ a plea being made for discontinuing the use of loading doses of antibiotics in treatment of Gram-negative bacteraemia and for reducing dosage or withdrawing it if signs of toxæmia appear. It is unfortunate that there is no easy method of estimating blood endotoxin levels. However, as function of the kidney is always affected before that of any other organs by endotoxin,⁶ a rise in blood creatinine could provide an adequate warning sign.

After all, typhoid is a Gram-negative infection and the pathological features, so carefully studied by Reilly and his colleagues, were shown by them to be a constant feature of all Gram-negative infections.⁷

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¹ Reilly J, Rivalier J, Compagnon A, Phan HC, Friedman E, Du Buit H. *Ann Med* 1936;30:138.

² Reilly J, Compagnon A, Tournier T, Bastin R, Du Buit H. *Ann Med* 1950;51:597-654.

³ Galpine JF. *Br Med J* 1949;ii:1047-8.

⁴ Reilly J, Compagnon A, Tournier P, Du Buit H. *Ann Med* 1954;55:22.

⁵ Hopkin DAB. *Lancet* 1978;ii:1193-4.

⁶ Reilly J, Compagnon A, Laporte A, Du Buit H. *Le rôle du système nerveux en pathologie rénale*. Paris: 1942;1, 2, 15, 16.

⁷ Hopkin, DAB, Laplane, R. *Ann R Coll Surg* 1978;60:108-16.

SIR,—A shift of emphasis away from newer antibiotics that are only impressive in vitro towards consideration of provision of appropriate antibody is not only welcome, as