gists stated that "the appearances are those of idiopathic retroperitoneal fibrosis. The histological appearances of practolol peritonitis are different..." This is not the appropriate comparison. The patient obviously had fibrosis in the retroperitoneal space and not the peritoneal cavity. The point is that idiopathic and drug-related (for example, methysergide) retroperitoneal fibrosis present the same histological picture.¹

Oxprenolol is also listed in reports of the Committee on Safety of Medicines as being ingested by patients developing sclerosing peritonitis or retroperitoneal fibrosis; this does not necessarily imply a causal relationship or that other drugs were not also being taken. Practolol, atenolol, and oxprenolol have thus been associated with fibrosing syndromes. A comparison of the structure of these beta-blockers with that of those which have not been so associated is therefore of interest.

The majority of beta-blockers contain an unsaturated six carbon ring with two side chains. The ring and one side chain, R, is common to metoprolol, atenolol, practolol, propranolol, and some other beta-blockers. R is $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{NHCH}(\text{CH}_3)_2$. Acebutalol contains this side chain and an additional ring substituent ortho to it.

The problems with practolol therefore presumably arose because of the unique structure of the second side chain. Practolol, atenolol, metoprolol, and acebutalol are substituted para to the first side chain, R, and oxprenolol ortho. Side chain sizes of the three drugs mentioned in relation to fibrosing syndromes are 58, 57, and 58 daltons for practolol, oxprenolol, and atenolol respectively. They all contain a double bond and would possess a somewhat similar electron cloud configuration. The side chains of practolol and atenolol are essentially identical—that is, acetamide (NH_2COCH_3)—with attachment to the ring via the nitrogen atom in the former case and the methyl carbon in the latter.

Oxprenolol has a side chain of similar size ($-\text{OCH}_2\text{CH}=\text{CH}_2$), also with a double bond.

On the other hand, metoprolol has a side chain of 59 daltons but no double bond and acebutalol a more bulky side chain of 86 daltons. Propranolol is a double ring structure.

The three beta-blockers under consideration therefore show a high degree of similarity in structure and further reports of their association with fibrosing syndromes will be of interest.

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¹ Graham JR, et al. *N Engl J Med* 1966;274:359-68.

Repeat exposure to Althesin

SIR,—For the past 18 months our department has offered a service to anaesthetists in the Avon area and surrounding districts in investigating the immunological basis of

hypersensitivity reactions to anaesthetic drugs. We are increasingly concerned about the number of such reactions which follow repeat exposure to Althesin (alphaxalone and alphadolone acetate). Routine investigations include immunological analysis of serial blood samples for consumption and conversion of the C3 and C4 complement components.

Of 22 patients with clinical signs of hypersensitivity to Althesin subsequently confirmed by laboratory investigation, 17 had received the drug on at least one previous occasion, while five had no known previous exposure. Nine of these 17 patients had severe clinical reactions, involving cardiovascular collapse; and, of these, eight had already received Althesin within the previous two months. Of the five who reacted on first exposure, only one had severe symptoms. The majority of our patients were receiving anaesthesia for minor gynaecological or orthopaedic procedures, and all were otherwise fit with no apparent haematological or immunological abnormality.

At present we do not have figures to show the frequency of uneventful anaesthesia following either first or repeat exposure to Althesin in the Avon area, but our results so far indicate that there is a greater possibility of hypersensitivity reactions in patients who are re-exposed to Althesin.

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Acute renal failure

SIR,—The leading article on acute renal failure (7 June, p 1333) raises important issues in relation to diagnostic screening and dialysis timing. Expert overview of uraemic patients is to be endorsed. An interested nephrologist reviewing "uraemic" biochemistry reports from his area laboratory daily enables timely advice to be given and permits realistic planning of acute renal services.

In the Sunderland area (population 400 000) this practice reveals 1200-1500 patients annually with a blood urea of 15 mmol/l (90 mg/100 ml) or more. The dominant causes are myocardial infarction 12%, stroke 8.7%, cardiac failure 9.8%, diabetes 10%, gastrointestinal tract and hepatic pathology 12.5%. From 50 to 60 cases of severe acute renal failure (blood urea ≥ 30 mmol/l (181 mg/100 ml) are diagnosed annually. There is rarely diagnostic difficulty affecting management of the uraemia, 78% being the result of hypovolaemia with or without sepsis.

Serum protein changes receive little comment, although an earlier review¹ did discuss the possible role of albumin infusion in preventing acute renal failure. In this area 72% of patients with severe acute renal failure are hypoalbuminaemic at the time of diagnosis. The effect of albumin on intrarenal haemodynamics still requires clarification. Nephrologists are all familiar with the dramatic effects of a small albumin load in an apparently diuretic-resistant nephrotic patient.

The problem of timing dialysis is raised and mention made of a urea level of 30 mmol/l. For the past two decades there has been little impact on the high mortality in acute renal failure despite "prophylactic daily dialysis." While patients who have chronic renal failure

seem to tolerate uraemia, an ongoing study in this unit suggests that those with acute renal failure are better if kept non-uraemic. This entails continuous haemodialysis or combined haemodialysis and peritoneal dialysis, treatment being continued until diuresis occurs, maintaining a blood urea level between 0 and 10 mmol/l (up to 60 mg/100 ml).

Preliminary results demonstrate that survival, well being, taste and appetite, haemoglobin levels, and resolution of infection and wounds are improved compared with those treated by short daily or alternate-day dialysis. This would suggest that if volume replacement and ionotropic drugs fail dialysis should be instituted at an earlier stage than has generally been recommended.

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¹ Anonymous. *Br Med J* 1980;280:2-3.

Distalgesic poisoning—cause for concern

SIR,—The tragic circumstances whereby individuals die as a result of poisoning, either accidental or deliberate, is bound to bring calls that the causative agent be removed from temptation. On the other hand, where that causative agent is a useful and safe medicinal product when correctly used the clamour for product withdrawal or reclassification has to be balanced against the scientific and clinical arguments for and against. At the present time, so far as dextropropoxyphene is concerned such an impartial review has yet to appear in the literature. The present authors are working with this objective. However, we would comment on some of the issues raised by Drs R J Young and A A H Lawson (12 April, p 1045).

The majority of the people who die from any drug overdose do so outside hospital.¹ The authors fail to mention this and subsequently appear to distort the mortality due to Distalgesic overdose in their paper. The death rate in all poisonings of 0.76% represents mortality in hospitals only.² This is compared with mortality in the community and hospital for Distalgesic (12.7%). The authors continue by calculating that 53.4% of the patients admitted after January 1976 were in a high-risk category (31/58). However, they then calculate the mortality from this group of 31 patients, but include the five deaths outside hospital in which Distalgesic was implicated. Further errors are made when the authors calculate the "potential death rate" (whatever this means). The five deaths occurring outside the hospital are again added, to provide an inflated figure of 60%.

Oral dextropropoxyphene undergoes extensive first-pass metabolism.³ Consequently changes would be expected to occur in the pharmacokinetics of the drug in patients with alcoholic liver disease. Six of the eight deaths attributed to Distalgesic in the paper by Drs Young and Lawson were in recognised alcoholics. We suggest, therefore, that the amount of unmetabolised drug reaching the systemic blood circulation and subsequently the central nervous system after an oral dose would be much higher in patients with

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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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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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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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