workers.¹ Over 15 different cytotoxic drugs had been used besides asparaginase in the 190 children after relapse, but the response was poor even when the drugs had not been used previously. It seems that leukaemia cells after relapse are resistant not only to most previously used drugs, as pointed out by Drs Cornblett and Chessells, but also to a wide variety of other cytotoxic drugs. The usual rationale for changing therapy in ALL after relapse assumes that resistance occurs at the metabolic site of action, and thus drugs acting at a different metabolic locus in the cell cycle should produce a therapeutic response. The poor response to drugs other than asparaginase may be more in favour of resistance occurring because of reduced uptake of drugs by the leukaemia cells. On the other hand the action of asparaginase is extracellular and its effect on leukaemia cells is independent of drug uptake by lymphoblasts. Certainly new approaches such as bone marrow transplantation are justifiable in selected cases; but the prospect of transplant in all relapses is daunting and is neither indicated nor feasible at present. The alternatives are palliative therapy or using protocols which test hypotheses about relapse. With this in mind a protocol could be designed to circumvent therapeutic resistance at cell membrane level. Asparaginase, glutaminase, asparagine synthetase inhibitors, and high-dose methotrexate could be tried in appropriate combinations. Some parents and patients may prefer this option to either palliative therapy or bone marrow transplantation.

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¹ Kung, F H, *et al*, *Cancer*, 1978, **41**, 428.

Quality of cervical mucus and Huhner's test

SIR,—The opinion of Mr G T Kovacs and his colleagues (1 April, p 818) that "any post-coital analysis which shows any motile spermatozoa per high-power field should be considered as indicating a normal result" puts a new interpretation on Huhner's postcoital test. It has been thought for some time that the number of sperms indicating a "good count" has been placed much higher than is necessary.¹ However, it would seem from the authors' statement that "the quality and quantity of mucus did not correlate with sperm counts or motility" that it is unnecessary to take at least the quality of the mucus into account when assessing the results of the test.

Many authors have demonstrated the differing properties of the mucus during the course of the menstrual cycle which enable it to play an active role in the migration of sperm into it and hence into the cervix after intercourse, this role depending on the fibrillar structure and its molecular alignment.² Moghissi³ found that sperm penetration occurs at approximately five or six days before ovulation and that penetrability increases gradually to a maximum at ovulation, with inhibition of penetration one or two days after ovulation. Dubois *et al*⁴ used a sensitive light-scattering technique to show variable migration rates of sperm into mucus.

Mr Kovacs and his colleagues state that all tests were performed during the ovulatory

phase of the cycle, but the methods they used to assess this phase⁵ would not enable it to be delineated precisely. The differing results for the two blood-stained specimens of mucus are therefore of interest. Without knowing the precise time of ovulation it is not certain whether these were specimens of premenstrual or of preovulatory mucus. Thus, while most of those mucus specimens which reflected enhanced numbers and higher percentage of motile spermatozoa were probably of type E of Odeblad,² in the absence of evidence to the contrary—for example, spinnbarkeit, fern test, or the woman's assessment of the quality of the mucus in accordance with the rules of the ovulation method¹—it is very possible that some of the specimens were of type G of Odeblad.

Huhner's test cannot be correctly interpreted unless the current state of the woman in regard to the cervical mucus is taken into account.

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¹ Billings, E L, Billings, J J, and Catarinich, M, in *Atlas of the Ovulation Method*, 3rd edn. Melbourne, Advocate Press, 1977.

² Odeblad, E, in *Cervical Mucus in Human Reproduction*, World Health Organisation Colloquium, Geneva, 1972, p 58. Copenhagen, Scriptor, 1973.

³ Moghissi, K S, in *Cervical Mucus in Human Reproduction*, World Health Organisation Colloquium, Geneva, 1972, p 128. Copenhagen, Scriptor, 1973.

⁴ Dubois, M, *et al*, *Nature*, 1974, **252**, 711.

⁵ Kovacs, G T, *British Medical Journal*, 1978, **1**, 1421.

Diflunisal (Dolobid) overdose

SIR,—A 47-year-old woman with chronic low backache took 116 diflunisal tablets, each containing 250 mg, in quick succession over 40 min on account of persisting pain. She also took pseudoephedrine hydrochloride for a cold. She felt giddy an hour later, having difficulty in maintaining balance, and eventually sank to her knees.

Three hours later she was admitted to the casualty department, where she was observed to be drowsy with blurred vision. Blood pressure was 130/90 mm Hg. Gastric lavage revealed food particles but no tablets. The patient deteriorated, becoming stuporose and then deeply unconscious over 10 h, unresponsive to painful stimuli. Forced diuresis was given but produced little clinical effect. Spontaneous recovery occurred and by 24 h consciousness had been regained.

Diflunisal is a new long-acting analgesic with a plasma half life of about 10 h. The recommended dose is two tablets a day. The compound, a salicylic acid derivative, is quickly absorbed, undergoes hepatic conjugation and is largely excreted in urine as the glucuronide metabolite. In considerable overdose depression of the central nervous system occurs, but the uneventful recovery in this case suggests that the drug is relatively non-toxic.

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Social problems of schizophrenics

SIR,—With reference to your leading article (8 July, p 76), in which you refer to the study of schizophrenia in the community carried out in Salford by myself and my colleagues,¹ you

might be interested to know that the problems of social withdrawal and consequent social isolation experienced by the more neurotically handicapped patients in our sample was explored by us in some depth.²

I fully agree that your very apt quotation from Thoreau ("Most men lead lives of quiet desperation") describes the lives of many of these patients, but it would be regrettable if the minimisation of these very profound personal/social problems (whether labelled "neurotic" or explained away as an inevitable cerebral defect (Dr G J Lodge, 22 July, p 280)) should gain these people any sort of "dismissive attitude."

To be more optimistic, I would hope that the acknowledgment and recognition of the seriousness of these problems might create a climate for the rethinking and reconstitution of more appropriate rehabilitation programmes and consequently help the mentally ill living in the community to avoid a chronic backward type of existence in the homes of our cities.

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¹ Cheadle, A J, Freeman, H L, and Korner, J R, *British Journal of Psychiatry*, 1978, **132**, 221.

² Korner, J R, Freeman, M C, and Cheadle, A J, *International Journal of Mental Health*, 1978, **6**, 45.

Relative activity of atenolol and metoprolol

SIR,—I would welcome the opportunity to reply to the comments made by Professor J H Barber (29 July, p 357) on my letter about the relative activities of atenolol and metoprolol (8 July, p 128).

Firstly, evidence is available from the recent study by Dr T Reybrouck and others (27 May, p 1386), in which hypertensive patients were given metoprolol for four weeks (300 mg once a day—higher than the doses used by Professor Barber), which is at variance with his own and more like my results obtained in volunteers. In this study after the four-week treatment the decrease over placebo in the mean heart rate increase on exercise was 60 beats/min 2 h after a dose and 28 beats/min 22 h afterwards—that is, a much lesser degree of beta-blockade at 22 h than at 2 h. The difference between the various sets of results is probably consequent upon different trial designs.

Professor Barber describes his study as "a well-designed general practice study." From the little detail given of the study the portion dealing with exercise testing falls short of the requirements to allow any conclusion about the relative potency of atenolol and metoprolol in patients on chronic therapy. In the first instance the study is a between-patient study (six only in each group) and further the level of exercise chosen (75 W for each patient—136 W in the trial of Dr Reybrouck and his colleagues) is indeed low (even perhaps lower than the kind of exercise taken by the patients in their daily lives) and such that the heart rates achieved by the patients if they had not been taking therapy could be achieved by "vagal withdrawal" with minimal sympathetic nerve stimulation. This is given support by the small increases in heart rate after taking the beta-blocker which would give actual exercise heart rates in the region of 90 beats/min—at least 10-20 beats below the intrinsic heart rate.¹ Consequently it is not surprising