of them,⁴ we suggest, is irrelevant and another two, from signatories to this letter,^{5,6} did in honesty mention this as a possibility without substantiating it with any evidence. In fact, in all our work with oral methionine in paracetamol poisoning we have never found any toxicity from it whatsoever.

In conclusion, we are happy to leave it to your readers to make up their own minds on the facts before them. After all, it is almost a question of "you pays your money and takes your choice." In these days of economic stringency, above all in the National Health Service, it might be worth mentioning that the course of oral methionine that we recommend in these circumstances will attract a charge of some 80p whereas the corresponding course of *N*-acetylcysteine as a "special intravenous preparation (Parvolex, Duncan Flockhart)" will cost more than £30.

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- ¹ Vale, J A, Meredith, T J, and Goulding, R, *Archives of Internal Medicine*, suppl, in press.
² Prescott, L F, et al, *Lancet*, 1971, 1, 519.
³ Fitzgerald, G A, and Drury, M I, *Journal of the Irish Medical Association*, 1977, 70, 448.
⁴ Hardwick, D F, et al, *Metabolism*, 1970, 19, 381.
⁵ Meredith, T J, Newmann, B, and Goulding, R, *British Medical Journal*, 1978, 2, 478.
⁶ Crome, P, et al, *Lancet*, 1976, 2, 829.
⁷ Rumack, B H, and Peterson, R G, *Pediatrics*, 1978, 62, suppl, p 898.
⁸ Prescott, L F, et al, *Lancet*, 1976, 2, 109.

Monitoring of psychotropic drug prescribing in general practice

SIR,—In his article on monitoring psychotropic drugs Dr P J Dennis makes the strong plea that "If repeat prescribing is carried out in a practice, then a facility for reassessment of treatment should be incorporated" (3 November, p 1115). He suggested a system using a repeat prescribing card for each patient as one method of achieving this.

The Birmingham research unit of the Royal College of General Practitioners is developing a programme of practice activity analyses and one of these concerns psychotropic drug prescribing. In the preliminary trials of this recording instrument, which involved about 100 general practitioners, the percentage distribution of psychotropic drug usage was similar to that in Dr Dennis's study. Eighteen per cent of the total psychotropic drug prescriptions were new prescriptions given at face-to-face consultations, and 36% were issued during consultations concerned with continuing management.¹ The residual 46% were repeat prescriptions given without consultation with a doctor. However, these average rates hide an enormous range of variability between different recorders. We would suggest that the RCGP practice activity analysis form, available from the Birmingham research unit, is an economic and simple way of establishing for any general practitioner his personal pattern of prescribing of psychotropic drugs.

Finally, it may well be that reliance on self-referral by elderly patients is misplaced, but this was not established by Shaw and Opit's

study.² We have questioned the value and relevance of this study elsewhere.^{3,4}

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- ¹ Royal College of General Practitioners, Birmingham Research Unit, *Journal of the Royal College of General Practitioners*, 1978, 28, 122.
² Shaw, S M, and Opit, L J, *British Medical Journal*, 1976, 1, 505.
³ *Journal of the Royal College of General Practitioners*, 1976, 26, 506.
⁴ Crombie, D L, et al, *British Medical Journal*, 1976, 1, 713.

Perinatal epidemiology in Wonderland

SIR,—Professor Leiv S Bakketeig and Mr Howard J Hoffman (22 September, p 693) have analysed the data on the Norwegian linked file in what they claim to be a more meaningful way than the traditional cross-sectional method. They showed that if the rate of fetal death is plotted for each pregnancy rank, according to the total number of pregnancies the woman eventually has, the risk to each succeeding pregnancy falls. This method had actually been demonstrated and discussed earlier by James^{1,2} and Billewicz.³

As Professor Nathan Mantel pointed out (3 November, p 1147), such a method is introducing enormous bias in that it is the woman herself who has the main choice in the number of pregnancies she has. The woman who has a fetal loss is far more likely to keep trying—until she has one or more successes. On the other hand, the woman who starts with one or two successes is then likely to stop reproducing.

The disturbing feature of the Norwegian paper is that the data have been interpreted by others in this country as indicating that for any individual woman the risk of fetal death decreases with successive pregnancies. It is this thesis in particular that I wish to dispute.

Given a group of pregnant women, even the most intuitive clinician is unlikely to be able to determine how many pregnancies the woman will eventually have, and thence which line of the accompanying figure she will be following. What he will know is how many pregnancies she has already had, and what their outcome was. The data from the 1958 survey⁴ show that even when the woman has had no previous stillbirths or neonatal deaths the risk of such an outcome to the current pregnancy rises from parity 1 to parity 4 or more (see accompanying table). In other words, given limited resources the clinician should still concentrate them in the traditional manner (that is, on women having their first pregnancy and on women of high parity).

Rate (per 1000) of stillbirth and neonatal death by parity and previous history, with number of deaths in parentheses (1958 British Perinatal Mortality Survey)⁴

Parity	Previous history		All
	1 or more stillbirths or neonatal deaths	No stillbirths or neonatal deaths	
0	—	37.0 (2793)	37.0 (2793)
1	70.4 (168)	24.1 (1450)	25.9 (1619)
2	67.1 (228)	30.8 (875)	34.7 (1104)
3	77.5 (159)	33.4 (463)	39.1 (622)
4	85.5 (118)	40.4 (272)	48.1 (390)
5-6	91.1 (129)	43.6 (250)	52.9 (379)
7+	59.0 (126)	103.8 (81)	71.0 (207)

How then has this paradox been produced? Lewis Carroll would have enjoyed teasing out the answer. I would like to stress what I consider to be the salient factors. Basically women desire families with living children. Thus the total number of pregnancies to women who started their reproductive life with a perinatal loss will be greater than the total number of pregnancies to women with successful first pregnancies. A combination of the two groups produces the extraordinary picture shown in the figure.

Perinatal mortality rate according to total number of pregnancies (adapted from Bakketeig and Hoffman).

More detailed evidence that such a picture can be produced in the way I have suggested has been submitted for publication. Meanwhile, it would be a pity if clinicians and epidemiologists alike were to consider the analysis by Professor Bakketeig and Mr Hoffman as anything other than an amusing artefact.

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- ¹ James, W H, *Annals of Human Genetics*, London, 1968, 32, 151.
² James, W H, *Journal of the Royal Statistical Society Series C*, 1969, 18, 276.
³ Billewicz, W Z, *British Journal of Preventive and Social Medicine*, 1973, 49, 27.
⁴ Butler, N R, and Bonham, D G, *Perinatal Mortality: The First Report of the British Perinatal Mortality Survey*. Edinburgh, E and S Livingstone, 1963.

SIR,—For some years it has been recognised that attempts to relate risk of pregnancy loss or immaturity to maternal age, parity, or birth interval, based on cross-sectional studies, are of limited value in view of the powerful confounding artefact effects relating principally to the ability of women to exercise a measure of choice in the matter of whether and when to initiate a pregnancy. Mr N Mantel (3 November, p 1147) has exposed a flaw in the argument of Professor Leiv Bakketeig and Mr H J Hoffman (22 September, p 693), who have aimed to compensate for the artefacts by a longitudinal approach.

Clearly the problem of how to estimate the true underlying dependence of risk on birth order is not trivial. A sequential approach seems indicated. It is desirable to have data on entire reproductive histories, and a set of data from which an appropriate analysis may readily be recovered was published by Roman et al,¹ whose study is quoted in the present

paper. A total of 3068 female doctors, a highly motivated group, were asked for details of their entire reproductive history. The outcome studied was fetal death—stillbirth, ectopic pregnancy, or detected spontaneous abortion. For present purposes the main limitation is the fact that reproductive histories are incomplete for some members of the later-born cohorts in the study.

The two most pertinent features of the results of Professor Bakketeig and Mr Hoffman may be observed in those of Roman also. Analysis of all pregnancies irrespective of final gravidity indicated a U-shaped dependence of failure rate on birth order, overall rates of fetal loss being 13.6%, 12.5%, 13.9%, and 18.3% in the first four pregnancies. Within groups defined according to gravidity reached by the time of the study the failure rate fell with increasing pregnancy order.

In order to compare loss rates in pregnancies 1 and 2 it is most appropriate to take into account all women of final gravidity 2 or more. In analysing Roman's data thus, we deduct the women of gravidity 1 from the "all pregnancies" figures, obtaining loss rates of 13.8% and 12.5% in pregnancies 1 and 2. Similarly, losses in pregnancies 2 and 3 may be compared among all women of ultimate gravidity 3 or higher—17.7% and 13.9%. The corresponding figures for pregnancies 3 and 4, among all women with four or more pregnancies, are 22.0% and 18.3%. Thus the biological processes involved are best represented by decreases in loss rate by factors of .904, .783, and .834 from each pregnancy to the next, or a decrease from 26.8% to 18.3%, a factor of .683, from first to fourth.

Nevertheless, it will be noted that each successive group defined according to ultimate gravidity has higher losses at a given birth order than the previous group. When we observe outcome in women pregnant for the fourth time, we observe the balance of a biological process that has apparently improved with each successive pregnancy against the possible implications of self-selection for such a gravidity.

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¹ Roman, E, et al, *Early Human Development*, 1978, 2, 131.

Non-compliance: does it matter?

SIR,—In questioning the value of programmes to improve compliance, your leading article (10 November, p 1168) deals exclusively with drug treatment. There are nevertheless other aspects of management which require the active co-operation of patients, one of which is that patients should attend for treatment in the first place.

A significant number of patients who are referred to psychiatric outpatient clinics fail to keep their first appointment. During a recent 12-month period, for instance, 26% of new outpatient appointments at this department were not kept, a figure of similar magnitude has been reported at other centres.^{1,2} Although many of these patients may have managed without specialist help—indeed it has been argued that a waiting list is a useful screening device for this very reason³—this degree of non-compliance with referral procedures represents, at the very least, an appreciable waste of administrative, clinical,

and teaching time. It is, however, probably that a significant proportion of patients who fail to co-operate in this way will remain unwell.⁴ Moreover, when outpatient time has been reserved for patients who do not use it, other patients—who may well have benefited from an earlier appointment—are subjected to unnecessary delay. Finally, a non-compliance rate of 26% raises important questions about the whole process of psychiatric referral such as the selection of patients for referral and the suitability of existing administrative procedures.

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¹ Skuse, D H, *British Medical Journal*, 1975, 3, 469.

² Whyte, R, *British Journal of Psychiatry*, 1975, 127, 160.

³ Robin, A, *British Journal of Psychiatry*, 1976, 128, 138.

⁴ Bridges, P, and Woollacott, S, *Comprehensive Psychiatry*, 1972, 13, 63.

Adverse reactions to drugs in general practice

SIR,—I welcome Dr C R Martys's study of adverse reactions to drugs in general practice (10 November, p 1194). It is good that the extent of such adverse reactions is being demonstrated and studied. Dr Martys found that 41% of the 817 patients given single-drug treatment were thought to have "certainly" or "probably" had a reaction to the drug prescribed. But unfortunately the frequency of adverse reactions to prescribed drugs is likely to be greater than this.

Dr Martys states that his study was restricted to patients given a single drug because "Most patients in general practice present with relatively straightforward clinical problems, for which treatment with a single drug is entirely appropriate." He gives no figures from his own practice of the proportion of patients receiving more than one drug. In a national study of people on the electoral register in 1969 it was found that the average number of prescribed medicines taken in two weeks by those taking any prescribed medicine was 2.0.¹ And in both this study and another similar one in 1977² half of those taking any prescribed medicine in a two-week period had taken another prescribed medicine.³ Since many adverse reactions are likely to result from interactions between drugs, Dr Martys's estimate of 41% must be regarded as a serious underestimate of the frequency with which such reactions occur.

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¹ Dunnell, K, and Cartwright, A, *Medicine Takers, Prescribers and Hoarders*. London, Routledge and Kegan Paul, 1972.

² Cartwright, A, and Anderson, R, *Journal of the Royal College of General Practitioners*, 1979, Occasional Paper 8.

³ Anderson, R. (In draft.)

Poisoning with chlormethiazole

SIR,—The letter by Dr G T McInnes and others (10 November, p 1218) reports two cases of cardiac arrest during the intravenous infusion of chlormethiazole. That the arrhythmias which occurred were the direct result of the drug must be seriously questioned.

In case 1 ventricular tachycardia developed

after approximately 10 g of chlormethiazole had been given over 16 hours. The tachycardia presumably changed to ventricular fibrillation or asystole if cardiac arrest occurred. How was the patient resuscitated and what was the time course? As the patient survived, one must presume that normal cardiac function resumed quickly despite the fact that the chlormethiazole plasma concentration would take several hours to decrease substantially.

In case 2 the arrest occurred after only 0.66 g of chlormethiazole given over one hour, a dose which in my experience would be expected to cause only a minor degree of sedation. This patient, with severe facial injuries, must have had at least a potential threat to his airway and one wonders if the restlessness for which chlormethiazole was given was not in fact due to hypoxia. The fact that no preceding arrhythmia is reported, no details are given of the cardiac arrest, and resuscitation was unsuccessful brings into doubt the degree of patient monitoring. The bland statement that there was no evidence of respiratory depression prior to arrest is not exactly conclusive.

Dr McInnes and his colleagues are correct in assuming a longer-than-usual half life for chlormethiazole in patients who receive large doses intravenously or who have liver dysfunction. It is difficult to see the relevance of this in regard to cardiac arrest, as neither of their patients would have achieved high plasma concentrations and in case 2 the concentration must have been very low.

Having used chlormethiazole for many years in anaesthesia and in seriously ill patients undergoing intensive care, employing doses much in excess of those reported in these two cases, one is distressed to read that it can cause "potentially lethal cardiac dysrhythmias." Such a charge is surely a complete condemnation of the drug, which if substantiated should lead to its total withdrawal as a sedative. That such an outcome might result from the very inadequate clinical details given by Dr McInnes and his colleagues would be most unfortunate.

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A reminder to remind the patient

SIR,—I hope you may allow me to respond to the somewhat misguided and subjective view of our poster and pamphlet *Alcohol and Drugs Do Not Mix—A Reminder to the Physician to Remind the Patient* (3 November, p 1138).

This is misguided because the reviewer has obviously not consulted the covering letter, which details the aims and objects of the pamphlet, nor has he given the name of the writer of the pamphlet, which would indicate the authenticity of the data contained in it. The writer is Professor P F D'Arcy, DSc, BPharm, professor of pharmacy at the Queen's University, Belfast, a noted authority on dangerous and adverse drug reactions and a member of the Medicines Commission.

That the pamphlet was intended to remind the physician to remind the patient is clearly stated on the pamphlet. Thus it did not arrogantly assume total ignorance on the part of the medical profession of one of its major concerns, the prescribing of curative drugs. It is quite clearly established that doctors do have many things on their minds and may forget to give these instructions. It is also well