showed an abnormal ratio after oral testing and 29.3% (s.d. = 17.7%) in those with a normal ratio, over a five-hour period, concluding that there was no significant difference between these two groups of patients in the metabolism or excretion of this probe molecule after absorption. These recovery rates after intravenous injection are extremely low; indeed, in their previous work (Cobden *et al,* 1985) a mean cellobiose recovery rate of 52.0% (s.d. = 14.3%) was reported, and Menzies (unpublished) obtained an 83.4% recovery rate in normal subjects over the same time period. Irrespective of whether the patients had a normal or abnormal cellobiose/mannitol recovery ratio, due to the low cellobiose recovery intravenously in both populations one might conclude that considerable systemic metabolism of this probe marker had occurred. However, cellobiose, in common with most other disaccharides, is not known to be significantly metabolised within the body (Menzies, 1974). As intravenous cellobiose was not administered to a population free of psychiatric illness, these results would equally well support the hypothesis that patients with chronic psychiatric illness demonstrate abnormal systemic metabolism of cellobiose.

The authors acknowledged the low recovery rates of both probe molecules, postulating that this may have been due to inaccurately timed urine collections, leading to a similar reduction in recovery of both molecules, leaving the cellobiose/mannitol ratio unaffected. However, the mean mannitol recovery rate of 49.45% (mean, abnormal/normal patients) is almost identical to the 49.9% recovery in normal controls (Cobden *et al,* 1985), but the cellobiose recovery ratio is some 23.35% lower (52.0%, compared with 28.65%). This disproportionate lowering of the cellobiose recovery rate is not compatible with error introduced by inaccurately timed urine collections.

Furthermore, it is unclear whether the test solution administered was hyperosmolar. If it was, it is important that subjects refrain from drinking water for at least two and a half hours before and after the commencement of the study, as water would act to dilute the hyperosmolar stress, leading to difficulties in interpreting the results. As the authors have alluded to difficulties in obtaining complete timed urine collections in this group of patients, it would be reassuring to know that 'fasting' included preventing the subjects swallowing water throughout this period, a somewhat natural reaction after ingesting an extremely sweet sugary drink.

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SIR: We are grateful to McGauley for drawing attention to the low five-hour recovery of cellobiose after i.v. injection in patients with chronic psychiatric disorder. As stated, the recovery is some 23% lower than in the previous study in fit, co-operative volunteers. In theory this could be due to altered metabolism, but may reflect difficulty ensuring complete bladder emptying before starting and at completion of the test in the patients we studied. It is incorrect to presume that the abnormality demonstrated in the oral test could have been due to metabolic differences, as this would have given rise to an apparent reduction in permeability to cellobiose, whereas in fact we have demonstrated the opposite.

The purpose of the i.v. test was to compare the group of psychiatric patients with abnormal oral tests with those who had a normal oral sugar test. The i.v. injection was given before the patient was allowed away from his bed and after a urine specimen was collected. The patients did not have access to food or water during the five-hour period when all urine passed was collected. Endoscopy was performed at the end of the i.v. test and no excessive gastric contents were noted. The i.v. test therefore confirmed no significant difference in metabolism or excretion in the two groups studied.

The composition of the oral test solution is clearly stated in the method section. Patients were asked not to drink, but in order to retain co-operation some freedom was allowed and it is possible that some may have drunk water during the study. However, this would tend to reduce permeability to cellobiose, whereas in fact the study demonstrated an increased permeability to cellobiose in the abnormal group.

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Mental handicap and double-blind trial design

SIR: The title "Lithium in the treatment of aggression in mentally handicapped patients: a double-blind trial" (*Journal,* May 1987, **150,** 685–689) raises an interesting question about how the limited conceptual ability implicit in mental handicap might interact with the conceptual sophistication necessary to understand a double-blind design. That the

interaction between mental handicap and a double-blind design might have undertones is conceded in the statement, "The nature of the trial and the procedures involved were explained to each patient (at an appropriate level) and to a relative or responsible guardian". Just how much each participant actually understood is unknown, however, because of the lack of operational criteria showing that they understood, as distinct from being in receipt of an explanation. It appears that an opportunity to establish such criteria was lost; for example, each participant should be able to explain the procedure back to the researcher.

However, the more compelling scientific issues concern the other half of the "double-blind" design, the researchers. The outcome variable, levels of aggression, was assessed daily by the nursing staff on duty, who differed during the study; none of them were asked to guess the allocation of the patients. This would have been a prudent precaution given that, "The initial daily dose of 800 mg lithium carbonate was not sufficient, in most cases, to bring the serum lithium concentrate above 0.7 mmol/litre, and subsequently dosage adjustments were needed . . .". But we are not told that equivalent adjustments were made for the patients receiving placebo, so that one wonders what the nursing staff made of a group of patients who were having their medication adjusted and another group who were not having such adjustments.

Also, side-effects may have betrayed treatment allocation. Although the medical officer assessed each patient for the occurrence of possible side-effects of lithium treatment both before the trial and after one, two, three, six, nine, and twelve weeks, it is naive and unnecessary to suppose that these results, arising as they do out of interviews at specific points of time, generalised to what may have passed between the patients and the nurses who look after them 24 hours a day. It would have been easy to test the nurses themselves. Again, what was the mnesic ability of these patients? How reasonable was it to suppose that at an interview at a given point in time they would recall what had happened in between those points in time?

With this perspective, the authors' claim that blindness was maintained because classical side-effects were noted in 36% of the lithium patients and 20% of placebo patients is unwarranted, particularly as the exact means whereby the side-effects were detected remain apocryphal. Did the medical officer await spontaneous complaints? Did he or she ask a direct question, and if so what question? Was a check-list used?

Why were the measures of aggression made by different members of nursing staff? Given that they were, why was there not a reliability study of these staff? Given that there wasn't such a study, why were the results not analysed for individual nurses? The five-point scale whereby level of aggression was assessed is, on paper, no better than ordinal, the more so given that it may have been used in different ways by the different nursing staff; there was therefore good reason to suppose that the scale did not have interval qualities, and no evidence was presented to gainsay that, so how do the authors justify the use of parametric statistics?

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SIR: According to the Declaration of Helsinki, "In any research on human beings each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail . . . . Where physical or mental incapacity makes it impossible to obtain informed consent . . . permission from a responsible relative replaces that of the subject in accordance with national legislation". Thus it is not necessary for a mentally handicapped patient to be able to understand a double-blind design in order to participate in such a trial.

Regarding blindness, in the method section of our paper we described how dummy results for serum lithium concentrations were provided for placebo patients. The medical officer responsible for each patient adjusted the dosage of trial medication accordingly, so that both he and the nursing staff remained unaware of whether the patient was being treated with lithium or placebo.

Records were kept by the nursing staff of the type, duration, and severity of side-effects, as and when they occurred, using a check-list of common lithium side-effects.

It cannot be possible in a hospital to have daily assessments carried out by the same person over a 16-week period. Before undertaking this trial we carried out a reliability study, using the same 5-point rating scale for aggression, to assess the correlation between scores given by different nurse assessors. Statistical analysis of the results showed that while the score of 2 (mood uncertain) was the least reliable, scores of 1 (well-behaved) and 3 or more (overt aggression) achieved satisfactory levels of correlation between separate assessors. For this reason the analysis of our trial results concentrated on these scores.

In our trial it seemed reasonable to use parametric methods for analysis of the scores obtained with the