report of the effectiveness of lithium in a case of hypersomnia accompanied with polyphagia occurring in an adolescent female (2, 3), I would expect the drug to be effective in typical Kleine-Levin syndrome, but this is yet to be confirmed.

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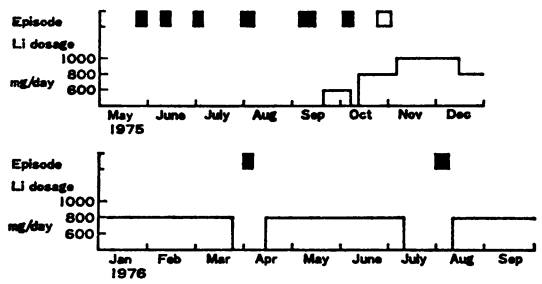

Fig 1—Hypersomniac episodes (shaded boxes) and lithium dosage. The unshaded box at the end of October 1975 refers to an episode of depersonalization.

PRENATAL PROGESTERONE AND EDUCATIONAL ATTAINMENTS

DEAR SIR,

The paper of Katherina Dalton (*Journal*, Nov. 1976, 129, 438–42) has received so much advance publicity, and presents such unexpected findings, that it deserves the closest scrutiny.

It essentially makes two claims: one that the effects of toxaemia in the mother and the intelligence of the child can be reversed by progesterone; the second, even more remarkable, that progesterone will increase the intelligence of the subsequent child above normal. Her results, however, do not warrant these conclusions.

The first claim would require that the mothers treated for toxaemia of pregnancy by progesterone were compared with an identical group treated with placebo injections. These conditions appear to have been satisfied with the first study reported in the *Journal* in 1968 ('Antenatal progesterone and intelligence', 114, 1377–82), but the only statistically significant result ($P = <\cdot05$) was that the progesterone children were more frequently walking at six months. The current study, however, gives insufficient information to support the first claim, let alone the second, largely because insufficient information is given about the control group. Progesterone mothers are likely to have been an unusual group to have opted for progesterone injections in the 1950s, 11 of them within the first trimester. It is not altogether fanciful to assume that they were both more open-minded and more concerned about the future health of their children than the controls, who were picked at random from obstetric wards or the General Practice Register. Not only is no evidence cited for the equivalent intensity of toxaemia for the toxaemic controls, but no comparison is made about any of the controls and the progesterone mothers, except to say that they belonged to classes 3–5.

Having, however, selected what one must hope are comparable controls, Dr Dalton uses the chi-squared test which distinguishes the groups qualitatively rather than quantitatively, but she does not quote the cut-off point used to divide the groups. More importantly, she assesses the three groups together, thus allowing the generally greater difference between the toxaemic controls and the progesterone group to obscure the significance, or lack of it, between the normal controls and the progesterone mothers. (To be fair, the only statistics where figures are provided 'Entrance to university'—actually distinguishes the progesterone group from the normals more significantly, $\chi^2 = 9\cdot53$ and $P = <\cdot01$). Under these circumstances, the presence of two more controls than can be accounted for by the double matching of four is merely a quibble.

It is all too easy to destroy exciting findings by over-zealous criticism. Nevertheless, it is sad that such an interesting paper should have been published in its present form, and we hope Dr Dalton will furnish us with sufficient details to confirm her remarkable claims.

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DEAR SIR,

In her article, Dr Katharina Dalton states that 'progesterone given to the mother (antenatally) not

only prevents the development of toxaemia and eliminates the diminished intelligence in the child but actually enhances the intelligence'. In her summary she relates the best academic results to a particular drug regime. These conclusions raise the possibility that, just as medication has been prescribed as the solution to educational problems in certain American States, so prenatal progesterone will be suggested as the answer to poor examination results in this country.

Do Dr Dalton's data justify her claims? To examine this it is necessary to read her current paper in conjunction with her earlier papers of 1968, which describes her sample and records the children's status and attainments at one year and 9 years. Points to be noted include:

1. Two control groups are used, one of normal women, one of toxaemic women. These two are combined for comparisons with the experimental group at age 9, but kept separate at later ages.

2. No attempt was made to control for the social class or education of the mothers. This is particularly important for the toxaemic group with the association of toxaemia with various indices of social disadvantage.

3. In each follow-up, approximately 50 per cent of each sample only were traced. Among the reasons for loss of sample members are adoption of the child and residence at a gypsy encampment. Details of types of losses are not given independently for each sample.

4. If the toxaemic group is excluded, there is no difference in the rates of academic success at 9 years and A and O level results between progesterone-treated and normal groups. More of the progesterone-treated group attended university, but this could be due to:

5. Differences are seen between the mothers of the normal and treated groups. Those from the latter are older. They are more likely to have breast-fed their infants to six months. Dr Dalton feels this latter finding could be a direct result of the progesterone treatment. It is surely as least as likely to be a direct reflection of the women's social status and educational background.

The data presented can in no way be seen to support the suggestion that progesterone 'actually enhances the intelligence'. Differences are seen within the progesterone-treated group, but these are difficult to evaluate. Early therapy and long duration of therapy increase O level passes, but not A levels. No social data, however, are given on the families in the various groups.

It may well be that Dr Dalton has found an interesting issue which needs studying. Unfortunately her unqualified claims could stimulate enthusiasts to attempt to raise the intelligence of various groups in the community, particularly as she suggests that there may be a specific effect which will raise scientific ability (? at the expense of interest in the arts).

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MIANSERIN

DEAR SIR,

The comparison of mianserin and amitriptyline reported recently by Coppen *et al* (*Journal*, October 1976, **129**, 342–45) is unsatisfactory in several respects. No doubt this trial will be quoted by advertisers of mianserin, and therefore certain comments are pertinent. I hope they may also be useful when considering plans for further drug trials.

(1) Mianserin was given thrice daily, while amitriptyline was given at night. This *may* have led to:

(a) patients giving clues to the 'unaware' investigator as to which medication they were taking;

(b) altered sleep in patients having all their medication at night, thus affecting changes in scores on the Hamilton Rating Scale. Scores might also be affected by other differences between effects of thrice daily and single nightly dosage;

(c) differences in side-effect scores. Patients having a single nightly dosage of amitriptyline are more likely to complain of certain side-effects than those on thrice daily medication (Snowdon, in press). It is likely that this would also apply to mianserin.

(2) There was a considerable difference in mean age (13·1 years) between patients in the two treatment groups. Patients in their sixties may well be more liable to some side-effects (e.g. postural hypotension), especially if the drug is given in undivided dose, than are those in their forties.

There is no mention in this report of how many patients dropped out of the trial (e.g. because of side-effects).

Mianserin is probably a useful additional antidepressant, and may have certain advantages. Evidence suggests that its side-effects are less troublesome than those of amitriptyline, and a trial comparing similar dosage regimens of the two drugs might well be convincing.

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