Drug dependence may be defined as a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes also to avoid the discomfort of its withdrawal.

This report of a case of oxazepam dependence described a 29-year-old male technician who had had periods of depression for the past nine years. His own doctor put him on oxazepam, 15 mg. t.d.s., later increased to 30 mg. t.d.s., and for some reason the patient was maintained on this dosage for approximately a year and a half before being sent, for the first time, to a psychiatrist.

The oxazepam was stopped and a small dose of amitriptyline was substituted. His depression continued, the worsening possibly arising from the exacerbation of the anxiety component of his depressive illness. There followed then a period of some months during which he was treated with a variety of medications, including an oxazepam placebo, all to little avail, until finally phenelzine was given with rapid and apparently lasting effect.

There are aspects to this case which merit attention, the first referring to the signs of withdrawal of oxazepam. Withdrawal manifestations as quoted in the report include agitation, restlessness, and depression, which symptoms were present before he was given Serenid-D initially. Secondly, the patient was allegedly on a high dose of oxazepam, yet the signs quoted in the article as associated with withdrawal after high doses, namely hallucinations, delirium and convulsions, are not described. Thirdly, in all cases of affective disorder, anxiety and depression are inextricably entwined (3): to damp one down may undoubtedly confer some temporary stability but the imbalance will eventually result in either the necessity for increasing dosages or overt signs of the presence of the untreated factor. The quoted withdrawal signs are evidence of the anxiety accompanying the patient's depressive illness, allowed to burst forth once the oxazepam was discontinued.

I would suggest that the patient was suffering from a recurrent depressive illness for which he was treated by oxazepam which was only partially successful by virtue of its anxiolytic properties. When eventually he was treated with the antidepressant, phenelzine, his depression was lifted together with his anxiety, rapidly removing the need and desire for any other medication. The phenelzine in fact did not affect the so-called withdrawal symptoms as such but effectively treated the responsible depressive illness. In my view there is no evidence of dependence produced by oxazepam in this case.

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MANIC-DEPRESSIVE PSYCHOSIS AND URINARY EXCRETION OF CYCLIC AMP

DEAR SIR,

With reference to the paper by Brown, Salway, Albano, Hullin and Ekins (1972 **120**, pp. 405–8) we too have made a number of studies on urinary cyclic AMP excretion using their saturation assay, after preliminary $ZnSO_4Ba(OH)_2$ treatment. Samples were analysed in triplicate at each of two dilutions (usually 1 : 5 and 1 : 25) and close agreement was generally obtained, but in a few cases the higher dilution consistently gave higher results which could be explained if a factor occurs in the concentrated urine which can enhance the protein binding of cyclic AMP. In such cases we have taken the result from the higher dilution as more likely to be accurate. Recoveries were monitored by the inclusion of internal standards. Very similar values to those of Brown *et al.* were found for the 24 hr. excretion by normal volunteers (mean $3 \cdot 25 \pm \cdot 21$ s.e.m., $n = 10$, range 2·03–4·36 μmoles/24 hr.). We have measured the daily excretion by a number of depressed and manic-depressive patients over periods covering several mood changes without being able to establish any consistent correlation between cyclic AMP excretion and mood, so in general we endorse the findings of Brown *et al.*

However, in one ususual case we have found a very marked correlation. This patient has a very regular 48-hour cycle of mood, and has been extensively studied by us (see, for example, Hanna, Jenner, Pearson, Sampson and Thompson (1972)). Urine was collected in 4 hr. periods except for the overnight sample, which was 8 hr., and the mood was noted during the collection periods by staff familiar with the patient. At this time, after being well for three years while taking lithium carbonate, he had relapsed on placebo tablets. The results as shown in Fig. 1 for cyclic AMP are expressed in n moles/mg. creatinine to compensate for changes in volume. Very regular swings coincident with mood changes can be

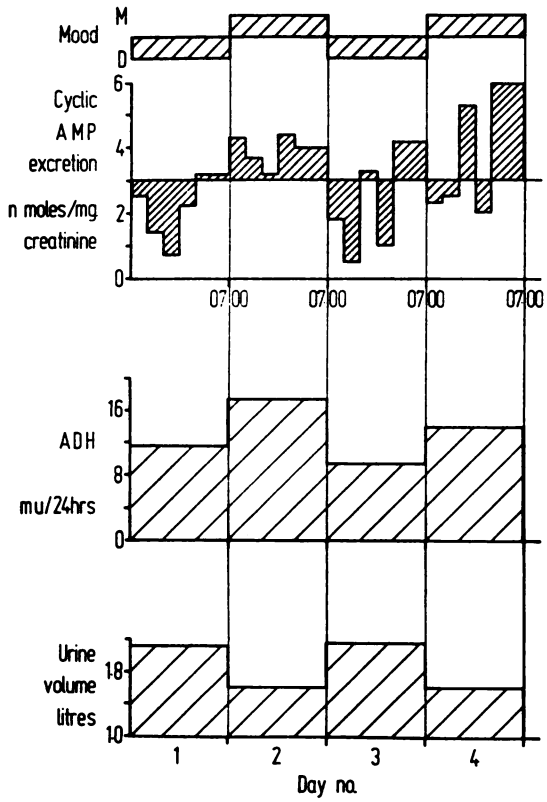

FIG. 1.—Shows the patient's mood schematically, his urine cyclic AMP, and antidiuretic hormone excretion and urine volume.

seen on days 1, 2 and 3, becoming more erratic on day 4. This patient is already known to show similar changes in water balance and electrolytes as well as in many other parameters (Jenner, Gjessing, Cox, Davis-Jones, Hullin and Hanna (1967)). The changes in water balance seem to be due at least in part to changes in vasopressin output by the pituitary. Fig. 1 also shows the patient's 48 hour cycle of urine volume changes and vasopressin excretion (by method of Bisset, 1962) consistent with this view. It is believed that the action of vasopressin on toad bladder permeability *in vitro* is mediated by cyclic AMP; certainly the mammalian kidney contains a vasopressin-responsive adenyl cyclase (see Robison, Butcher, and Sutherland (1971) for a summary of the evidence on these points). It seems likely, therefore, that the changes in cyclic AMP which we find are secondary to hormone changes, possibly resulting from a pituitary or hypothalamic defect which may be the primary origin of the syndrome and of the other cyclical changes which have been found in the patient. If this is so, it is entirely conceivable that other defects may be possible which could result in mood changes without affecting cyclic AMP excretion, and hence that cyclic AMP variation is not a necessary or even a frequent accompaniment of manic-depressive illness.

It is nevertheless also of some interest that in this patient lithium is very effective (Hanna, Jenner, Pearson, Sampson and Thompson, 1972), and also that we have shown that lithium inhibits the action of vasopressin on the kidney as well as the effect of vasopressin and of cyclic AMP on the toad bladder's transport of water (Harris and Jenner, 1972).

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BEHAVIOR MODIFICATION IN MENTAL RETARDATION, BY W. I. GARDNER

DEAR SIR,

I would like to bring to the attention of your

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