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Correspondence

Letters for publication in the Correspondence columns should be addressed to:
The Editor, British Journal of Psychiatry, Chandos House, 2 Queen Anne Street, London, W1M 9LE

CHOREIFORM MOVEMENTS AFTER DEPOT INJECTIONS OF FLUPENTHIXOL

DEAR SIR,

I was most interested by Dr. Alan Gibson's account of chorea associated with flupenthixol (*Journal*, July 1974, p. 111). Unequivocal choreiform dyskinesia—'irregular and rapid darting, flexing, writhing or grimacing movements' (mainly around the mouth)—occurred in 41 per cent of a series of patients maintained on oral phenothiazines (Kennedy *et al.*, 1971); and Hunter *et al.* (1964) described irreversible movement disorders in minimally brain-damaged schizophrenics following the withdrawal of phenothiazines.

A 60-year-old ex-waitress with a very long history of schizophrenia and a tendency to drink to excess was, after four years in a mental hospital, placed on fluphenazine depot injections. She soon developed quasi-purposeful writhing and shock-like movements of her limbs, rocking of her trunk, a tremulous undulating gait, grimacing, oral dyskinesia and ataxia, which persisted after the injections were stopped and failed to respond to a variety of anti-parkinsonian drugs. There was nothing in her life story suggestive of rheumatic fever, encephalitis or poisoning by carbon monoxide or heavy metal; nor was there any family history of spontaneous movements or of mental illness. The movements persisted over the three years for which I followed her up.

It would seem, therefore, that movement disorders, reversible and irreversible, can occur with both thioxanthines and phenothiazines, whether given parenterally or orally.

M. W. P. CARNEY.

Northwick Park Hospital,
Watford Road,
Harrow, Middlesex, HA1 3UJ.

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URINARY CYCLIC AMP AND DEPRESSION

DEAR SIR,

The implication by Hullin *et al.* (*Journal*, November 1974, p. 457), that the 24-hour urinary excretion of cyclic AMP is not related to mood in affective disorders is in direct conflict with our findings in a double blind study of depressed patients and control subjects in which we measured the 24-hour urinary excretion of cyclic AMP in 27 patients suffering from 'classical endogenous' depression, 15 patients suffering from 'classical neurotic' depression and 25 healthy control subjects.

Comparison of mean and S.D. of urinary cyclic AMP (μ mole/24 hr.) in the first 24-hour urine samples

	Control (N = 25)	Neurotic (N = 15)	Endogenous (N = 27)
Mean ..	3·98	2·27	2·88
S.D. ..	±1·55	±1·77	±1·55

Difference between control and neurotic significant $P < 0.0025$.
Difference between control and endogenous significant $P < 0.01$.
Difference between endogenous and neurotic non-significant $P < 0.20$.
(Student's 't' test used for comparison of means.)
(N = number of subjects sampled.)

It can be seen from the above table that depressed patients showed a very significantly decreased 24-hour urinary excretion of cyclic AMP when compared to control subjects. This decreased level of 24-hour urinary cyclic AMP increased significantly to reach and maintain control values as the patients recovered, while the 24-hour urinary excretion of cyclic AMP by the control subjects remained constant. Naylor *et al.* (*Journal*, September 1974, p. 275) reported that in 12 female patients recovering from a depressive psychosis the 24-hour urinary excretion of cyclic AMP increased significantly with recovery, which supports our findings.

Hullin *et al.* report on an example, not a sample, and therefore their conclusions are open to statistical criticism. It would be extremely interesting if they

would tell us the normal 4-hour urinary excretion of cyclic AMP in control subjects and if they could compare this with data collected from sufficient patients who exhibit a rapid change in mood to make a sample large enough from which to draw a statistically valid conclusion.

KENNETH SINANAN.

Cluain Mhuire Family Centre,
Newtownpark Avenue,
Blackrock, Co. Dublin.

W. CLAYTON-LOVE.
ATHENE M. B. KEATINGE.

Clinical Biochemistry Laboratory,
Trinity College, Dublin 2.

EMOTIONAL ILLNESS IN PSYCHIATRIC TRAINEES

DEAR SIR,

Dr. Waring's study (*Journal*, July, **125**, 10–11), contains, I believe, two serious methodological problems which may largely invalidate his findings. First, the General Health Questionnaire, as the author correctly states, is a '. . . reliable, valid and sensitive screening schedule for detecting emotional illness in general practice'. The same cannot, unfortunately, be assumed for the population to which it was applied. Secondly, as I am informed by Dr. Waring, the covering letter to those doctors in the control group began as follows:

'Dear Doctor:

I have been carrying out a study at the Institute of Psychiatry on attitudes, personality features and emotional factors in doctors training in psychiatry. Over 86 per cent of the doctors in the survey at the Institute have kindly responded. I am in need of a control group of doctors in training, but not training in psychiatry, etc.' Thus these respondents knew they were to be a control group and further that the study concerned assessment of their colleagues in psychiatry. One can only speculate on how this may have biased the outcome.

I believe we must consider the questions posed by Dr. Waring as still unanswered.

PAUL LATIMER.

Behavior Therapy Unit,
Temple Department of Psychiatry,
c/o Eastern Pennsylvania Psychiatric Inst.,
Henry Ave. at Abbottsford Road,
Philadelphia, Pennsylvania 19129.

COMBINED ANTIDEPRESSANT MEDICATION

DEAR SIR,

There is still much controversy concerning the relative benefits and potential hazards of using combined antidepressant medication, namely the concurrent administration of a tricyclic antidepressant and a monoamine oxidase inhibitor (MAOI) (1). Winston (2), Schuckit *et al.* (3) and Sethna (4) have put forward the case for combined antidepressant treatment in refractory cases that do not respond to one or other treatment alone, and psychiatrists at St. Thomas' Hospital are well known for their views that many more depressed patients could be successfully treated if doctors were less fearful of the hazards of combined antidepressant medication.

Successful results were obtained by Winston (2) using 25 to 100 mg. amitriptyline daily combined with isocarboxazid, 10 to 20 mg. daily, whereas Sethna (4) used 50 to 75 mg. amitriptyline daily with phenelzine 15 mg. three times a day. Further, Pollitt (5) reports good results using only small daily doses of amitriptyline (50 mg.) combined with isocarboxazid or phenelzine. If combined antidepressant medication is more effective than either antidepressant alone it is of importance to discover the pharmacological basis for this apparent synergism.

The effect of many drugs is said to be potentiated by the concurrent administration of MAO inhibitors (including tricyclic antidepressants), narcotics, barbiturates, tranquillizers, anaesthetics and alcohol (1, 6). Because of their 'enzyme-inhibiting' properties, the MAOI drugs have been reported by some workers to interfere with the hepatic microsomal enzyme system which is responsible for the metabolism of many of the above mentioned drugs, including the tricyclic antidepressants (6–10).

We wish to report our observations of the effect of MAOI (isocarboxazid) administration upon plasma concentrations of a tricyclic antidepressant (amitriptyline). Eight patients from an out-patient clinic were selected for the study; six were receiving 50 mg. amitriptyline at night and two 25 mg. nightly. One patient was also receiving diazepam, but the dose was not changed throughout the duration of the study. Isocarboxazid in daily divided doses of 15 to 20 mg. was given to or withdrawn from patients who were already receiving amitriptyline. Heparinized venous blood samples were obtained from each patient before, during, and/or after at least one month of combined tricyclic/MAOI administration, at the same time of day (3.00 p.m.) on each occasion. Plasma samples were analysed for amitriptyline and its major active metabolite, nortriptyline, using a gas-chromatographic technique (11) which has a lower limit of sensitivity for both drugs of approximately 20 ng./ml.

Results in all eight patients showed that plasma levels of both amitriptyline and nortriptyline did not exceed 30 ng./ml. before, after or during combined antidepressant administration. Even though it was