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.

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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.

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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