Brit. J. Psychiat. (1963), **109**, 447–449

Correspondence

A CORRECTION

DEAR SIR,

I should be grateful if a correction could be published concerning the paper by Oswald, I., Berger, R. J., Jaramillo, R. A., Keddie, K. M. G., Olley, P. C., and Plunkett, G. B., in the *British Journal of Psychiatry*, 1963, pages 66 to 78. On page 74 of this in Table I, where reference is made to % Time A Stage, this should in fact read "Time A Stage (min.)". All other references to percentages are correct.

IAN OSWALD

University of Edinburgh,
Department of Psychological Medicine.

POST-ENCEPHALITIC SYNDROMES

DEAR SIR,

The parents of a patient recently in this hospital have it in mind to try and ascertain the size of the problem produced by Encephalitis. They would like as a first step to compose an index of sufferers from post-encephalitic states, in the hope that some organization on the lines of those working for Spastics might eventually be formed.

There must be many post-encephalitic patients whose conditions are slight and possibly subclinical, and others in whom the true diagnosis is never reached. Where the diagnosis is established, it would be of the greatest possible assistance if doctors would persuade their patients (or families) to communicate (or permit the doctors to do so) with Mr. W. A. C. Myers, 1 St. Leonards Lodge, Maze Hill, St. Leonards on Sea (Telephone: Hastings 6266). Mr. Myers hopes to compile a register giving at least the following particulars:

Name, age (with date of birth), address (and telephone number if known), degree of disablement (in general terms), and approximately at what age the attack of encephalitis occurred.

Hellingly Hospital,
Hailsham, Sussex.

DAVID RICE,
Medical Superintendent.

PHENOTHIAZINES IN URINE

DEAR SIR,

With reference to a recent paper by S. Gold, P. D. Griffiths and R. G. Huntsman in the *Journal of Mental Science*, **108**, 88–94 (1962) on "Phenothiazines in Urine", we would like to call the authors' attention to an article of ours "Review of Rapid Urine Tests for Phenothiazine and Related Drugs" (1) in which the limitations of the individual tests were discussed.

We do not know the dosage ranges of the individual drugs for which urine tests were performed, but would like to stress the fact that the high percentage of negative tests encountered by these authors cannot be confirmed by us on the basis of many thousands of specimens tested.

In contrast, we wish to emphasize the following points:

1. False negative tests are almost entirely due to failure of patients to actually ingest the drugs. Many cases of apparent false negative tests reported to us by physicians or nurses were carefully re-checked by us: tablet medication was replaced with liquid medication or intramuscular injection. Especially paranoid patients were not allowed to use the bathroom for 30 minutes after oral drug administration in order to prevent them from disposing of liquid medication by self-induced vomiting. Without exception, all previously negative tests were found positive under such "foolproof" supervision. In many hundreds of such closely supervised administrations it became obvious that as little as 20 mg. of any phenothiazine drug or imipramine yields a reliably positive urine colour test, since even fractions of a microgram of these drugs per ml. of urine produce distinct colour reactions. We therefore believe the authors' conclusion that negative tests are unreliable to be erroneous. We are confident that with rigorous checking on drug ingestion or with an occasional switching to i.m. injection the same results would be seen.

2. In contrast thereto, the problem of false positives, especially in the low intensity levels of some of the colour reactions, was of genuine concern to us. Both endogenous and exogenous factors were found to account for these, and our experiences were reported in the above-mentioned review. The authors seem to trust any positive test result implicitly, but should be aware of the necessary precautions.

3. Frequently urines do not show the expected drug level, but a lesser one. This may occur even in patients most conscientiously ingesting all prescribed

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medication, but drinking large volumes of liquids, usually several cups of tea or coffee with each of three meals plus an undetermined amount of water, coffee, coca-cola, etc., between meals. Some of the phenothiazine drugs cause dry mouth, especially thioridazine. Patients on thioridazine therapy have shown the largest number of incongruent test results, a fact for which we had no ready explanation until a substantial number of quantitative 24-hour urine collections were seen. It then became obvious that urine outputs exceeding 3,000 ml.—frequently up to 5,000 ml.—were the rule rather than the exception. As this results in large fluctuations between colour tests in patients on the same drug dose, we routinely tested only first morning specimens. Even with observing these precautionary measures, there are individual deviations from the prepared colour chart, as some urines produce pinkish to purple colour tests, while others will show more bluish shades on the same drug dose. An explanation came forth when a quantitative procedure for determining total urinary thioridazine was developed. Due to the methylmercapto ring substituent of thioridazine two sulphoxides may be formed at positions 2 and 5 of the nucleus. Apparently individual patients show slight differences in patterns of drug metabolism with resulting differences in the ratio of the various oxidative drug metabolites. Qualitatively this is manifested by differences in the colours of rapid urine tests, and quantitatively a corresponding difference in the absorption spectra was seen.

4. From quantitative drug determinations we also learned that higher percentages of a daily dose are excreted in the urine under continuous drug administration. Single or sporadic drug doses invariably showed lesser aliquots of administered drug in the first 24-hour urine collection. Therefore, drugs administered in low daily doses such as trifluoperazine or fluphenazine, may show only traces of drug in the initial days of therapy.

5. In our hands the imipramine test was a sensitive and satisfactory procedure (2). A comparison of results obtained by a most sensitive quantitative spectrofluorometric procedure performed at the Geigy Research Laboratories, Ardsley, New York, by Dr. G. Quinn with those of rapid urine colour tests in the same urine specimens, showed excellent coincidence: rapid test results of ++, + and trace corresponded to 3·5, 1·6 and 0·16 microgram of imipramine per ml. of urine. The fact that phenothiazines also react with the imipramine test solution was duly stressed in our publications (2) and was indeed used to demonstrate both types of drugs in the same specimen: if phenothiazines and imipramine are used in combination therapy, the phenothiazines will show a clear-cut but fleeting purple colour reaction with the imipramine test solution, before the more stable green colours of the imipramine reaction appear. We specified that at simultaneous presence of substantial amounts of phenothiazine, 2 ml. of imipramine test reagent are needed to demonstrate urinary imipramine, as otherwise all available reagent may be used up by the phenothiazine present.

6. As far as specificity of individual test reagents is concerned: those designed for phenothiazines obviously react with all drugs of this class, a fact used in our FPN test (3). As this is a sensitive test, it may serve in the detection of low dosage drugs as well as with those given in the medium and high dosage ranges. It is also suitable for evaluating approximate total urinary level of phenothiazines when mixtures of drugs are used in combination chemotherapy. If only a single rapid test can be performed, e.g. to determine presence or absence of phenothiazine drugs, the FPN test would be the most eligible procedure. In cases in which a single, known drug has been administered, the various specific tests such as the one for chlorpromazine, promazine and mepazine (4) or for thioridazine (5) usually yield the most characteristic colour results, as the specific test reagents were designed for the normal psychiatric dosage range of the individual drugs to yield an optimal scale of colours.

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DEAR SIR,

We have enjoyed the article to which Forrest *et al.* refer ("Review of Rapid Urine Tests for Phenothiazines and Related Drugs") but unfortunately this was not available to us when our article was written.

We have read with interest the points raised in their letter, most of which were covered in our article however, and which we therefore feel cannot affect our conclusions significantly.

We feel bound to reiterate that in hands less skilled than those of the originators of these tests it is unlikely that the results will be so uniformly successful.

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