psychiatric services ought to be developed in the future.

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COMPARISONS OF HYPNOTIC DRUGS

DEAR SIR,

Drs. Andersen and Lingjaerde (*Journal*, December 1969, pp. 1393–7) describe a comparison of nitrazepam and phenobarbitone which prompts comments of a kind I have made before (Oswald, 1968), and will now repeat, because I want to urge that phenobarbitone should not be used as an hypnotic.

They write of phenobarbitone promoting, in their patients, 'a better *quality* of sleep'. We know so little about the nature of sleep that any remarks about its quality are hazardous, even more so when based upon the reports patients made in the morning when they would still be under the influence of ninety per cent of the bed-time dose of phenobarbitone. Phenobarbitone is very slowly excreted, and blood levels fall only 23 per cent or less in 24 hours (Butler *et al.*, 1954). Judgements about oneself made under the influence of barbiturates can be unrealistically self-satisfied (Smith and Beecher, 1960). Comments about the night's sleep may be presumed to be influenced by the drugged state at the time the judgement is made.

I hope that before deciding to prescribe phenobarbitone as an hypnotic a doctor would reflect that a patient's claim to have slept well after morphine would not constitute a reason for its routine nightly employment. I hope, too, he would reflect upon the fact that trials, such as the one referred to, tell us nothing about the drug-induced impairment of skill in, for example, driving during the following afternoon (especially if alcohol is taken at lunch time). I hope especially that he would remember the contemporary epidemic of self-poisoning. An overdose of nitrazepam very rarely causes coma. Coma after phenobarbitone overdose, because of the slow excretion, is liable to last several days; assuming the patient does not die, tolerance develops during the coma, leading to eventual drug-withdrawal features. These features, such as broken sleep, may not reach a peak until three weeks later, at the time the drug is finally cleared from the body (Haider and Oswald, 1970).

Drs. Andersen and Lingjaerde term the night nurse's report an *objective* measure. We may assume the night nurse gave the sleeping pills, and we are told that the placebos looked different. Consequently the difference between placebo and active tablets on 'objective' assessment loses validity. I have yet to encounter identical-looking hypnotic and dummy tablets where the bitter taste of the active tablets was not immediately recognizable, so I wonder whether the patients really were much more often 'blind' than the night nurse.

The authors also make the usual error of assuming that one night is independent of the next. Phenobarbitone is so slowly excreted that obviously nights could not be independent in this trial. There is, moreover, ample evidence from published all-night electrophysiological studies, conducted in this department and in various centres in the U.S.A., that after the distortion of sleep caused by such hypnotics as barbiturates or nitrazepam a 'rebound' occurs when the drugs cease (e.g. Oswald and Priest, 1965). The rebound is in a direction opposite to the drug's effect and includes restless sleep, shortened sleep and vivid, anxious dreams. If therefore a patient gets an hypnotic on night 1 and placebo on night 2 he may be expected to say he slept badly on night 2 *because he had the drug the night before*.

The rebound effects persist for days, in fact, weeks. Consider, therefore, a trial like that of Drs. Andersen and Lingjaerde where there is a sequence—placebo, drug, A, drug A, drug A, placebo, placebo, drug B, drug B, drug B. We may expect (we were not told) that most patients would have been on hypnotic drugs on prior nights. If we were to assume that the prior drug was potent and that drug A and drug B are both inert, then, in the above design, where, overall, placebo precedes drugs A and B, sleep will be less disturbed on drugs A and B nights, providing withdrawal 'rebound' is maximal on the first (placebo) night and declines appreciably over a nine-day period. In this way drugs A and B could appear superior to placebo even though inert.

If all patients were equally accustomed to prior hypnotic drugs, and if drug A and drug B were switched equally among the patients, so that for half of the patients drug B preceded drug A, then A and B should appear equal. On the other hand if this switching procedure were imperfect or failed to match patients for age (to take but one factor into account) then one of these two possibly inert drugs could appear not only superior to placebo but also superior to the other.

If, alternatively, we were to assume that in a study of this nature no patients had received prior drugs for a couple of months, and if drug A were potent and drug B inert, drug B could still appear superior to placebo because two of the placebo nights im-

mediately followed three nights on the potent drug. Such an effect would, of course, be diluted by ensuring that half the patients got drug B first.

I am not suggesting that either phenobarbitone or nitrazepam is inert, but just hope more notice may be taken of modern knowledge about sleep and drugs.

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DEAR SIR,

A short presentation of a clinical trial does not permit, unfortunately, a detailed discussion on all problems encountered during the study. Actually, we were aware of the more important points discussed by Dr. Oswald, even if this does not appear clearly from our paper. Although some of his objections seem to us rather irrelevant, we welcome this opportunity to comment on his letter.

We agree with Dr. Oswald that phenobarbitone is no ideal hypnotic, at least not for prolonged use. It is not used in the daily routine at our clinic (in fact, we use very little barbiturates). We would also like to point out that in our paper we did not recommend the use of this drug—we only pointed out some differences in its clinical action versus nitrazepam, which was the main subject of our study. We are quite confident that the readers of this journal are aware that other factors than those discussed in our paper must be taken into consideration when choosing among the many available hypnotics. However, we found that phenobarbitone could be used in our particular study, in which it was given in the low dosage of 100 mg, for three successive nights only, and with a 'wash-out' period of two nights in between the active drugs. Dr. Oswald points out the well-known fact that the blood level of phenobarbitone decreases very slowly. There is, however, no simple correlation between blood level, or even total body level, of barbiturates, and their effect on sleep (see Goodman and Gilman 1965). In our study there were several indications that phenobarbitone did not have as long-lasting effects as would have been expected from the slow elimination from blood: (1) The frequency of 'hangover' was exactly the same after phenobarbitone and placebo, and only slightly (not significantly) less after nitrazepam. (2) The average time-profile of sleep during the night (objectively measured) was almost exactly the same for phenobarbitone as for nitrazepam. (3) Sleep on phenobarbitone, whether objectively or subjectively assessed, did not differ significantly between the first, second or third night on this drug.

If phenobarbitone in our study had a shorter duration of action than has been found in experiments on 'normal' subjects, the reason may have been that most of our patients had previously received drugs which are known to increase the rate of metabolic degradation of barbiturate in the liver.

Still, there is the possibility that the patients' judgements of their sleep when using phenobarbitone were in part influenced by some subtle persistent effect of the drug, as suggested by Dr. Oswald. However, if the patients were generally 'unrealistically self-satisfied' in the mornings after the phenobarbitone nights, one would have expected a higher over-all ratio of subjective : objective assessment of sleep on phenobarbitone than on nitrazepam. In actual fact, these ratios were exactly the same (as can be seen from Table I in our paper). But in one subgroup of patients there was a discrepancy: patients who had difficulties in going to sleep because of disturbing thoughts were rated relatively higher on the subjective than on the objective scale when using phenobarbitone. In our paper we do not give any definite explanation of this finding, but offer some discussion on it. It could be that 'unrealistic self-satisfaction' should also be taken into consideration, although it is difficult to see why this should be important in this type of patient only.

Dr. Oswald states that we 'make the usual error in assuming that one night is independent of the next'. As a matter of fact, we were not quite unaware of this—it was, for example, the main reason why we used placebo between the active drugs. The possibility of carry-over effects in a cross-over study is certainly a disadvantage, but in our opinion it must be weighed against the greater advantage of using each patient as his own control, in a study like ours. We do not think that carry-over effects between the